National Institute for Health and Care Excellence

Draft for consultation

Chronic Heart Failure

Chronic Heart Failure: Management of chronic heart failure in adults in primary and secondary care (update)

NICE guideline <number>

Appendices A – S

March 2018

Draft for consultation

Developed by the National Guideline Centre, hosted by the Royal College of Physicians

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Appendix A: Clinical review protocols

A.1 BNP and NT-proBNP in diagnosing heart failure

Table 1: Diagnostic accuracy review protocol: BNP and NT-proBNP in diagnosis of heart failure

Component	Description
Review question	In people with suspected heart failure, what thresholds of N-terminus pro-B-type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP) are most accurate in identifying heart failure (as indicated by the reference standard)?
Objectives	To evaluate the accuracy of BNP and NT-proBNP (at different thresholds) in the diagnostic pathway of heart failure (both rule in and rule out).
Study design	Single gate diagnostic accuracy studies (cross sectional studies/cohort studies)
Population / Target condition	Population: People with suspected heart failure in a community or outpatient setting. Patients would commonly present with the following symptoms: breathlessness (exertional dysnpnoea, orthopnoea and paroxysmal nocturnal dyspnoea), fatigue and ankle swelling. Target condition: Heart failure
Setting	Community or outpatient setting (not admitted to hospital).
Index tests	NTproBNP (at any reported threshold) BNP (at any reported threshold) Different thresholds will not be grouped together when presenting the results.
Reference standard (could be more than one)	A clinical diagnosis based on the opinion of at least one cardiologist, considering symptoms (potentially with some signs) and objective evidence of cardiac dysfunction (either structural or functional).
Statistical measures	Diagnostic accuracy of BNP and NT-proBNP. 2x2 tables Specificity Sensitivity PPV/NPV ROC curve or Area under Curve
Other exclusions	< 100 participants total
Search Strategy	October 2009 onwards (update of previous question)
Review Strategy	Stratification – groups that will be considered separately if data are available: N/A Subgroups where diagnostic tests may be more or less accurate – to investigate heterogeneity (only when trials can be split at this level): Age (18 to 75 years versus 75 years and over) Ejection fraction (reduced v preserved) BMI (obese v normal weight)

Component	Description
	Sex Background medication (optimal v suboptimal) Clinical signs (reported v not reported) Appraisal of methodological quality: The methodological quality of each study will be assessed using the QUADAS-II checklist (per target condition). Synthesis of data Diagnostic meta-analysis will be conducted where appropriate using hierarchical methods.

Table 2: Diagnostic RCT review protocol: BNP and NT-proBNP in diagnosis of heart failure

Review question	In people with suspected heart failure, what is the clinical and cost effectiveness of N-terminus pro-B-type natriuretic peptide (NT-proBNP) compared to B-type natriuretic peptide (BNP), when each is followed by the appropriate patient pathway, in order to improve patient outcomes?
Guideline condition and its definition	Chronic heart failure. Definition: People diagnosed with heart failure, who are in a community or outpatient setting.
Objectives	To evaluate the clinical and cost effectiveness of NT-proBNP compared to BNP when followed by the appropriate patient pathway.
Population and target condition	Population: People with suspected heart failure in a community or outpatient setting. Patients would commonly present with the following symptoms: breathlessness (exertional dysnpnoea, orthopnoea and paroxysmal nocturnal dyspnoea), fatigue and ankle swelling. Target condition: Heart failure
Index diagnostic test + treatment	NTproBNP assay (at any reported threshold) Treatment/next step in pathway: Echocardiography
Comparator index diagnostic tests + treatment	BNP assay (at any reported threshold) Treatment/next step in pathway: Echocardiography
Outcomes	Efficacy outcomes: - All-cause mortality at During study (Time to event) CRITICAL - Quality of life at 12 months (Continuous) CRITICAL - Unplanned hospitalisation at During study (Count rate) CRITICAL Process outcomes: - Number of people receiving echocardiography, i.e., including people who may not have needed it such as those with false positive results at 12 months (Dichotomous) IMPORTANT - Repeat testing / additional testing at 12 months (Dichotomous) IMPORTANT Secondary accuracy outcomes: - Sensitivity / specificity and other test accuracy measures IMPORTANT
Study design	Diagnostic RCTs

Review question	**In people with suspected heart failure, what is the clinical and cost effectiveness of N-terminus pro-B-type natriuretic peptide (NT-proBNP) compared to B-type natriuretic peptide (BNP), when each is followed by the appropriate patient pathway, in order to improve patient outcomes?**
	Systematic reviews of diagnostic RCTs
Sample size exclusion criteria	< 100 Overall
Sensitivity/other analysis	Mortality data will only be extracted if it is at least 12 months. Other outcome data will only be extracted if it is at least 3 months. For dichotomous and continuous outcomes where a study reports multiple time points, the closest time point to the specified time point will be extracted. For subgroup analyses, average outcome values / majorities within a study population will not be used to assign the study to a subgroup. For inclusion in a subgroup, study populations should be similar to one of the specified subgroups. Where studies split results by age but this does not align with the specified subgroups, the results will be included in the subgroup analysis so long as the cut point is at least 65 years. Where all-cause mortality is not reported but data on CV mortality is reported, the CV mortality data will be extracted but will not be pooled with the all-cause data. Where unplanned hospitalisaton data is not reported but data on HF-related unplanned hospitalisation is reported, the HF-related data will be extracted but will not be pooled with the all-cause data.
Subgroup analyses if there is heterogeneity	Age (18 to 75 years versus 75 years and over) Ejection fraction (reduced v preserved) BMI (obese v normal weight) Sex Background medication (optimal v suboptimal) Clinical signs (reported v not reported)
Search Strategy	Date limits for search: From October 2009 (update of previous review question) Language: English only

Table 3: Diagnostic accuracy review protocol: BNP and NT-proBNP in diagnosis of heart failure in people with atrial fibrillation

Component	Description
Review question	In people with suspected heart failure who also have atrial fibrillation, what thresholds of N-terminus pro-B-type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP) are most accurate in identifying heart failure (as indicated by the reference standard)?
Objectives	To evaluate the accuracy of BNP and NT-proBNP at different thresholds in the diagnostic pathway of heart failure (both rule in and rule out) in people who also have atrial fibrillation.
Study design	Single gate diagnostic accuracy studies (cross sectional studies/cohort studies)
Population / Target condition	Population: People with suspected heart failure in a community or outpatient setting, who also have ECG diagnosed atrial fibrillation (paroxysmal, persistent or permanent). People would commonly present with the following symptoms: breathlessness (exertional dysnpnoea, orthopnoea and paroxysmal nocturnal dyspnoea), fatigue and ankle swelling. Target condition: Heart failure
Setting	Community or outpatient setting (not admitted to hospital).
Index tests	NTproBNP (at any reported threshold) BNP (at any reported threshold)

Component	Description
	Different thresholds will not be grouped together when presenting the results.
Reference standard (could be more than one)	A clinical diagnosis based on the opinion of at least one cardiologist, considering symptoms (potentially with some signs) and objective evidence of cardiac dysfunction (either structural or functional).
Statistical measures	Diagnostic accuracy of BNP and NT-proBNP. 2x2 tables Specificity Sensitivity PPV/NPV ROC curve or Area under Curve
Other exclusions	< 100 participants total
Search Strategy	No date limits
Review Strategy	Stratification – groups that will be considered separately if data are available: N/A Subgroups where diagnostic tests may be more or less accurate – to investigate heterogeneity (only when trials can be split at this level): Age (18 to 75 years versus 75 years and over) Ejection fraction (reduced v preserved) BMI (obese v normal weight) Sex Background medication (optimal v suboptimal) Clinical signs (reported v not reported) Appraisal of methodological quality: The methodological quality of each study will be assessed using the QUADAS-II checklist (per target condition). Synthesis of data Diagnostic meta-analysis will be conducted where appropriate using hierarchical methods.

Table 4: Diagnostic RCT review protocol: BNP and NT-proBNP in diagnosis of heart failure in people with atrial fibrillation

Review question	In people with suspected heart failure who also have atrial fibrillation, what is the clinical and cost effectiveness of N-terminus pro-B-type natriuretic peptide (NT-proBNP) compared to B-type natriuretic peptide (BNP), when each is followed by the appropriate patient pathway, in order to improve patient outcomes?
Guideline condition and its definition	Chronic heart failure. Definition: People diagnosed with heart failure , who are in a community or outpatient setting.
Objectives	To evaluate the clinical and cost effectiveness of NT-proBNP compared to BNP when followed by the appropriate patient pathway, in people with heart failure who also have atrial fibrillation.
Population and target condition	Population: People with suspected heart failure in a community or outpatient setting, who also have ECG diagnosed atrial fibrillation (paroxysmal, persistent or permanent).

Review question	In people with suspected heart failure who also have atrial fibrillation, what is the clinical and cost effectiveness of N-terminus pro-B-type natriuretic peptide (NT-proBNP) compared to B-type natriuretic peptide (BNP), when each is followed by the appropriate patient pathway, in order to improve patient outcomes?
	Patients would commonly present with the following symptoms: breathlessness (exertional dysnpnoea, orthopnoea and paroxysmal nocturnal dyspnoea), fatigue and ankle swelling. Target condition: Heart failure
Index diagnostic test + treatment	NTproBNP assay (at any reported threshold) Treatment/next step in pathway: Echocardiography
Comparator index diagnostic tests + treatment	BNP assay (at any reported threshold) Treatment/next step in pathway: Echocardiography
Outcomes	Efficacy outcomes: - All-cause mortality at During study (Time to event) CRITICAL - Quality of life at 12 months (Continuous) CRITICAL - Unplanned hospitalisation at During study (Count rate) CRITICAL Process outcomes: - Number of people receiving echocardiography, i.e., including people who may not have needed it such as those with false positive results at 12 months (Dichotomous) IMPORTANT - Repeat testing / additional testing at 12 months (Dichotomous) IMPORTANT Secondary accuracy outcomes: - Sensitivity / specificity and other test accuracy measures IMPORTANT
Study design	Diagnostic RCTs Systematic reviews of diagnostic RCTs
Sample size exclusion criteria	< 100 Overall
Sensitivity/other analysis	Mortality data will only be extracted if it is at least 12 months. Other outcome data will only be extracted if it is at least 3 months. For dichotomous and continuous outcomes where a study reports multiple time points, the closest time point to the specified time point will be extracted. For subgroup analyses, average outcome values / majorities within a study population will not be used to assign the study to a subgroup. For inclusion in a subgroup, study populations should be similar to one of the specified subgroups. Where studies split results by age but this does not align with the specified subgroups, the results will be included in the subgroup analysis so long as the cut point is at least 65 years. Where all-cause mortality is not reported but data on CV mortality is reported, the CV mortality data will be extracted but will not be pooled with the all-cause data. Where unplanned hospitalisation data is not reported but data on HF-related unplanned hospitalisation is reported, the HF-related data will be extracted but will not be pooled with the all-cause data.
Subgroup analyses if there is heterogeneity	Age (18 to 75 years versus 75 years and over) Ejection fraction (reduced v preserved) BMI (obese v normal weight) Sex Background medication (optimal v suboptimal) Clinical signs (reported v not reported)
Search Strategy	Date limits for search: From October 2009 (update of previous review question)

Review question	In people with suspected heart failure who also have atrial fibrillation, what is the clinical and cost effectiveness of N-terminus pro-B-type natriuretic peptide (NT-proBNP) compared to B-type natriuretic peptide (BNP), when each is followed by the appropriate patient pathway, in order to improve patient outcomes?
	Language: English only

Table 5: Diagnostic accuracy review protocol: BNP and NT-proBNP in diagnosis of heart failure in people with chronic kidney disease

Component	Description
Review question	In people with suspected heart failure who also have chronic kidney disease, what thresholds of N-terminus pro-B-type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP) are most accurate in identifying heart failure (as indicated by the reference standard)?
Objectives	To evaluate the accuracy of BNP and NT-proBNP at different thresholds in the diagnostic pathway of heart failure (both rule in and rule out) in people who also have chronic kidney disease.
Study design	Single gate diagnostic accuracy studies (cross sectional studies/cohort studies)
Population / Target condition	Population: People with suspected heart failure in a community or outpatient setting, who also have chronic kidney disease (at least 3A). Studies in people on dialysis will be excluded, unless the results are presented separately in non-dialysis patients. People would commonly present with the following symptoms: breathlessness (exertional dysnpnoea, orthopnoea and paroxysmal nocturnal dyspnoea), fatigue and ankle swelling. Target condition: Heart failure
Setting	Community or outpatient setting (not admitted to hospital).
Index tests	NTproBNP (at any reported threshold) BNP (at any reported threshold) Different thresholds will not be grouped together when presenting the results.
Reference standard (could be more than one)	A clinical diagnosis based on the opinion of at least one cardiologist, considering symptoms (potentially with some signs) and objective evidence of cardiac dysfunction (either structural or functional).
Statistical measures	Diagnostic accuracy of BNP and NT-proBNP. 2x2 tables Specificity Sensitivity PPV/NPV ROC curve or Area under Curve
Other exclusions	< 100 participants total
Search Strategy	No date limits
Review Strategy	Stratification – groups that will be considered separately if data are available: N/A Subgroups where diagnostic tests may be more or less accurate – to investigate heterogeneity (only when trials can be split at this level): Age (18 to 75 years versus 75 years and over)

Component	Description
	Ejection fraction (reduced v preserved) BMI (obese v normal weight) Sex Background medication (optimal v suboptimal) Clinical signs (reported v not reported) Appraisal of methodological quality: The methodological quality of each study will be assessed using the QUADAS-II checklist (per target condition). Synthesis of data Diagnostic meta-analysis will be conducted where appropriate using hierarchical methods.

Table 6: Diagnostic RCT review protocol: BNP and NT-proBNP in diagnosis of heart failure in people with chronic kidney disease

Review question	In people with suspected heart failure who also have chronic kidney disease, what is the clinical and cost effectiveness of N-terminus pro-B-type natriuretic peptide (NT-proBNP) compared to B-type natriuretic peptide (BNP), when each is followed by the appropriate patient pathway, in order to improve patient outcomes?
Guideline condition and its definition	Chronic heart failure. Definition: People diagnosed with heart failure, who are in a community or outpatient setting.
Objectives	To evaluate the clinical and cost effectiveness of NT-proBNP compared to BNP when followed by the appropriate patient pathway, in people with heart failure who also have chronic kidney disease.
Population and target condition	Population: People with suspected heart failure in a community or outpatient setting, who also have chronic kidney disease (at least 3A). Studies in patients on dialysis will be excluded, unless the results are presented separately in non-dialysis patients. Patients would commonly present with the following symptoms: breathlessness (exertional dysnpnoea, orthopnoea and paroxysmal nocturnal dyspnoea), fatigue and ankle swelling. Target condition: Heart failure
Index diagnostic test + treatment	NTproBNP assay (at any reported threshold) Treatment/next step in pathway: Echocardiography
Comparator index diagnostic tests + treatment	BNP assay (at any reported threshold) Treatment/next step in pathway: Echocardiography
Outcomes	Efficacy outcomes: - All-cause mortality at During study (Time to event) CRITICAL - Quality of life at 12 months (Continuous) CRITICAL - Unplanned hospitalisation at During study (Count rate) CRITICAL Process outcomes: - Number of people receiving echocardiography, i.e., including people who may not have needed it such as those with false positive results at 12 months (Dichotomous) IMPORTANT - Repeat testing / additional testing at 12 months (Dichotomous) IMPORTANT Secondary accuracy outcomes: - Sensitivity / specificity and other test accuracy measures IMPORTANT

Review question	In people with suspected heart failure who also have chronic kidney disease, what is the clinical and cost effectiveness of N-terminus pro-B-type natriuretic peptide (NT-proBNP) compared to B-type natriuretic peptide (BNP), when each is followed by the appropriate patient pathway, in order to improve patient outcomes?
Study design	Diagnostic RCTs Systematic reviews of diagnostic RCTs
Sample size exclusion criteria	< 100 Overall
Sensitivity/other analysis	Mortality data will only be extracted if it is at least 12 months. Other outcome data will only be extracted if it is at least 3 months. For dichotomous and continuous outcomes where a study reports multiple time points, the closest time point to the specified time point will be extracted. For subgroup analyses, average outcome values / majorities within a study population will not be used to assign the study to a subgroup. For inclusion in a subgroup, study populations should be similar to one of the specified subgroups. Where studies split results by age but this does not align with the specified subgroups, the results will be included in the subgroup analysis so long as the cut point is at least 65 years. Where all-cause mortality is not reported but data on CV mortality is reported, the CV mortality data will be extracted but will not be pooled with the all-cause data. Where unplanned hospitalisaton data is not reported but data on HF-related unplanned hospitalisation is reported, the HF-related data will be extracted but will not be pooled with the all-cause data.
Subgroup analyses if there is heterogeneity	Age (18 to 75 years versus 75 years and over) Ejection fraction (reduced v preserved) BMI (obese v normal weight) Sex Background medication (optimal v suboptimal) Clinical signs (reported v not reported)
Search Strategy	Date limits for search: From October 2009 (update of previous review question) Language: English only

A.2 Cardiac Magnetic Resonance Imaging in heart failure

Table 7: Review protocol: cMRI in heart failure.

Review question	In people with heart failure what is the clinical and cost effectiveness of cardiac MRI followed by the appropriate patient pathway?
Guideline condition and its definition	Chronic Heart Failure. Definition: People diagnosed with heart failure, who are in a community or outpatient setting
Objectives	To evaluate the clinical and cost effectiveness of cardiac MRI in patients with HF when followed by the appropriate patient pathway. Performing cardiac MRI provides clinicians with additional information about the aetiology of HF, which may lead to a change of management and the improvement of patient outcomes.
Review population	People with HF in a community or outpatient setting.
	Adults (aged 18 years and over)
	Line of therapy not an inclusion criterion
Interventions and comparators: generic/class;	Echocardiography; Echo plus routine cardiac MRI Echocardiography; Echo plus selective cardiac MRI Echocardiography; Echo alone

Review question	In people with heart failure what is the clinical and cost effectiveness of cardiac MRI followed by the appropriate patient pathway?
specific/drug (All interventions will be compared with each other, unless otherwise stated)	
Outcomes	- All-cause mortality at As reported (Time to event) CRITICAL - Quality of life at 12 months (Continuous) CRITICAL - Hospitalisation at As reported (Count rate) CRITICAL - Adverse events – non-specific fibrosis in the presence of renal dysfunction at As reported (Dichotomous) IMPORTANT - Change in management at As reported (Dichotomous) IMPORTANT - Reclassification of specific HF aetiology (including the ability to classify previous unclassified patients) at As reported (Dichotomous) IMPORTANT - Change in HF medication at As reported (Dichotomous) IMPORTANT - HF advanced therapy use, including disease specific therapies at As reported (Dichotomous) IMPORTANT - Need for repeat testing/additional testing at As reported (Dichotomous) IMPORTANT
Study design	Systematic Review RCT
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	Not defined
Population stratification	Age < 75 years Age ≥ 75 years
Reasons for stratification	Intervention may be more effective in younger patients.
Other stratifications	None.
Sensitivity/other analysis	Mortality data will only be extracted if it is at least 12 months. Other outcome data will only be extracted if it is at least 3 months. For dichotomous and continuous outcomes where a study reports multiple time points, the closest time point to the specified time point will be extracted. For subgroup analyses and strata, average outcome values / majorities within a study population will not be used to assign the study to a subgroup or strata. For inclusion, study populations should be similar to one of the specified subgroups or strata. Where studies split results by age but this does not align with the specified strata, the results will be included in the strata analysis so long as the cut point is at least 65 years. Where all-cause mortality is not reported but data on CV mortality is reported, the CV mortality data will be extracted but will not be pooled with the all-cause data. Where unplanned hospitalisation data is not reported but data on HF-related unplanned hospitalisation is reported, the HF-related data will be extracted but will not be pooled with the all-cause data.
Subgroup analyses if there is heterogeneity	- Chronic kidney disease (Not applicable; Not stated / Unclear; Patients with renal failure) - Atrial fibrillation (Patients with; without atrial fibrillation) - Ejection fraction (Reduced ejection fraction; Preserved ejection fraction)

Review question	In people with heart failure what is the clinical and cost effectiveness of cardiac MRI followed by the appropriate patient pathway?
	- BMI (BMI ≥ 30 kg/m2; BMI <30 kg/m2) - Sex (Male; Female)
Search criteria	Databases: Pubmed, EMBASE, Medline and Cochrane library. Date limits for search: No limits. Language: English only

A.3 Salt and fluid restriction

Table 8: Review protocol: Salt and fluid restriction for heart failure

Review question	What is the clinical and cost effectiveness of salt and/or fluid restriction in people with heart failure?
Guideline condition and its definition	Chronic heart failure. Definition: People diagnosed with heart failure, who are in a community or outpatient setting.
Objectives	To establish whether salt and/or fluid consumption should be restricted in people with heart failure.
Review population	People diagnosed with heart failure in a community or outpatient setting.
	Adults (aged 18 years and over)
	Line of therapy not an inclusion criterion
Interventions and comparators: generic/class; specific/drug (All interventions will be compared with each other, unless otherwise stated)	Programme; Salt restriction programme Programme; Fluid restriction programme Programme; Salt and fluid restriction programme Advice; General advice to restrict salt and/or fluid intake Usual care; No advice
Outcomes	- Quality of life at 12 months (Continuous) CRITICAL - Unplanned Hospitalisation at As reported (Count rate) CRITICAL - Adverse events - Renal function at 12 months (Dichotomous) IMPORTANT - Adverse events - Hyperkalaemia at 12 months (Dichotomous) IMPORTANT - Change in appetite at 12 months (Continuous) IMPORTANT - Change in weight at 12 months (Continuous) IMPORTANT - Change in oedema at 12 months (Continuous) IMPORTANT - Change in sodium level at 12 months (Continuous) IMPORTANT
Study design	Systematic Review RCT
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	6 months
Population	Low sodium at baseline

Review question	What is the clinical and cost effectiveness of salt and/or fluid restriction in people with heart failure?
stratification	Normal sodium at baseline Mixed
Reasons for stratification	Patients with low serum sodium at baseline are likely to see greater improvements in outcomes.
Sensitivity/other analysis	Outcome data will only be extracted if it is at least 3 months. For dichotomous and continuous outcomes where a study reports multiple time points, the closest time point to the specified time point will be extracted. Where unplanned hospitalisation data is not reported but data on HF-related unplanned hospitalisation is reported, the HF-related data will be extracted but will not be pooled with the all-cause data. Where quality of life is not reported but data showing change in NYHA class is reported, the data on change in NYHA class will be extracted.
Subgroup analyses if there is heterogeneity	None specified
Search criteria	Databases: The databases to be searched are Medline, Embase, The Cochrane Library. Date limits for search: None. Language: English only.

A.4 Beta-blockers in people with heart failure and atrial fibrillation

Table 9: Review protocol: Beta-blockers vs placebo in people with CHF and concomitant atrial fibrillation

Review question	What is the clinical and cost effectiveness of beta-blockers in the management of chronic heart failure in people with heart failure with reduced ejection fraction (HFREF) and atrial fibrillation (AF)?
Guideline condition and its definition	Chronic heart failure. Definition: People diagnosed with heart failure, who are in a community or outpatient setting.
Objectives	To evaluate the clinical and cost effectiveness of beta-blockers in people diagnosed with HFREF, who also have AF.
Review population	People diagnosed HFREF and concomitant AF, which is persistent (i.e. not paroxysmal AF).
	Adults (aged 18 years and over)
Strata	18-75 years 75 years and over
Line of therapy	Line of therapy not an inclusion criterion
Interventions and comparators: generic/class; specific/drug (All interventions will be compared with each other, unless otherwise stated)	Beta-blockers; Beta-blockers (mixed) Beta-blockers; Bisoprolol Beta-blockers; Carvedilol Beta-blockers; Nebivolol Beta-blockers; Metoprolol CR/XL Placebo
Outcomes	- All-cause mortality at 12 months (Time to event) CRITICAL

Review question	What is the clinical and cost effectiveness of beta-blockers in the management of chronic heart failure in people with heart failure with reduced ejection fraction (HFREF) and atrial fibrillation (AF)?
	- Quality of life at 12 months (Continuous) CRITICAL - Unplanned hospitalisation at 12 months (Count rate) CRITICAL - Improvement of NYHA class at 12 months (Dichotomous) IMPORTANT - Adverse events - Stroke at 12 months (Dichotomous) IMPORTANT - Adverse events - Bradycardia at 12 months (Dichotomous) IMPORTANT - Adverse events - Hypotension at 12 months (Dichotomous) IMPORTANT
Study design	Systematic Review of RCTs RCT
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	6 months
Sample size exclusion criteria	100 < Overall
Other exclusions	Post-hoc subgroup analysis of a beta-blocker trial in the general heart failure population without baseline characteristics of AF Within class comparison, not compared with placebo
Population stratification	18 - 75 75 and over Overall
Reasons for stratification	People will be stratified by age: 18 - 75 years and 75 years and over. People aged 75 years and over are more likely to experience a greater number of adverse events (hypotensive events and falls).
Sensitivity/other analysis	Mortality data will only be extracted if it is at least 12 months. Other outcome data will only be extracted if it is at least 3 months. For dichotomous and continuous outcomes where a study reports multiple time points, the closest time point to the specified time point will be extracted. For subgroup analyses, average outcome values / majorities within a study population will not be used to assign the study to a subgroup. For inclusion in a subgroup, study populations should be similar to one of the specified subgroups. Where studies split results by age but this does not align with the specified strata, the results will be included in the strata analysis, so long as the cut point is at least 65 years. Studies that only report overall data, and are not stratified by age, will also be included in the review. Where all-cause mortality is not reported but data on CV mortality is reported, the CV mortality data will be extracted but will not be pooled with the all-cause data. Where unplanned hospitalisaton data is not reported but data on HF-related unplanned hospitalisation is reported, the HF-related data will be extracted but will not be pooled with the all-cause data.
Subgroup analyses if there is heterogeneity	- Anti-coagulant use (Anti-coagulant use; No anti-coagulant use) - Heart rate on entry (Heart rate on entry ≤90 bpm; Heart rate on entry >90 bpm)
Search criteria	Databases: The databases to be searched are Medline, Embase, The Cochrane Library. Date limits for search: None. Language: English

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A.5 Mineralocorticoid Receptor Antagonists

Table 10: Review protocol: Mineralocorticoid receptor antagonists for heart failure with preserved ejection fraction (HFPEF)

Review question	What is the clinical and cost effectiveness a mineralocorticoid receptor antagonists in people with heart failure with preserved ejection fraction (HFPEF)?
Guideline condition and its definition	Chronic heart failure. Definition: People diagnosed with heart failure, who are in a community or outpatient setting.
Objectives	To determine the clinical and cost effectiveness of mineralocorticoid receptor antagonists in people with HFPEF.
Review population	People diagnosed with heart failure with preserved ejection fraction (HFPEF). Adults (aged 18 years and over) Line of therapy not an inclusion criterion
Interventions and comparators: generic/class; specific/drug (All interventions will be compared with each other, unless otherwise stated)	Mineralocorticoid receptor antagonist; Spironolactone (up to 50mg/day) Mineralocorticoid receptor antagonist; Eplerenone (up to 50mg/day) Placebo
Outcomes	- All-cause mortality at During study (Time to event) CRITICAL - Quality of life at 12 months (Continuous) CRITICAL - Unplanned hospitalisation at During study (Count rate) CRITICAL - Improvement of NYHA class at 12 months (Dichotomous) IMPORTANT - Adverse events - Renal function at 12 months (Dichotomous) IMPORTANT - Adverse events - Gynaecomastia at 12 months (Dichotomous) IMPORTANT - Adverse events - Hypotension at 12 months (Dichotomous) IMPORTANT - Adverse events - Hyperkalaemia at 12 months (Dichotomous) IMPORTANT
Study design	Systematic Review RCT
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	6 months
Sample size exclusion criteria	< 100 Overall
Other exclusions	Within class comparison, not compared with placebo
Sensitivity/other analysis	Mortality data will only be extracted if it is at least 12 months. Other outcome data will only be extracted if it is at least 3 months. For dichotomous and continuous outcomes where a study reports multiple time points, the closest time point to the specified time point will be extracted.

	For subgroup analyses, average outcome values / majorities within a study population will not be used to assign the study to a subgroup. For inclusion in a subgroup, study populations should be similar to one of the specified subgroups. Where studies split results by age but this does not align with the specified subgroups, the results will be included in the subgroup analysis so long as the cut point is at least 65 years. Where all-cause mortality is not reported but data on CV mortality is reported, the CV mortality data will be extracted but will not be pooled with the all-cause data. Where unplanned hospitalisaton data is not reported but data on HF-related unplanned hospitalisation is reported, the HF-related data will be extracted but will not be pooled with the all-cause data.
Subgroup analyses if there is heterogeneity	- Renal function (Abnormal (creatinine >130 µmol/l or EGFR < 60mL/min); Normal (creatinine ≤130 µmol/l or EGFR ≥ 60mL/min - Diabetes status (Diabetic; Nondiabetic - Age (18-75 years; Over 75 years)
Search criteria	Databases: The databases to be searched are Medline, Embase, The Cochrane Library. Date limits for search: 2009 (update of existing question in current guideline) Language: English

Table 11: Review protocol: Mineralocorticoid receptor antagonists for heart failure with reduced ejection fraction (HFREF)

Review question	**What is the clinical and cost effectiveness of adding a mineralocorticoid receptor antagonist to existing standard first line treatment in people with heart failure with reduced ejection fraction (HFREF)?**
Guideline condition and its definition	Chronic heart failure. Definition: People diagnosed with heart failure, who are in a community or outpatient setting.
Objectives	To establish the clinical and cost effectiveness of adding a mineralocorticoid receptor antagonist to existing standard first line treatment in people with HFREF
Review population	People diagnosed with HFREF receiving standard first line treatment (see exclusions). Adults (aged 18 years and over)
Interventions and comparators: generic/class; specific/drug (All interventions will be compared with each other, unless otherwise stated)	Mineralocorticoid receptor antagonist; Spironolactone (up to 50mg/day) Mineralocorticoid receptor antagonist; Eplerenone (up to 50mg/day) Placebo
Outcomes	- All-cause mortality at During study (Time to event) CRITICAL - Quality of life at 12 months (Continuous) CRITICAL - Unplanned hospitalisation at During study (Count rate) CRITICAL - Improvement of NYHA class at 12 months (Dichotomous) IMPORTANT - Adverse events - Renal function at 12 months (Dichotomous) IMPORTANT - Adverse events - Gynaecomastia at 12 months (Dichotomous) IMPORTANT - Adverse events - Hypotension at 12 months (Dichotomous) IMPORTANT - Adverse events - Hyperkalaemia at 12 months (Dichotomous) IMPORTANT
Study design	Systematic Review RCT
Unit of randomisation	Patient

Review question	What is the clinical and cost effectiveness of adding a mineralocorticoid receptor antagonist to existing standard first line treatment in people with heart failure with reduced ejection fraction (HFREF)?
Crossover study	Not permitted
Minimum duration of study	6 months
Sample size exclusion criteria	< 100 Overall
Other exclusions	Background treatment not standard first line treatment subject to intolerances (that is, participants should be receiving one of the following combinations: Angiotensin-converting-enzyme inhibitor (ACEI) plus Beta-blocker (BB), Angiotensin II receptor blocker (ARB) plus BB, Isosorbide/hydralazine plus BB, ACEI alone, ARB alone, or Isosorbide/hydralazine alone). Within class comparison, not compared with placebo
Sensitivity/other analysis	Mortality data will only be extracted if it is at least 12 months. Other outcome data will only be extracted if it is at least 3 months. For dichotomous and continuous outcomes where a study reports multiple time points, the closest time point to the specified time point will be extracted. For subgroup analyses, average outcome values / majorities within a study population will not be used to assign the study to a subgroup. For inclusion in a subgroup, study populations should be similar to one of the specified subgroups. Where studies split results by age but this does not align with the specified subgroups, the results will be included in the subgroup analysis so long as the cut point is at least 65 years. Where all-cause mortality is not reported but data on CV mortality is reported, the CV mortality data will be extracted but will not be pooled with the all-cause data. Where unplanned hospitalisaton data is not reported but data on HF-related unplanned hospitalisation is reported, the HF-related data will be extracted but will not be pooled with the all-cause data.
Subgroup analyses if there is heterogeneity	- Renal function (Abnormal (creatinine >130 µmol/l or EGFR < 60mL/min); Normal (creatinine ≤130 µmol/l or EGFR ≥ 60mL/min)) - Diabetes status (Diabetic; Nondiabetic) - Age (18-75 years; Over 75 years)
Search criteria	Databases: The databases to be searched are Medline, Embase, The Cochrane Library. Date limits for search: 2009 (update of existing question in current guideline) Language: English

A.6 Iron supplementation for iron deficiency in heart failure

Table 12: Review protocol: Iron supplementation for iron deficiency in heart failure

Review question	What is the clinical and cost effectiveness of iron supplementation in people with heart failure and iron deficiency?
Guideline condition and its definition	Chronic heart failure. Definition: People diagnosed with heart failure, who are in a community or outpatient setting.
Objectives	To establish the clinical and cost effectiveness of iron supplementation in people with heart failure and iron deficiency.
Review population	People diagnosed with heart failure who also have iron deficiency (serum ferritin < 100 ng/mL or serum ferritin between 100-299 ng/mL if iron saturation (TSAT) < 20 %). Patients may or may not be anaemic. Patients should be on optimal medical therapy for heart failure. Patients should be in a community or outpatient setting.

Review question	What is the clinical and cost effectiveness of iron supplementation in people with heart failure and iron deficiency?
	Adults (aged 18 years and over)
	Line of therapy not an inclusion criterion
Interventions and comparators: generic/class; specific/drug (All interventions will be compared with each other, unless otherwise stated)	Iron supplementation; Intravenous iron Iron supplementation; Oral iron Placebo
Outcomes	- Mortality at during study (Time to event) CRITICAL - Quality of life at 12 months (Continuous) CRITICAL - Unplanned hospitalisation (all-cause) at during study (Count rate) CRITICAL - Improvement in exercise tolerance at 12 months (Continuous) IMPORTANT - Change in haemoglobin in anaemic patients at 12 months (Continuous) IMPORTANT - Withdrawal due to adverse events/tolerability at during study (Dichotomous) IMPORTANT - Adverse events - hypertension at during study (Dichotomous) IMPORTANT - Adverse events - anaphylaxis/hypersensitivity at during study (Dichotomous) IMPORTANT - Adverse events - stroke at during study (Dichotomous) IMPORTANT - Adverse events - gastrointestinal at during study (Dichotomous) IMPORTANT
Study design	Systematic Review RCT
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	3 months
Other exclusions	Intervention started during a hospital admission for heart failure
Sensitivity/other analysis	Outcome data will only be extracted if it is at least 3 months. For adverse events where a study reports multiple time points, the latest time point will be extracted. For efficacy outcomes, where a study reports multiple time points, the closest time point to the time specified will be extracted. For subgroup analyses, average outcome values / majorities within a study population will not be used to assign the study to a subgroup. For inclusion in a subgroup, study populations should be similar to one of the specified subgroups. Where all-cause mortality is not reported but data on CV mortality is reported, the CV mortality data will be extracted but will not be pooled with the all-cause data. Where unplanned hospitalisation data is not reported but data on HF-related unplanned hospitalisation is reported, the HF-related data will be extracted but will not be pooled with the all-cause data. Where quality of life is not reported but data showing change in NYHA class is reported, the data on change in NYHA class will be extracted.
Subgroup analyses if there is heterogeneity	Anaemia (Not applicable; Not stated / Unclear; All patients anaemic; All patients non-anaemic)
Search criteria	Databases: The databases to be searched are Medline, Embase, The Cochrane Library. Date limits for search: None.

Review question	What is the clinical and cost effectiveness of iron supplementation in people with heart failure and iron deficiency?
	Language: English only.

A.7 Pharmacological treatment for heart failure in people with heart failure and chronic kidney disease

Table 13: Review protocol: Pharmaceuticals in CKD

Review question	How will the use of pharmacological interventions for people with heart failure be different in people with heart failure who also have chronic kidney disease (CKD)?
Guideline condition and its definition	Chronic heart failure. Definition: People diagnosed with heart failure, who are in a community or outpatient setting
Objectives	This review aims to establish the clinical and cost effectiveness of standard heart failure therapies in people with heart failure who also have CKD, by reviewing trials of standard heart failure medications in this population.
Review population	People diagnosed with heart failure who also have chronic kidney disease (CKD) (at least stage 3A / eGFR <60 mL/min). Patients should be in a community or outpatient setting.
	Adults (aged 18 years and over)
	Line of therapy not an inclusion criterion
Interventions and comparators: generic/class; specific/drug (All interventions will be compared with each other, unless otherwise stated)	Angiotensin converting enzyme (ACE) inhibitors Angiotensin receptor antagonists/blockers (ARB) Beta-blockers (BB) Mineralocorticoid receptor antagonists (MRA) Digoxin Loop diuretics Ivabradine Sacubitril-valsartan Hydralazine + nitrate Placebo Compared against each other (class versus class and within class comparisons), against the same drug at a different dose, or against placebo. Only oral administration will be considered.
Outcomes	- Mortality at during study (Time to event) CRITICAL - Quality of life at 12 months (Continuous) CRITICAL - Unplanned hospitalisation (all-cause) at during study (Count rate) CRITICAL - Renal function at during study (Continuous) IMPORTANT - Adverse events - arrhythmic at during study (Dichotomous) IMPORTANT - Adverse events - bradycardia at during study (Dichotomous) IMPORTANT - Adverse events - progression to stage 5 CKD / unplanned dialysis at during study (Dichotomous) IMPORTANT - Adverse events - hypotension at during study (Dichotomous) - Adverse events - hyperkalaemia at during study (Dichotomous)
Study design	Systematic Review RCT
Unit of randomisation	Patient
Crossover study	Not permitted

Minimum duration of study	12 months
Other inclusions	100 or more patients with CKD in analysis
Other exclusions	Patients on dialysis
Population stratification	Overall (CKD any stage) CKD stage 3a CKD stage 3b/4/5 CKD stage 3a/3b CKD stage 4/5
Reasons for stratification	Heart failure treatments may be less effective and have higher rates of adverse events in patients with more severe CKD (stages 3b/4/5).
Sensitivity/other analysis	Where a study reports multiple time points, the latest time point will be extracted. Subgroup analyses of trials where the subgroup reflects the review population will be included, regardless of whether those subgroups were explicitly pre-specified and regardless of whether baseline characteristics of the subgroup (split by intervention and comparator) are provided (though trials without this data will be downgraded for risk of bias). For the review's subgroup analyses, average outcome values / majorities within a study population will not be used to assign the study to a subgroup. For inclusion in a subgroup, study populations should be similar to one of the specified subgroups. Where all-cause mortality is not reported but data on CV mortality is reported, the CV mortality data will be extracted but will not be pooled with the all-cause data. Where unplanned hospitalisation data is not reported but data on HF-related unplanned hospitalisation is reported, the HF-related data will be extracted but will not be pooled with the all-cause data. Where quality of life is not reported but data showing change in NYHA class is reported, the data on change in NYHA class will be extracted.
Subgroup analyses if there is heterogeneity	Diabetes (Not applicable; Not stated / Unclear; All patients diabetic; All patients not diabetic) Hypertension (All patients hypertensive; All patients not hypertensive) Ejection fraction (Not applicable/mixed; All patients reduced EF; All patients preserved EF) NYHA class (All patients class III or IV; All patients class I or II Ethnicity (All patients of African or Carribbean origin; No patients of African or Carribbean origin)
Search criteria	Databases: The databases to be searched are Medline, Embase, The Cochrane Library. Date limits for search: None. Language: English only.

A.8 Coronary revascularisation

Table 14: Review protocol: Coronary Revascularization in heart failure

Review question	What is the clinical and cost effectiveness of coronary revascularisation with coronary artery bypass grafting or angioplasty in people with heart failure with reduced ejection fraction (HFREF)?

Review question	What is the clinical and cost effectiveness of coronary revascularisation with coronary artery bypass grafting or angioplasty in people with heart failure with reduced ejection fraction (HFREF)?
Guideline condition and its definition	Chronic heart failure. Definition: People diagnosed with heart failure, who are in a community or outpatient setting
Objectives	To determine the clinical and cost effectiveness of coronary revascularisation with coronary artery bypass grafting or angioplasty in people with HFREF.
Review population	People diagnosed with HFREF.
Age	Adults (aged 18 years and over)
Line of therapy	Line of therapy not an inclusion criterion
Interventions and comparators: generic/class; specific/drug (All interventions will be compared with each other, unless otherwise stated)	Coronary revascularization; CABG Coronary revascularization; CABG + ventricular reconstruction Coronary revascularization; PCI Medical management
Outcomes	- All-cause mortality at 30 days (Time to event) CRITICAL - All-cause mortality at during study (Time to event) CRITICAL - Quality of life at 12 months (Continuous) CRITICAL - Unplanned hospitalisation at 12 months (Count rate) CRITICAL - Additional revascularisation events at 24 months (Count rate) IMPORTANT - Improvement of NYHA class at 12 months (Dichotomous) IMPORTANT - Improvement in ejection fraction at 12 months (Dichotomous) IMPORTANT - Adverse events - stroke at 12 months (Dichotomous) IMPORTANT
Study design	Systematic Review RCT
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	12 months
Other exclusions	Within class comparison, not compared with medical management Any study prior to 2001, as prescribing of beta-blockers as standard first line treatment for HF only became standard practice in 2001.
Population stratification	CABG PCI Mixed
Reasons for stratification	Patients with a lower disease severity tend to be offered angioplasty, whereas those of higher disease severity (and with comorbidities such as diabetes) are more likely to receive bypass surgery. The complication rate is also higher in bypass surgery than in angioplasty.
Sensitivity/other analysis	Mortality data will only be extracted if it is at least 12 months. Other outcome data will only be extracted if it is at least 3 months. For dichotomous and continuous outcomes where a study reports multiple time points, the closest time point to the specified time point will be extracted. For subgroup analyses, average outcome values/majorities within a study population will not be used to assign the study to a subgroup. For inclusion in a subgroup, study

Review question	What is the clinical and cost effectiveness of coronary revascularisation with coronary artery bypass grafting or angioplasty in people with heart failure with reduced ejection fraction (HFREF)?
	populations should be similar to one of the specified subgroups. Where studies split results by age but this does not align with the specified subgroups, the results will be included in the subgroup analysis so long as the cut point is at least 65 years. Where all-cause mortality is not reported but data on CV mortality is reported, the CV mortality data will be extracted but will not be pooled with the all-cause data. Where unplanned hospitalisation data is not reported but data on HF-related unplanned hospitalisation is reported, the HF-related data will be extracted but will not be pooled with the all-cause data. Where quality of life is not reported but data showing change in NYHA class is reported, the data on change in NYHA class will be extracted.
Subgroup analyses if there is heterogeneity	- Age (18 - 75 years; 75 years or older) - Diabetes (Diabetic population; Non diabetic)
Search criteria	Databases: Pubmed, EMBASE, Medline and Cochrane library. Date limits for search: 2002 (update of previous search completed for 2003 CHF guideline) Language: English publications only.

A.9 Home-based versus centre-based rehabilitation

Table 15: Review protocol: Home- versus centre-based rehabilitation

Review question	What is the clinical and cost effectiveness of home-based versus centre-based rehabilitation (that includes an exercise element) for people with heart failure (HF)?
Guideline condition and its definition	Chronic heart failure. Definition: People diagnosed with heart failure, who are in a community or outpatient setting.
Objectives	To assess the clinical effectiveness of home-based versus centre-based rehabilitation in patients with HF. To assess the cost-effectiveness of home-based versus centre-based rehabilitation in patients with HF. Review conducted by Cochrane Heart Group as part of their update of their review "Home-based versus centre-based cardiac rehabilitation".
Review population	People diagnosed with HF.
Interventions	Home-based cardiac rehabilitation service. Programme must be structured, with clear objectives for the participants, and include a monitoring component. Programme must include an exercise component. Programmes will be included whether they are based solely on exercise or include other intervention elements such as education and/or psychological support ('comprehensive cardiac rehabilitation'). No minimum duration of intervention.
Comparators	Centre-based cardiac rehabilitation service (including community-based rehabilitation service and hospital-based rehabilitation service). Programme must be structured, with clear objectives for the participants, and include a monitoring component. Programme must include an exercise component. Programmes will be included whether they are based solely on exercise or include other intervention elements such as education and/or psychological support ('comprehensive cardiac rehabilitation').

Review question	What is the clinical and cost effectiveness of home-based versus centre-based rehabilitation (that includes an exercise element) for people with heart failure (HF)?
Outcomes	- All-cause mortality (dichotomous) CRITICAL - Cardiovascular mortality (dichotomous) CRITICAL - Health-related quality of life (continuous) CRITICAL - All cause hospitalisation (dichotomous) CRITICAL - HF-related hospitalisation (dichotomous) CRITICAL - Exercise capacity (continuous) IMPORTANT - Adverse events (withdrawal from the exercise programme) (dichotomous) IMPORTANT - Adherence (including maintenance of exercise/physical activity) (dichotomous) IMPORTANT Where trials report outcomes at multiple time points, the following will be extracted: latest time point up to 12 months, and latest time point beyond 12 months.
Study design	RCTs (individual or cluster level, including parallel group, cross-over or quasi-randomised designs) Systematic reviews and meta-analyses will be identified as a means to identify additional RCTs.
Search criteria	Databases: As per Cochrane methods (CENTRAL, MEDLINE, Embase, PsychINFO, CINAHL Plus) Date limits for search: from 14 October 2014 (date of previous search) Language: No restriction as per Cochrane methods.
Crossover study	Only data from the 1st period of cross-over trials will be included, unless there is formal evidence of period effects in which case data from both 1st and 2nd periods will be included.
Minimum duration of study	None
Other exclusions	None
Sensitivity/other analysis Meta-regression factors limited to those at trial level (not patient level)	Univariate meta-regression to examine potential treatment effect modifiers where sufficient trials (≥ 10), including: Mode of delivery of intervention (individualised/personalised versus group exercise) Supervision of intervention (supervised versus unsupervised) Content of intervention (exercise only versus comprehensive package (exercise, education and psychological support)) Setting of comparator rehabilitation service (community based versus hospital based) Pharmaceutical management (optimal versus suboptimal – likely that we use calendar year as a proxy i.e. pre 2001 vs 2001 and later) Assessment of publication bias for all outcomes with ≥ 10 trials.

A.10 Monitoring

Table 16: Review protocol: Monitoring in HF

Review question	What is the clinical and cost effectiveness of biomarker-based monitoring, monitoring with cardiac MRI, and monitoring with repeated echocardiography in people with heart failure?

Review question	What is the clinical and cost effectiveness of biomarker-based monitoring, monitoring with cardiac MRI, and monitoring with repeated echocardiography in people with heart failure?
Guideline condition and its definition	Chronic heart failure. Definition: People diagnosed with heart failure, who are in a community or outpatient setting
Objectives	The aim of this review is to assess the clinical and cost-effectiveness of monitoring heart failure using: •biomarker measurement •cardiac MRI •echocardiography.
Review population	People diagnosed with heart failure in a community or outpatient setting
	Adults (aged 18 years and over)
	Line of therapy not an inclusion criterion
Interventions and comparators: generic/class; specific/drug (All interventions will be compared with each other, unless otherwise stated)	Biomarker monitoring; NTproBNP Biomarker monitoring; BNP Biomarker monitoring; Troponin Biomarker monitoring; Combination Biomarker monitoring; NTproBNP or BNP (mixed) Imaging monitoring; Cardiac MRI Imaging monitoring; Echocardiography Usual care; Usual care: clinical monitoring Usual care; Usual care: no monitoring protocol
Outcomes	- Mortality at during study (Time to event) CRITICAL - Quality of life at 12 months (Continuous) CRITICAL - Unplanned hospitalisation (all-cause) (Count rate) CRITICAL - Adverse events - hypotension (Dichotomous) IMPORTANT - Adverse events - hyperkalaemia (Dichotomous) IMPORTANT - Adverse events - renal function (Continuous) IMPORTANT - Adverse events - bradycardia (Dichotomous) IMPORTANT - Adverse events - arrhythmic events (Dichotomous) IMPORTANT
Study design	Systematic Review RCT
Unit of randomisation	Patient Cluster
Crossover study	Not permitted
Minimum duration of study	6 months
Population stratification	Mixed Age < 75 years Age ≥ 75 years
Reasons for stratification	Younger patients may derive greater benefit from advanced biomarker/imaging monitoring.
Sensitivity/other analysis	Mortality data will only be extracted if it is at least 12 months. Other outcome data will only be extracted if it is at least 3 months. For dichotomous and continuous outcomes where a study reports multiple time points, the closest time point to the specified time point will be extracted. For subgroup analyses and strata, average outcome values / majorities within a study population will not be used to assign the study to a subgroup. For inclusion in a subgroup, study populations should be similar to one of the specified subgroups or strata. Where studies split results by age but this does not align with the specified subgroups, the results will be included in the subgroup analysis so long as the cut point is at least 65 years. Where all-cause mortality is not reported but data on CV mortality is reported, the CV

Review question	What is the clinical and cost effectiveness of biomarker-based monitoring, monitoring with cardiac MRI, and monitoring with repeated echocardiography in people with heart failure?
	mortality data will be extracted but will not be pooled with the all-cause data. Where unplanned hospitalisation data is not reported but data on HF-related unplanned hospitalisation is reported, the HF-related data will be extracted but will not be pooled with the all-cause data. Where quality of life is not reported but data showing change in NYHA class is reported, the data on change in NYHA class will be extracted.
Subgroup analyses if there is heterogeneity	- Patient risk status (Not applicable; Not stated / Unclear; Recruited following acute admission; Recruited in community) - Ejection fraction (Reduced ejection fraction; Preserved ejection fraction; Mixed)
Search criteria	Databases: The databases to be searched are Medline, Embase, The Cochrane Library. Date limits for search: None. Language: English only.

1 **Table 17: Review protocol: Monitoring in HF and AF**

Review question	What is the clinical and cost effectiveness of biomarker-based monitoring, monitoring with cardiac MRI, and monitoring with repeated echocardiography in people with heart failure who also have atrial fibrillation?
Guideline condition and its definition	Chronic heart failure.
Objectives	The aim of this review is to assess the clinical and cost-effectiveness of monitoring heart failure in people who also have atrial fibrillation using: •biomarker measurement •cardiac MRI •echocardiography.
Review population	People diagnosed with heart failure who also have ECG diagnosed atrial fibrillation (paroxysmal, persistent or permanent) in a community or outpatient setting
	Adults (aged 18 years and over)
	Line of therapy not an inclusion criterion
Interventions and comparators: generic/class; specific/drug (All interventions will be compared with each other, unless otherwise stated)	Biomarker monitoring; NTproBNP Biomarker monitoring; BNP Biomarker monitoring; Troponin Biomarker monitoring; Combination Biomarker monitoring; NTproBNP or BNP (mixed) Imaging monitoring; Cardiac MRI Imaging monitoring; Echocardiography Usual care; Usual care: clinical monitoring Usual care; Usual care: no monitoring protocol Monitoring (other than usual care) must involve serial measurement (more than one measurement) and must be protocol-driven.
Outcomes	- Mortality at during study (Time to event) CRITICAL - Quality of life at 12 months (Continuous) CRITICAL - Unplanned hospitalisation (all-cause) (Count rate) CRITICAL - Adverse events - hypotension (Dichotomous) IMPORTANT - Adverse events - hyperkalaemia (Dichotomous) IMPORTANT - Adverse events - renal function (Continuous) IMPORTANT - Adverse events - bradycardia (Dichotomous) IMPORTANT - Adverse events - arrhythmic events (Dichotomous) IMPORTANT
Study design	Systematic Review

Review question	What is the clinical and cost effectiveness of biomarker-based monitoring, monitoring with cardiac MRI, and monitoring with repeated echocardiography in people with heart failure who also have atrial fibrillation?
	RCT
Unit of randomisation	Patient Cluster
Crossover study	Not permitted
Minimum duration of study	6 months
Population stratification	Mixed Age < 75 years Age ≥ 75 years
Reasons for stratification	Younger patients may derive greater benefit from advanced biomarker/imaging monitoring.
Sensitivity/other analysis	Mortality data will only be extracted if it is at least 12 months. Other outcome data will only be extracted if it is at least 3 months. For dichotomous and continuous outcomes where a study reports multiple time points, the closest time point to the specified time point will be extracted. For subgroup analyses and strata, average outcome values / majorities within a study population will not be used to assign the study to a subgroup. For inclusion in a subgroup, study populations should be similar to one of the specified subgroups or strata. Where studies split results by age but this does not align with the specified subgroups, the results will be included in the subgroup analysis so long as the cut point is at least 65 years. Where all-cause mortality is not reported but data on CV mortality is reported, the CV mortality data will be extracted but will not be pooled with the all-cause data. Where unplanned hospitalisation data is not reported but data on HF-related unplanned hospitalisation is reported, the HF-related data will be extracted but will not be pooled with the all-cause data. Where quality of life is not reported but data showing change in NYHA class is reported, the data on change in NYHA class will be extracted.
Subgroup analyses if there is heterogeneity	- Patient risk status (Not applicable; Not stated / Unclear; Recruited following acute admission; Recruited in community) - Ejection fraction (Reduced ejection fraction; Preserved ejection fraction; Mixed)
Search criteria	Databases: The databases to be searched are Medline, Embase, The Cochrane Library. Date limits for search: None. Language: English only.

1 **Table 18: Review protocol: Monitoring in HF and CKD**

Review question	What is the clinical and cost effectiveness of biomarker-based monitoring, monitoring with cardiac MRI, and monitoring with repeated echocardiography in people with heart failure who also have chronic kidney disease?
Guideline condition and its definition	Chronic heart failure.
Objectives	The aim of this review is to assess the clinical and cost-effectiveness of monitoring heart failure in people who also have chronic kidney disease using: •biomarker measurement •cardiac MRI •echocardiography.
Review population	People diagnosed with heart failure who also have chronic kidney disease (at least stage 3A) in a community or outpatient setting
	Adults (aged 18 years and over)
	Line of therapy not an inclusion criterion

Review question	What is the clinical and cost effectiveness of biomarker-based monitoring, monitoring with cardiac MRI, and monitoring with repeated echocardiography in people with heart failure who also have chronic kidney disease?
Interventions and comparators: generic/class; specific/drug (All interventions will be compared with each other, unless otherwise stated)	Biomarker monitoring; NTproBNP Biomarker monitoring; BNP Biomarker monitoring; Troponin Biomarker monitoring; Combination Biomarker monitoring; NTproBNP or BNP (mixed) Imaging monitoring; Cardiac MRI Imaging monitoring; Echocardiography Usual care; Usual care: clinical monitoring Usual care; Usual care: no monitoring protocol
Outcomes	- Mortality at during study (Time to event) CRITICAL - Quality of life at 12 months (Continuous) CRITICAL - Unplanned hospitalisation (all-cause) (Count rate) CRITICAL - Adverse events - hypotension (Dichotomous) IMPORTANT - Adverse events - hyperkalaemia (Dichotomous) IMPORTANT - Adverse events - renal function (Continuous) IMPORTANT - Adverse events - bradycardia (Dichotomous) IMPORTANT - Adverse events - arrhythmic events (Dichotomous) IMPORTANT
Study design	Systematic Review RCT
Unit of randomisation	Patient Cluster
Crossover study	Not permitted
Minimum duration of study	6 months
Population stratification	Mixed Age < 75 years Age ≥ 75 years
Reasons for stratification	Younger patients may derive greater benefit from advanced biomarker/imaging monitoring.
Sensitivity/other analysis	Mortality data will only be extracted if it is at least 12 months. Other outcome data will only be extracted if it is at least 3 months. For dichotomous and continuous outcomes where a study reports multiple time points, the closest time point to the specified time point will be extracted. For subgroup analyses and strata, average outcome values / majorities within a study population will not be used to assign the study to a subgroup. For inclusion in a subgroup, study populations should be similar to one of the specified subgroups or strata. Where studies split results by age but this does not align with the specified subgroups, the results will be included in the subgroup analysis so long as the cut point is at least 65 years. Where all-cause mortality is not reported but data on CV mortality is reported, the CV mortality data will be extracted but will not be pooled with the all-cause data. Where unplanned hospitalisation data is not reported but data on HF-related unplanned hospitalisation is reported, the HF-related data will be extracted but will not be pooled with the all-cause data. Where quality of life is not reported but data showing change in NYHA class is reported, the data on change in NYHA class will be extracted.
Subgroup analyses if there is heterogeneity	- Patient risk status (Not applicable; Not stated / Unclear; Recruited following acute admission; Recruited in community) - Ejection fraction (Reduced ejection fraction; Preserved ejection fraction; Mixed)

Review question	What is the clinical and cost effectiveness of biomarker-based monitoring, monitoring with cardiac MRI, and monitoring with repeated echocardiography in people with heart failure who also have chronic kidney disease?
Search criteria	Databases: The databases to be searched are Medline, Embase, The Cochrane Library. Date limits for search: None. Language: English only.

A.11 Telemonitoring and self-monitoring

Table 19: Review protocol: Telemonitoring

Review question	What is the clinical and cost effectiveness of telemonitoring and self-monitoring using telephone technology, compared with usual care, in people with heart failure?
Guideline condition and its definition	Chronic heart failure. Definition: People diagnosed with heart failure, who are in a community or outpatient setting
Objectives	Traditionally, heart failure patients are monitored in outpatient clinics or in primary care. The aim of this review is to assess the clinical and cost-effectiveness of monitoring heart failure through telemonitoring or self-monitoring using telephone technology. These monitoring techniques may be less resource intensive and may enable more frequent and responsive monitoring, improving outcomes for patients. This review will be conducted as an update to the existing Cochrane review Structured telephone support or non-invasive telemonitoring for patients with heart failure.
Review population	People diagnosed with heart failure who are in a community or outpatient setting
	Adults (aged 18 years and over)
	Line of therapy not an inclusion criterion
Interventions and comparators: generic/class; specific/drug (All interventions will be compared with each other, unless otherwise stated)	Structured telephone support; Structured telephone support (monitoring or self-care management using simple telephone technology) Usual care; Usual care (standard post discharge care without intensified attendance at cardiology or HF disease management clinic, or home visiting). Telemonitoring; Telemonitoring (digital/broadband/satellite/wireless or Bluetooth transmission of physiological or other non-invasive data)
Outcomes	- All-cause mortality at during study (Dichotomous) CRITICAL - Quality of life at during study (Continuous) CRITICAL - All-cause hospitalisation at during study (Dichotomous) CRITICAL - Adherence to intervention at during study (Dichotomous) IMPORTANT
Study design	Systematic Review RCT
Unit of randomisation	Patient Cluster
Crossover study	Not permitted
Minimum duration of	None

study	
Other inclusions	Intervention must be scheduled (as opposed to on an 'as needed' basis) Intervention must be initiated by a healthcare professional (medical, nursing, social work, pharmacist) Intervention must be delivered as the only aftercare intervention, without protocol-driven home visits or intensified follow-up Intervention must be targeted at the person (not caregivers)
Other exclusions	Primary purpose of intervention is education/information-giving Previous exposure to telemonitoring or structured telephone support for the usual care or intervention arms prior to start of study Intervention group visited at home by specialist heart failure healthcare professional or study personnel for the purpose of education or clinical assessment (other than as an initiation visit to set up equipment)
Population stratification	Mixed Recent admission Community
Reasons for stratification	Patients with a recent acute admission may respond differently to telemonitoring compared with patients recruited in an outpatient clinic or community care setting.
Sensitivity/other analysis	General analysis as per methods in Cochrane review
Subgroup analyses if there is heterogeneity	- Age (Not applicable; Not stated / Unclear; < 70 years; >= 70 years); - Technology (Not applicable; Not stated / Unclear; Telephone calls; Videophone; Interactive voice response; Complex clinical telemonitoring) - Intensity (Office hours; 24/7) - Publication year (pre 2000; 2000-2007; 2008 onwards) - Focus of telephone support (Clinical monitoring; Self-management education)
Search criteria	Databases: The databases to be searched are Medline, Embase, The Cochrane Library. Date limits for search: Update of Cochrane review search conducted in January 2015. Language: English only.

A.12 Multi-Disciplinary Teams

Table 20: Review protocol: MDTs in HF

Review question	What competencies should be present in the multidisciplinary teams involved in the outpatient or community-based care of people with heart failure?
Guideline condition and its definition	Chronic heart failure. Definition: People diagnosed with heart failure, who are in a community or outpatient setting.
Objectives	To establish the competencies that should be present in the multidisciplinary teams (MDTs) involved in the outpatient or community-based care of people with heart failure. Studies may not specify the composition of an MDT in terms of competencies, but instead be designed to investigate the impact of an MDT or MDT intervention on patient outcomes. The competencies of the skilled professionals in studies showing a benefit of MDTs will be used to draw conclusions about the competencies that MDTs in heart failure should have, to enable MDTs to provide high quality care to patients and improve patient outcomes. The review will also consider the way in which effective MDTs deliver care to the broad spectrum of patients with heart failure, including the effectiveness of MDT-based interventions in different heart failure risk groups.
Review population	People diagnosed with heart failure in a community or outpatient setting that is applicable to UK practice.

Review question	What competencies should be present in the multidisciplinary teams involved in the outpatient or community-based care of people with heart failure?
	Adults (aged 18 years and over)
	Line of therapy not an inclusion criterion
Interventions and comparators: generic/class; specific/drug (All interventions will be compared with each other, unless otherwise stated)	Multidisciplinary team; MDT Multidisciplinary team; Nurse Multidisciplinary team; Palliative care Multidisciplinary team; Pharmacist Usual care; Clinic Usual care; Primary care
Outcomes	- Mortality at during study (Time to event) CRITICAL - Quality of life at 12 months (Continuous) CRITICAL - Unplanned hospitalisation (all-cause) at during study (Count rate) CRITICAL - Dying in preferred place at 12 months (Dichotomous) IMPORTANT - Medicine optimisation/adherence at 12 months (Dichotomous) IMPORTANT - Adverse events - hypotension at 12 months (Dichotomous) IMPORTANT - Adverse events - hyperkalaemia at 12 months (Dichotomous) IMPORTANT - Adverse events - renal function at 12 months (Continuous) IMPORTANT - Patient and carer experience at 12 months (Continuous) IMPORTANT
Study design	Systematic Review RCT
Unit of randomisation	Patient Cluster
Crossover study	Not permitted
Minimum duration of study	None
Other inclusions	Clear description of collaborative working between professions/disciplines
Other exclusions	Intervention started during a hospital admission for heart failure and did not include the delivery of at least one face to face meeting after discharge Intervention included the delivery of fewer than two face to face meetings (on average) Intervention covered elsewhere in guideline Primary purpose of intervention is education/information-giving Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country) Last outcome measure less than 3 months after intervention commenced
Population stratification	Mixed Higher risk Lower risk
Reasons for stratification	Higher risk patients (including patients with a recent hospital admission due to HF, newly diagnosed patients, patients with severe and/or unresponsive disease, or patients requiring medicine titration, device implantation or other surgical intervention) may derive greater benefit from MDTs than patients recruited in an outpatient clinic or community care setting (lower risk).
Sensitivity/other analysis	For dichotomous and continuous outcomes where a study reports multiple time points, the latest time point will be extracted. The results will be presented separately depending on the length of intervention (short: <= 3 months; mid: > 3 months, <= 6 months; long: > 6 months). Where study length varied due to the needs of the patient, the shortest duration of protocol was used. The results will also be presented separately depending on the type of MDT used. Where all-cause mortality is not reported but data on CV mortality is reported, the CV

Review question	What competencies should be present in the multidisciplinary teams involved in the outpatient or community-based care of people with heart failure?
	mortality data will be extracted but will not be pooled with the all-cause data. Where unplanned hospitalisation data is not reported but data on HF-related unplanned hospitalisation is reported, the HF-related data will be extracted but will not be pooled with the all-cause data. Where quality of life is not reported but data showing change in NYHA class is reported, the data on change in NYHA class will be extracted.
Subgroup analyses if there is heterogeneity	None
Search criteria	Databases: The databases to be searched are Medline, Embase, The Cochrane Library. Date limits for search: None. Language: English only.

A.13 Transition between heart failure care settings

Table 21: Review protocol: Transitions in HF care

Review question	What are the experiences and preferences of staff and patients during transition between different heart failure care settings (including primary, secondary and community care)?
Objective	Often, after a period of intense management by specialists as outpatients in secondary care, stabilised heart failure patients are discharged to on-going management in primary care. The care pathway in chronic heart failure also often includes community heart failure nurses and heart failure pharmacists, community multi-disciplinary meetings, rapid access back to outpatient specialist care, and use of hospital at home for fluid overload as appropriate. Transitions between care settings and services are significant points at which heart failure patients are particularly vulnerable to loss of continuity. The aim of this review is to explore patient and staff experiences and preferences regarding transition and continuity of care at the interface of different care settings in heart failure. This may enable the identification of barriers (where the problems are) and facilitators (examples of good practice) to continuity of care when transitioning between heart failure care settings. While the heart failure pathway may often also include use of end of life care pathways and advance care planning, these will not be considered in this review as they are covered by separate review questions around palliative care.
Population and setting	Patients with heart failure in a primary care, outpatient or community setting. Studies of patients who are currently hospitalised that relate to their experiences during hospitalisation will not be included. Similarly, studies of inpatient healthcare staff views regarding inpatient care will not be included. Both patient views and healthcare staff views will be considered.
Context	Any description of patient or staff member experiences or preferences regarding transition and continuity of care at the interface of different care settings. For example: Patient experiences/preferences: After an intense and protracted period of care by specialist (after diagnosis or an acute event), being discharged to primary care can make some patients feel anxious as they still feel vulnerable but are unable to contact their specialist team and they are

Review question	What are the experiences and preferences of staff and patients during transition between different heart failure care settings (including primary, secondary and community care)?
	uncertain that their GP will understand their management Patients psychological needs and continuing rehabilitation needs at the point of transition are often not addressed Support, information and reassurance about the quality and continuity of care (including managing patient expectations about models of care from the outset) may help patients cope with the uncertainty Enabling patients to have direct access to their specialist team after discharge may improve patients' experience of their care Different models of care may be more or less preferable to patients Patients may feel that their educational needs, i.e. the specifics of their condition and its management, may not have been addressed Staff experiences/preferences: Some generalist primary care staff may experience practical barriers to referral from primary care to rapid access HF clinics (for example, blocking by NHS administration) Some generalist primary care staff may lack confidence to manage CHF patients in primary care, whether due to a lack of time or expertise Communication and knowledge transfer between generalist primary care and specialist teams could be improved Findings that may be found: Communication – between providers and patients Variability in care Responsibility of care/clinical responsibility Access to support services/specialist services Access to patient records Decision making Information and support provision Follow-up care process Care-seeking
Exclusions	Papers that do not do a qualitative analysis of the results will be excluded (for example, papers that only make quantitative claims (eg 75% were satisfied with their experience) based on survey results, without analysing the free text responses to the open questions). Studies conducted in non-OECD countries or the US will be excluded, given the substantial differences in service configuration likely in such countries.
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL, PsychINFO Studies will be restricted to English language only. No date limits.
Review strategy	Study designs to be considered: Qualitative studies (for example, interviews, focus groups, observations) Review strategy: Population size and directness: No minimum sample size Studies with indirect populations will not be considered [for example, studies in heart failure in an acute setting, in other cardiac conditions or in mixed populations] Appraisal of methodological quality The methodological quality of each study will be assessed using NGC modified NICE

Review question	What are the experiences and preferences of staff and patients during transition between different heart failure care settings (including primary, secondary and community care)?
	checklists and the quality of the body of evidence as a whole will be assessed by a GRADE CerQual approach for each review finding. Data synthesis Synthesis of qualitative research: thematic analysis – information synthesised into main review findings. Results presented in a detailed narrative (with accompanying diagrams if appropriate) and in table format with summary statements of main review findings.

A.14 Communication needs regarding diagnosis and prognosis

Table 22: Review protocol: communication needs

Review question	What are the information and support needs to be considered when communicating a diagnosis and consequent prognosis, to people with heart failure, their families and carers?
Objective	A diagnosis of heart failure often carries a poor prognosis due to the chronic progressive nature of the condition, with high rates of mortality and significant morbidity. A number of qualitative studies have found that a substantial proportion of patients with a diagnosis of heart failure do not understand the nature and seriousness of their condition, in part due to a lack of information supplied by healthcare providers and use of poorly understood terminology. The aim of this review is to identify the information and support needs of people with heart failure, their families and carers, when healthcare professionals are communicating a diagnosis and prognosis.
Population and setting	Patients with heart failure in a primary care, outpatient or community setting. Studies that relate to patient/staff experiences of communication regarding diagnosis or prognosis that occur during a patient's hospitalisation for heart failure will be included, where the issues identified are also relevant to communication in the community/outpatient setting. Patient, family and carer information and support needs will be considered.
Context	Any description of support and information needs of patients, families or carers relating to communication of a diagnosis or the prognosis of heart failure. Views can be provided by patients, families, carers or healthcare staff. For example: Patients may feel that they lack basic information about their condition Patients may not be provided with written information about their condition, which limits their ability to learn more about and fully understand their condition in their own time Patients may feel that doctors shy away from providing honest information about prognosis, with little recognition that heart failure usually continues to deteriorate and that end-stage heart failure is a terminal illness. Patients may appreciate an honest, two-way dialogue. However, some patients may not want to know their prognosis at the diagnosis stage. Patients may feel that they are not involved in decision-making and are given little information about their treatment options Patients may have questions they feel unable to able to ask their doctors A diagnosis of heart failure can have a significant psychological impact on patients, and

Review question	What are the information and support needs to be considered when communicating a diagnosis and consequent prognosis, to people with heart failure, their families and carers?
	this may not be appreciated or managed appropriately by healthcare staff. Patients may require help or advice on how to access the tools, support and resources they need ("signposting"), to set them up to live their life well. Patients may also need more information and encouragement to self-manage their condition. The MDT may plan a very important role here. Information provision should be tailored to the patient preferences with regard to format (written, verbal, web/apps etc) and level of detail. Information provision should also be sensitive to cultural differences, language barriers, and patient comorbidies (other aspects of the patient's health may be causing them greater problems than their heart failure). The phraseology heart failure has negative connotations and some patients may be particularly sensitive to the language and terminology. Findings that may be found: Honestly/frankness about prognosis Ability to ask questions Sensitivity Emotional/psychological support Written/tailored information Involvement in decision-making
Exclusions	Papers that do not do a qualitative analysis of the results will be excluded (for example, papers that only make quantitative claims (eg 75% were satisfied with their experience) based on survey results, without analysing the free text responses to the open questions). Studies conducted outside the UK will be excluded given the cultural & linguistic differences in communication preferences (unless there is insufficient UK data in which case data from OECD countries excluding the US will be considered, followed by data from any other country). Studies conducted over 15 years ago will be excluded given the changes in patient communication preferences and expectations over time and the advent of patient centred-care (unless there is insufficient recent data).
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL, PsychINFO Studies will be restricted to English language only. Limit to last 15 years.
Review strategy	Study designs to be considered: Qualitative studies (for example, interviews, focus groups, observations) Review strategy: Population size and directness: No minimum sample size Studies with indirect populations will not be considered [for example, studies in other cardiac conditions or in mixed populations] Appraisal of methodological quality The methodological quality of each study will be assessed using NGC modified NICE checklists and the quality of the body of evidence as a whole will be assessed by a GRADE CerQual approach for each review finding. Data synthesis Synthesis of qualitative research: thematic analysis – information synthesised into main review findings. Results presented in a detailed narrative (with accompanying diagrams

Review question	What are the information and support needs to be considered when communicating a diagnosis and consequent prognosis, to people with heart failure, their families and carers?
	if appropriate) and in table format with summary statements of main review findings.

A.15 Diuretics in advanced heart failure

Table 23: Review protocol: Diuretics in advanced heart failure

Review question	Which route of administration of diuretics (intravenous (IV), subcutaneous or oral) is most clinically and cost effective in people with advanced heart failure who are in the community, including patients receiving palliative care?
Guideline condition and its definition	Chronic heart failure. Definition: People diagnosed with heart failure, who are in a community or outpatient setting.
Objectives	Diuretics provide symptomatic relief, particularly in the presence of oedema, and are a key part of managing patients with advanced heart failure. For many advanced heart failure patients, some of whom may be approaching the end of their life, the focus of treatment may shift to symptom relief, admission avoidance, maintaining quality of life and minimising discomfort. These patients may become less responsive to conventional oral doses of loop diuretics and resistance may occur. IV diuretics may be more effective than oral and subcutaneous diuretics in managing symptoms, but they are invasive, may not be feasible in very unwell patients, and are more costly to administer as they require delivery by healthcare professionals. Traditionally, administration of IV diuretics has required admission to hospital for at least several days. Subcutaneous diuretics may be more effective than oral diuretics but also require delivery by healthcare professionals. The aim of this review is to compare the effectiveness of IV, subcutaneous and oral diuretics, in patients with advanced heart failure who are in the community.
Review population	People diagnosed with advanced heart failure. Patients may be living in a community residential facility (care home), at home or in a hospice. These patients will typically have experienced a recent drop in their NYHA class, have fluid overload/oedema that is no longer well controlled by oral diuretics, and have a series of recent hospital admissions. Patients may be receiving palliative care services. Studies of diuretics delivered to ambulatory patients will be included regardless of whether the patient is at home or in an outpatient setting (for example, a “diuretic lounge”). Studies will also be included where a patient has been admitted to hospital, if that admission is solely for the purposes of administration of IV diuretics and the patient is not acutely unwell. Community administration of IV diuretics is not widespread and usually patients require hospital admission just to enable their administration. The relative effectiveness of IV diuretics in these patients is not expected to differ between settings, and so any evidence in such patients will be informative for this review. Studies where diuretics are delivered during a patient’s admission for an acute decompensation will be excluded.
	Adults (aged 18 years and over)
	Line of therapy not an inclusion criterion
Interventions and comparators:	IV diuretics (furosemide or torsemide) (continuous or bolus) + oral metolazone/thiazides

Review question	Which route of administration of diuretics (intravenous (IV), subcutaneous or oral) is most clinically and cost effective in people with advanced heart failure who are in the community, including patients receiving palliative care?
generic/class; specific/drug (All interventions will be compared with each other, unless otherwise stated)	IV diuretics (furosemide or torsemide) (continuous or bolus) alone Subcutaneous diuretics (furosemide or torsemide) +/- oral metolazone/thiazides Oral diuretics (bumetanide or furosomide and/or metolazone/thiazides). Thiazides are limited to: Bendroflumethiazide (Bendrofluazide) Cyclopenthiazide Chlorthalidone / Chlortalidone Indapamide Xipamide Metolazone Classes will be compared with each other, and different drugs and doses will be combined in each class. Any intraclass comparisons will be excluded as the focus of the review is on the class effects of different modes of administration. The intervention must be repeated and regular (administered for more than three consecutive days).
Outcomes	- Quality of life at 2 weeks & 4 weeks (Continuous) CRITICAL - Unplanned hospitalization at 2 weeks & 4 weeks (Count rate) CRITICAL - Unplanned hospitalization at 2 weeks & 4 weeks (Number of bed days) CRITICAL - Change in dyspnoea (for example, patient questionnaire VAS) at 2 weeks & 4 weeks (Continuous) IMPORTANT - Weight change / change in oedema at 2 weeks & 4 weeks (Continuous) IMPORTANT - Change in NYHA class at 2 weeks & 4 weeks (Continuous) IMPORTANT - Patient and carer satisfaction 2 weeks & 4 weeks (Continuous) IMPORTANT - Time to death (survival) during study (Time-to-event) IMPORTANT - Successful administration of intervention during study (Dichotomous) IMPORTANT
Study design	Systematic Review RCT
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	No
Other exclusions	None
Sensitivity/other analysis	For dichotomous and continuous outcomes where a study reports multiple time points, the closest time point to the specified time point will be extracted. Data will not be extracted if it is collected more than 1 month after delivery of the intervention. Shorter term time points will also be extracted if reported in the studies but may be downgraded for indirectness in consultation with the GC. Where unplanned hospitalisation data is not reported but data on HF-related unplanned hospitalisation is reported, the HF-related data will be extracted but will not be pooled with the all-cause data.
Subgroup analyses if there is heterogeneity	None
Search criteria	Databases: The databases to be searched are Medline, Embase, The Cochrane Library. Date limits for search: None Language: English

A.16 Domiciliary oxygen therapy in people with advanced heart failure

Table 24: Review protocol: Domiciliary oxygen therapy in advanced heart failure

Review question	What is the effectiveness of domiciliary oxygen therapy in people with advanced heart failure (HF)?
Guideline condition and its definition	Chronic heart failure. Definition: People diagnosed with heart failure, who are in a community or outpatient setting.
Objectives	The objective of this review is to establish whether there is any value in prescribing oxygen to people with advanced heart failure, and in particular whether oxygen results in an improvement of patient symptoms (particularly breathlessness). This review will consider whether oxygen therapy may be valuable in patients with advanced heart failure who do not have hypoxaemia, and is not limited to the last days of life.
Review population	Adults (aged 18 years and over) with advanced heart failure (whether living in a care home (community residential facility), at home or in a hospice)
	Adults (aged 18 years and over)
	Line of therapy not an inclusion criterion
Interventions and comparators: generic/class; specific/drug (All interventions will be compared with each other, unless otherwise stated)	Domiciliary oxygen therapy ; repeated long term use (daily availability) Domiciliary oxygen therapy ; repeated long term use (night time use) No oxygen therapy; Medical air No oxygen therapy; Handheld fan No oxygen therapy; No treatment
Outcomes	- Quality of life at 2 weeks (Continuous) CRITICAL - Unplanned hospitalisation at 4 weeks (Dichotomous) CRITICAL - Unplanned hospitalisation at 4 weeks (Continuous) CRITICAL - Change in dyspnea at 2 weeks (Continuous) CRITICAL - Patient and carer satisfaction at 2 weeks (Continuous) CRITICAL - Change in exercise capacity at 2 weeks (Continuous) IMPORTANT - Change in NYHA class at 2 weeks (Continuous) IMPORTANT
Study design	Systematic Review RCT
Unit of randomisation	Patient
Crossover study	Not permitted
Minimum duration of study	None
Other exclusions	Studies in patients who have hypoxemia and who meet existing NICE criteria for oxygen therapy (for example, under CG101 or NG31), unless such patients make up <30% of the trial participants.

	Patients who are on non-invasive ventilation
Sensitivity/other analysis	For dichotomous and continuous outcomes where a study reports multiple time points, the closest time point to the specified time point will be extracted. Where unplanned hospitalisation data is not reported but data on HF-related unplanned hospitalisation is reported, the HF-related data will be extracted.
Subgroup analyses if there is heterogeneity	None
Search criteria	Databases: Medline, Embase, The Cochrane Library Date limits for search: None Language: English

A.17 Discussing Implantable Cardioverter Defibrillator (ICD) deactivation

Table 25: Review protocol: Discussing ICD deactivation

Review question	What criteria should determine when to discuss defibrillator deactivation?
Objective	The benefit of implantable cardiac defibrillators (ICDs) in patients with cardiac conditions including heart failure is well documented. However, aging and the burdens of progressive heart failure or the development of other life limiting conditions such as cancer or dementia may begin to raise questions on the continuing benefit of ICD therapy. Defibrillation can cause physical discomfort and emotional distress to the patient, and also cause emotional distress to their families. Healthcare professionals should consider withdrawal of non-contributory therapies and the distress caused by resuscitation measures in those near the end of life with a progressive and irreversible decline in their condition. However, initiating a conversation with a patient about deactivation is challenging and the most appropriate timing of that discussion is often unclear. The aim of this review is to understand the views of patients, family, carers and healthcare staff regarding the timing of discussions about the deactivation of ICDs. This should inform the development of criteria for considering when it might be appropriate for healthcare staff to initiate such a conversation with their patients.
Population and setting	Patients with heart failure in a primary care, outpatient or community setting. Studies that relate to patient/staff experiences of communication regarding deactivation of ICDs that occur during a patient's hospitalisation for heart failure will be included, where the issues identified are also relevant to the community/outpatient setting.
Context	Any description of patient, family, carer or healthcare staff experiences or preferences relating to the timing of discussions regarding the deactivation of an ICD. For example: Patients Patients may find a conversation about ICD deactivation difficult and unexpected, especially if the possibility of deactivation was not mentioned at the time of implantation. Patients may not feel like they have sufficient support and information to participate in the decision making process and may not understand what ICD deactivation means for their prognosis or future treatment.

Review question	What criteria should determine when to discuss defibrillator deactivation?
	Patients may feel like they are being 'abandoned' or that their trusted healthcare professionals are not 'doing all they can' to best treat their condition. Patients may feel like they lack sufficient psychological and emotional support to come to terms with a revised prognosis. Family, carers and healthcare staff Bereaved relatives and healthcare professionals may describe witnessing the distressing effects of inappropriate ICD activity in terminally ill patients. Healthcare professionals may feel reluctant to raise the challenging issue with patients and their families, particularly if there are concerns that the patient lacks capacity to make an informed decision. Themes that may be found: Informed consent Importance of advanced care planning Open, sensitive two-way communication at all stages of pathway Emotional/psychological support Written/personalised information Shared decision-making Importance of multidisciplinary team approach
Exclusions	Papers that do not do a qualitative analysis of the results will be excluded (for example, papers that only make quantitative claims (eg 75% were satisfied with their experience) based on survey results, without analysing the free text responses to the open questions). Studies conducted outside the UK will be excluded given the cultural & linguistic differences in communication preferences (unless there is insufficient UK data, in which case data from OECD countries excluding the US will be considered first, after which data from any country will be considered if data remains insufficient). Studies conducted over 15 years ago will be excluded given the changes in patient communication preferences and expectations over time and the advent of patient centred-care.
Search strategy	The databases to be searched are Medline, Embase, The Cochrane Library, CINAHL, PsychINFO Studies will be restricted to English language only. Limit to last 15 years.
Review strategy	Study designs to be considered: Qualitative studies (for example, interviews, focus groups, observations) Review strategy: Population size and directness: No minimum sample size Studies with indirect populations will not be considered [for example, studies in other cardiac conditions or in mixed populations] Appraisal of methodological quality The methodological quality of each study will be assessed using NGC modified NICE checklists and the quality of the body of evidence as a whole will be assessed by a GRADE CerQual approach for each review finding. Data synthesis Synthesis of qualitative research: thematic analysis – information synthesised into main review findings. Results presented in a detailed narrative (with accompanying diagrams if appropriate) and in table format with summary statements of main review findings.

A.18 Identifying patients with an increased risk of mortality

Table 26: Review protocol: Risk tools for 1 year mortality in HF

Review question	**In adults with heart failure, which validated risk tools best identify patients who are at increased risk of mortality in the short term (up to 1 year)?**
Objectives	To determine which prognostic risk tools are the most accurate at predicting patient mortality, to support decisions about involvement of palliative care services and the use of palliative care processes.
Population	People with heart failure in an acute, community or outpatient setting. The results will be stratified based on the setting in which the tools were validated in the study (admitted versus recently discharged versus community).
Index tests (risk assessment tools)	Validated risk tools identified in the literature
Outcomes	Mortality (all-cause at up to 1 year)
Statistical measures	Area under the ROC curve Sensitivity, specificity, negative predictive value, positive predictive value Other statistical measures eg measures of calibration
Study design	Prospective cohort studies Retrospective cohort studies will be included only if insufficient prospective cohort studies are identified
Other exclusions	Studies reporting on tools that are not validated in a separate cohort to the derivation cohort. Studies with less than 500 participants.
Search Strategy	Databases: The databases to be searched are Medline, Embase and the Cochrane Library. Date limits for search: None Language: English only
Review Strategy	Subgroups (to be investigated if heterogeneity is identified): HFREF and HFPEF Appraisal of methodological quality: The methodological quality of each study will be assessed using the PROBAST checklist. Synthesis of data: Prognostic meta-analysis will be conducted where appropriate using hierarchical methods. The validation may be conducted by the same study authors or it may be independent, with greater weight placed on studies with independent validation.

Appendix B: Health economic review protocol

Table 27: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the individual review protocol above. • Studies must be of a relevant economic study design (cost-utility analysis, cost-effectiveness analysis, cost-benefit analysis, cost-consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	An economic study search will be undertaken using population-specific terms and an economic study filter – see Appendix G *[in the Full guideline]*. For questions being updated from the previous guidelines, the search will be run from the previous guideline (CG5 or CG108) cut-off date (2002 or October 2009, respectively). Literature for any new questions introduced in this update will be searched from 2001.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2001 will be excluded. Abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2001 that were included in the previous guidelines will be re-assessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in Appendix G of the 2012 NICE guidelines manual.[1049] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. An economic evidence table will be completed and it will be included in the economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then an economic evidence table will not be completed and it will not be included in the economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the Committee if required. The ultimate aim is to include economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the Committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation as excluded

	economic studies in Appendix M. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will have been excluded before being assessed for applicability and methodological limitations. *Economic study type:* • Cost-utility analysis (most applicable). • Other type of full economic evaluation (cost-benefit analysis, cost-effectiveness analysis, cost-consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will have been excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2001 or later that were included in the previous guidelines but that depend on unit costs and resource data entirely or predominantly from before 2001 will be rated as 'Not applicable'. • Studies published before 2001 will be excluded. *Quality and relevance of effectiveness data used in the economic analysis:* • The more closely the clinical effectiveness data used in the economic analysis matches with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix C: Clinical study selection

Figure 1: Flow diagram of clinical article selection for the review of BNP and NT-proBNP in diagnosing chronic heart failure

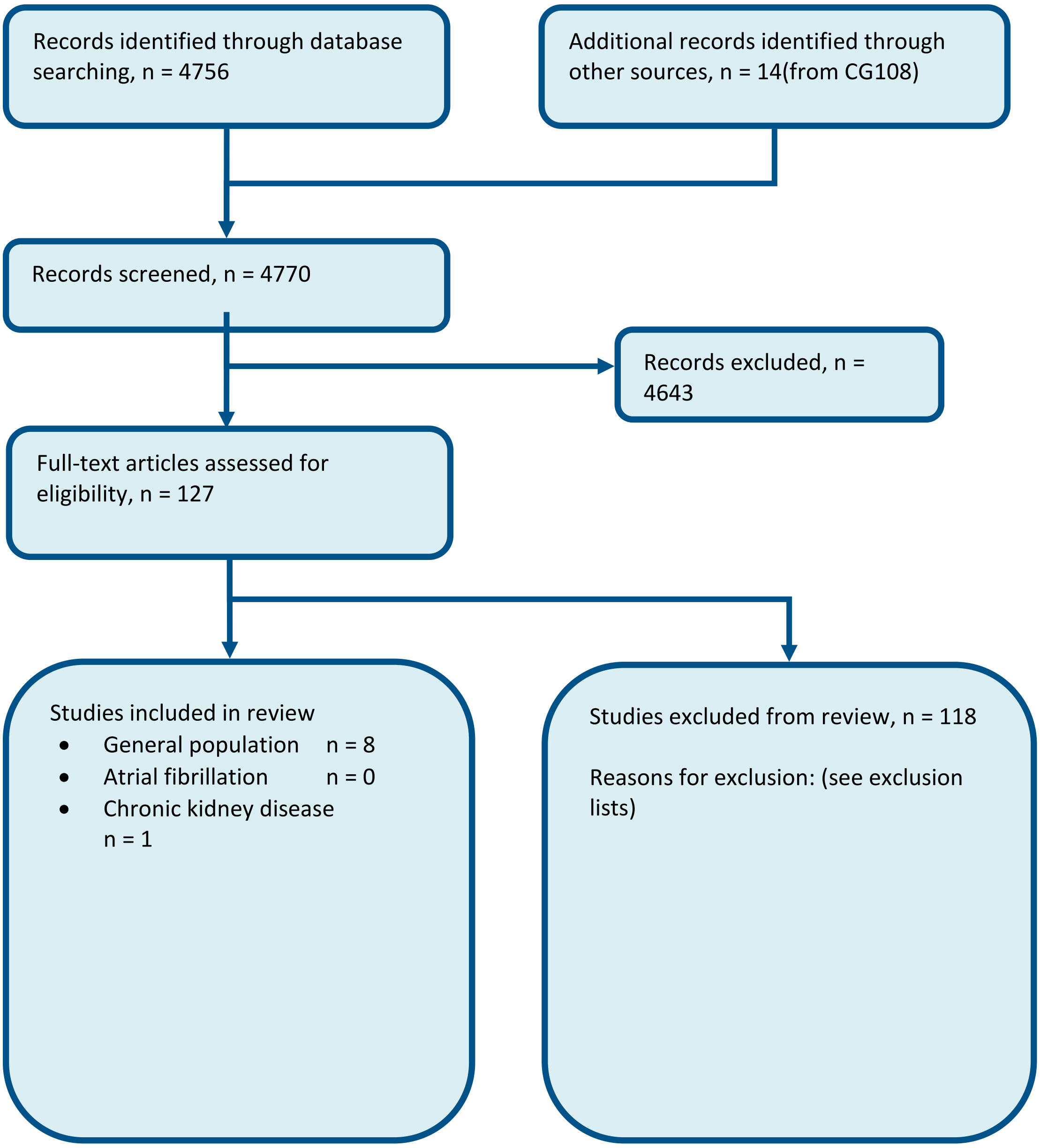


Figure 2: Flow chart of clinical study selection for the review of cMRI versus Echo in HF

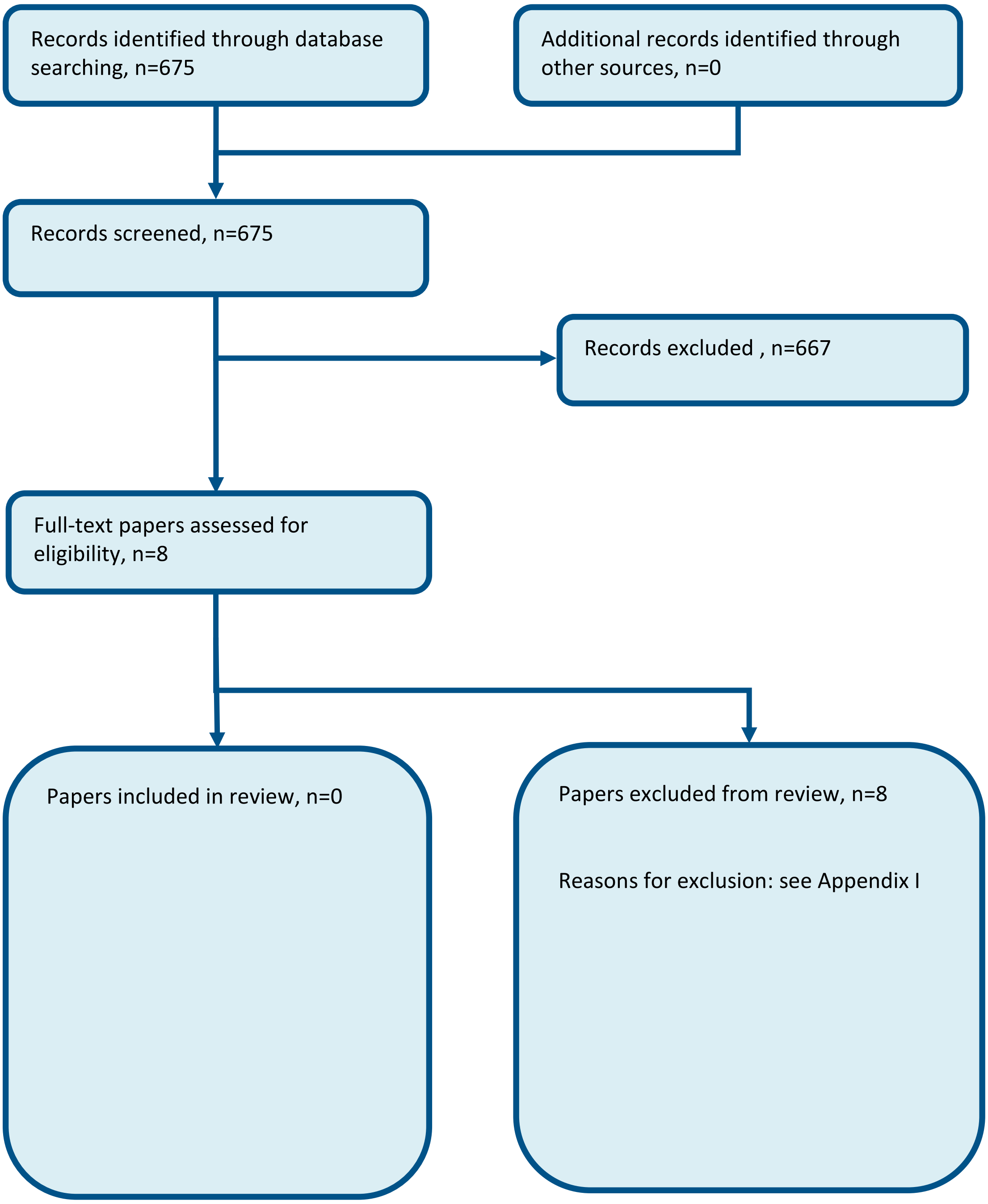


Figure 3: Flow chart of clinical study selection for the review of salt and fluid restriction

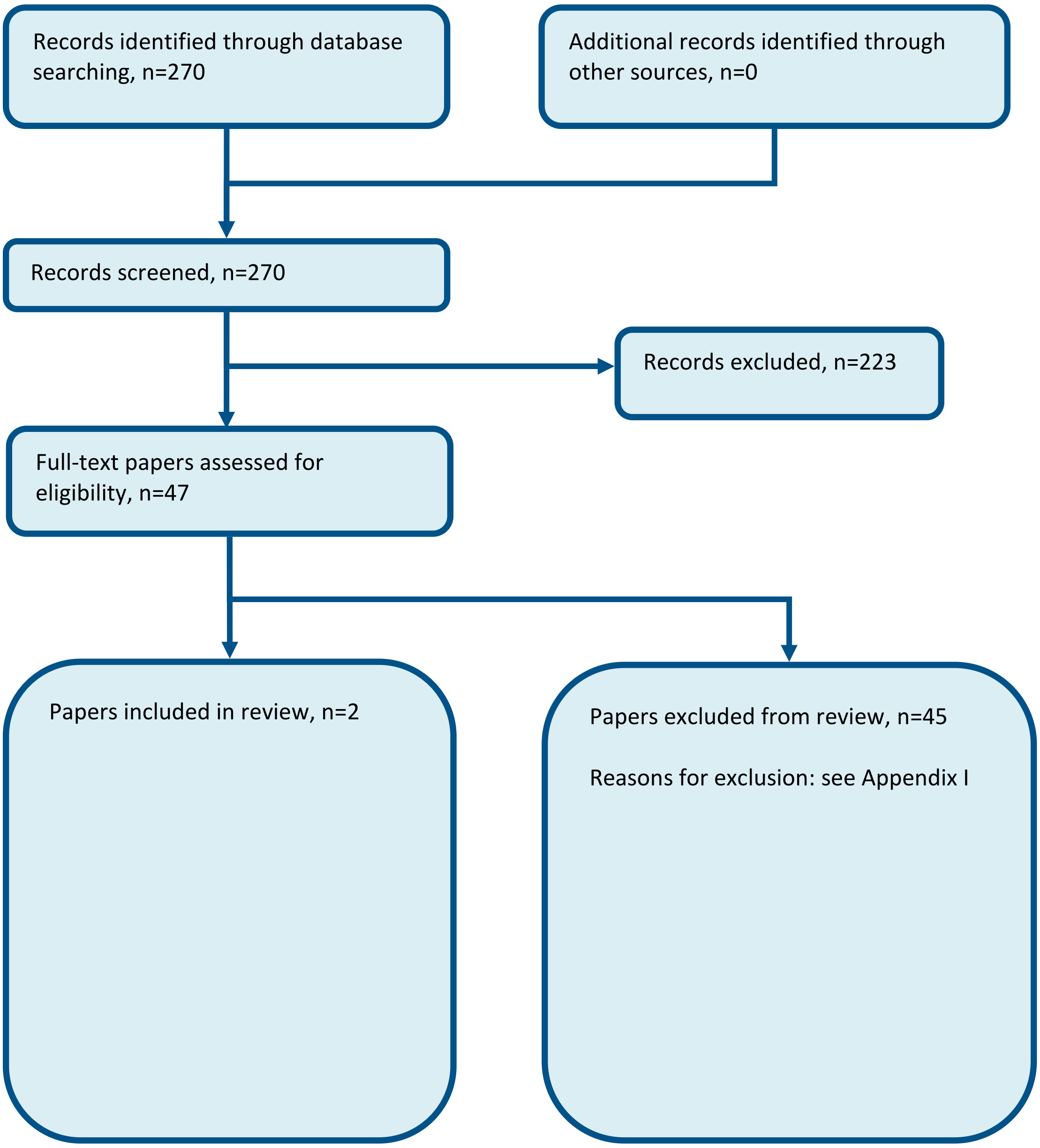


Figure 4: Flow chart of clinical study selection for the review of beta-blockers vs placebo in people with CHF and atrial fibrillation

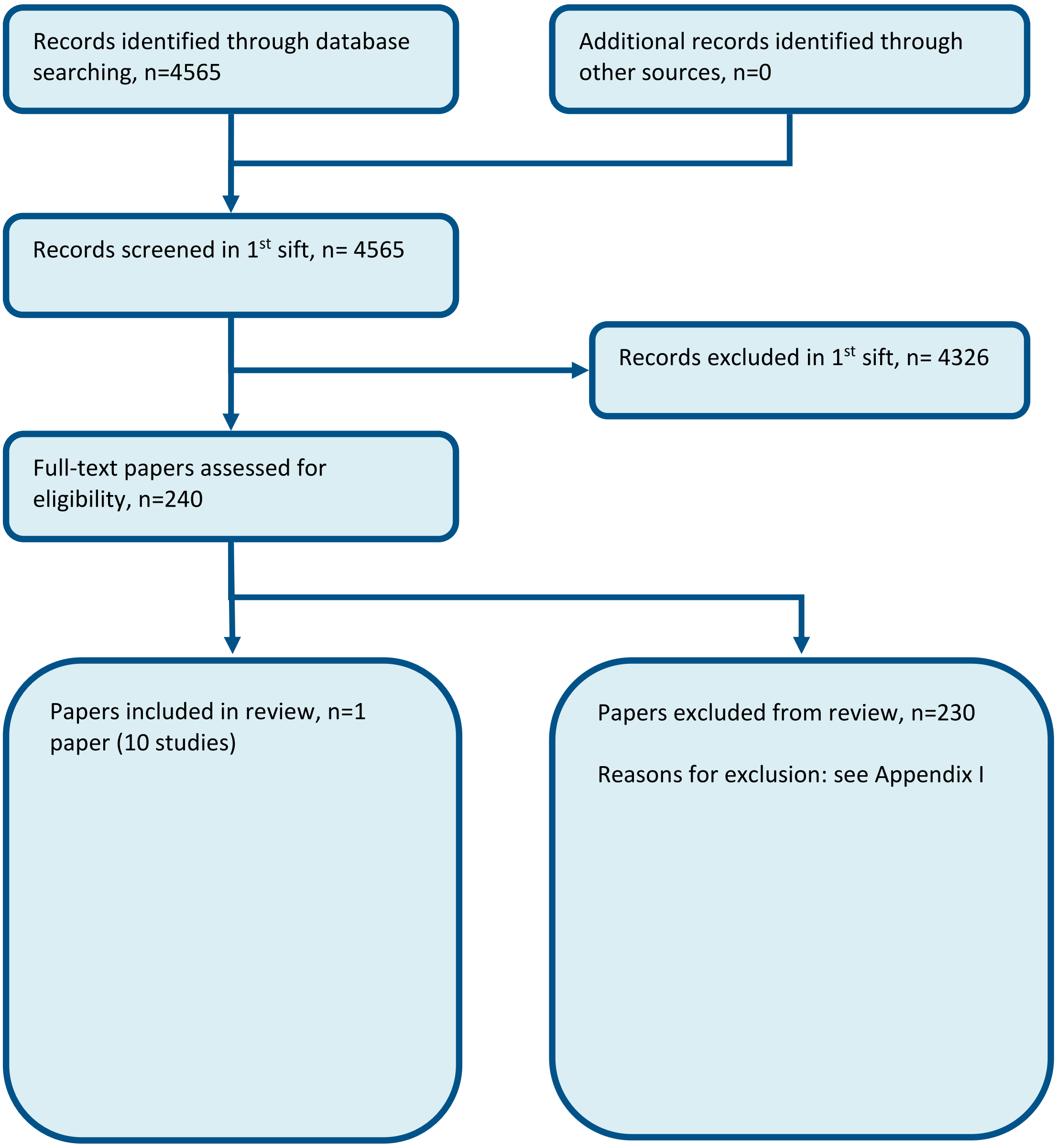


Figure 5: Flow chart of clinical study selection for the review of mineralocorticoid receptor antagonists for heart failure

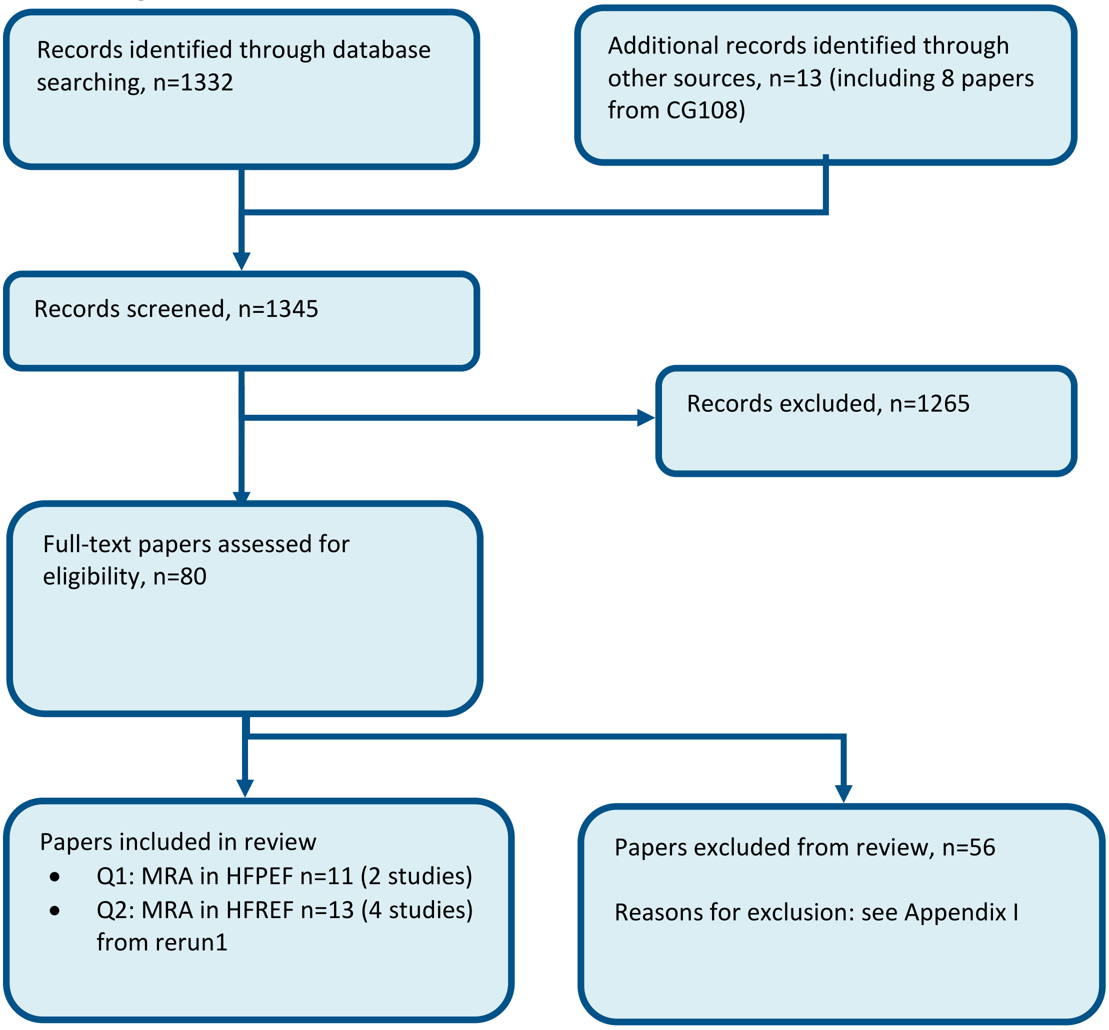


Figure 6: Flow chart of clinical study selection for the review of iron supplementation for iron deficiency in heart failure

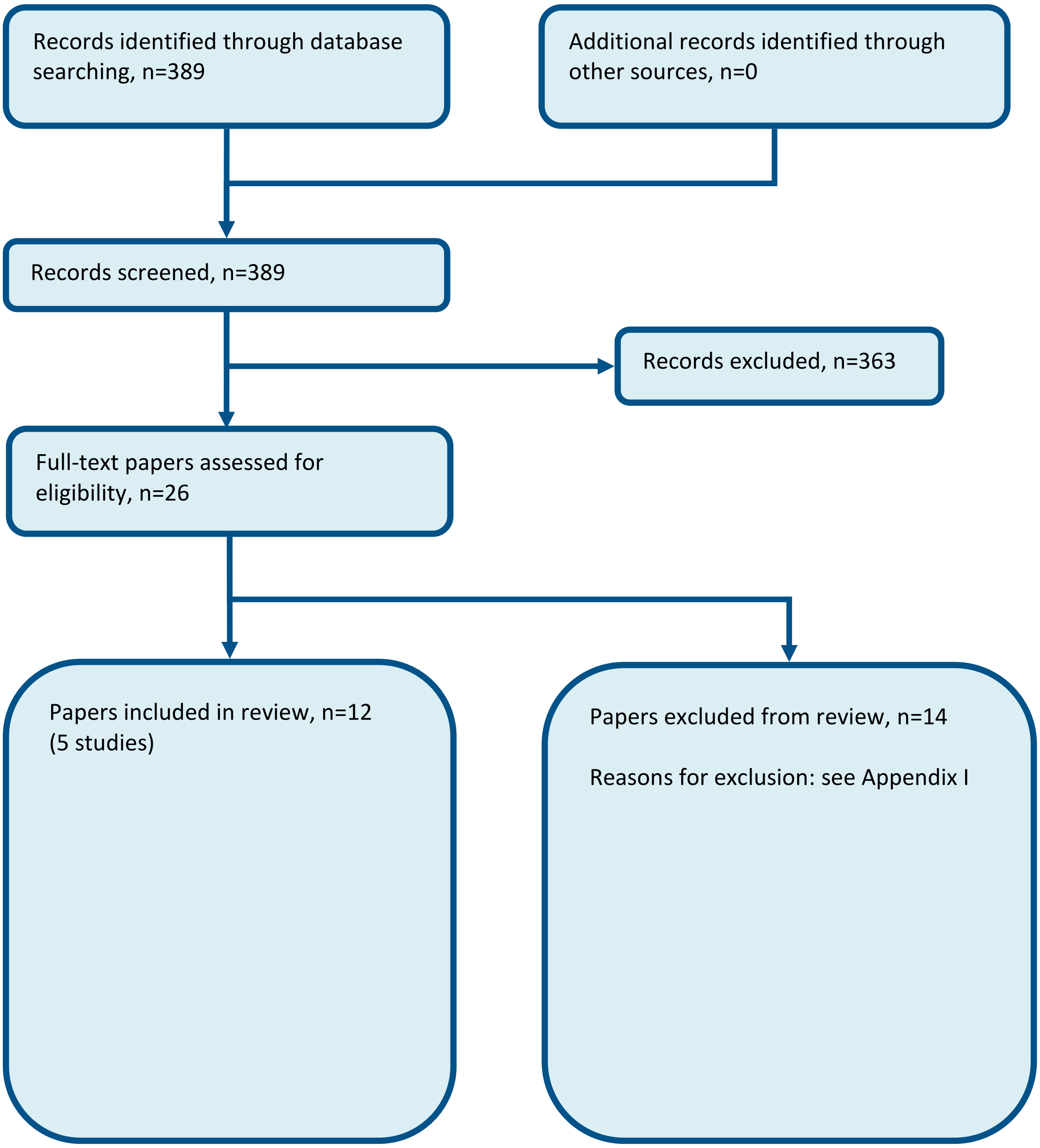


Figure 7: Flow chart of clinical study selection for the review of pharmaceuticals in CKD

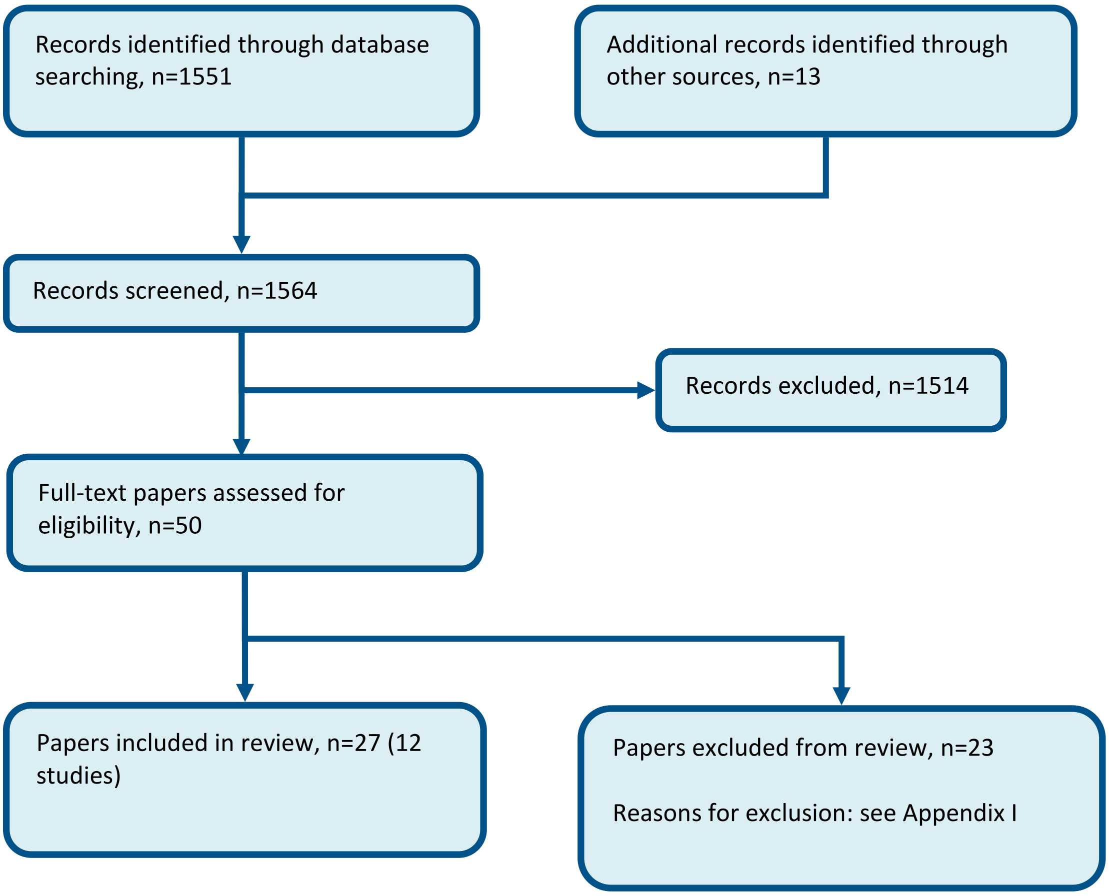


Figure 8: Flow chart of clinical study selection for the review of coronary revascularization in people with heart failure

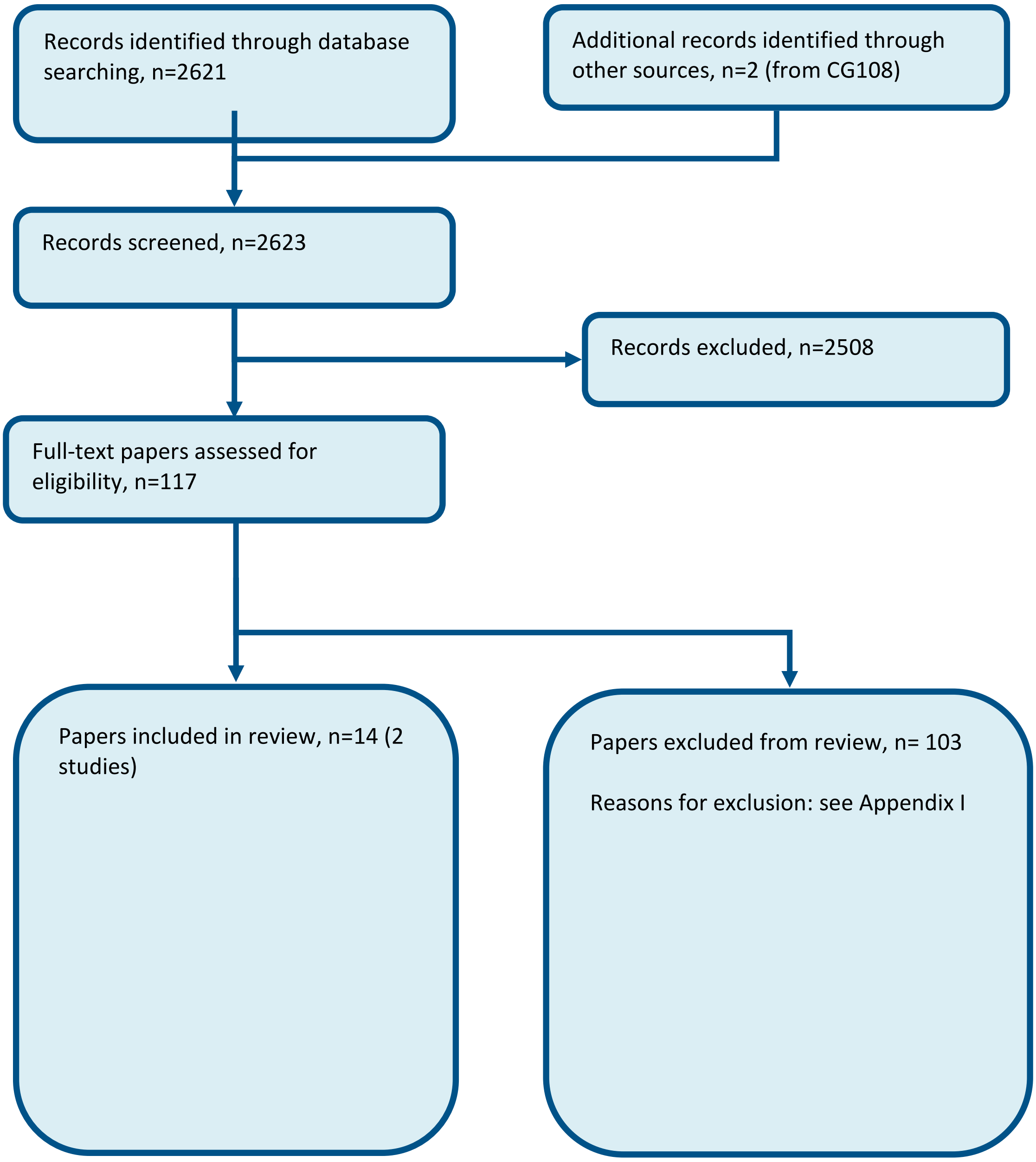


Figure 9: Flow chart of clinical study selection for the review of home-based versus centre-based rehabilitation

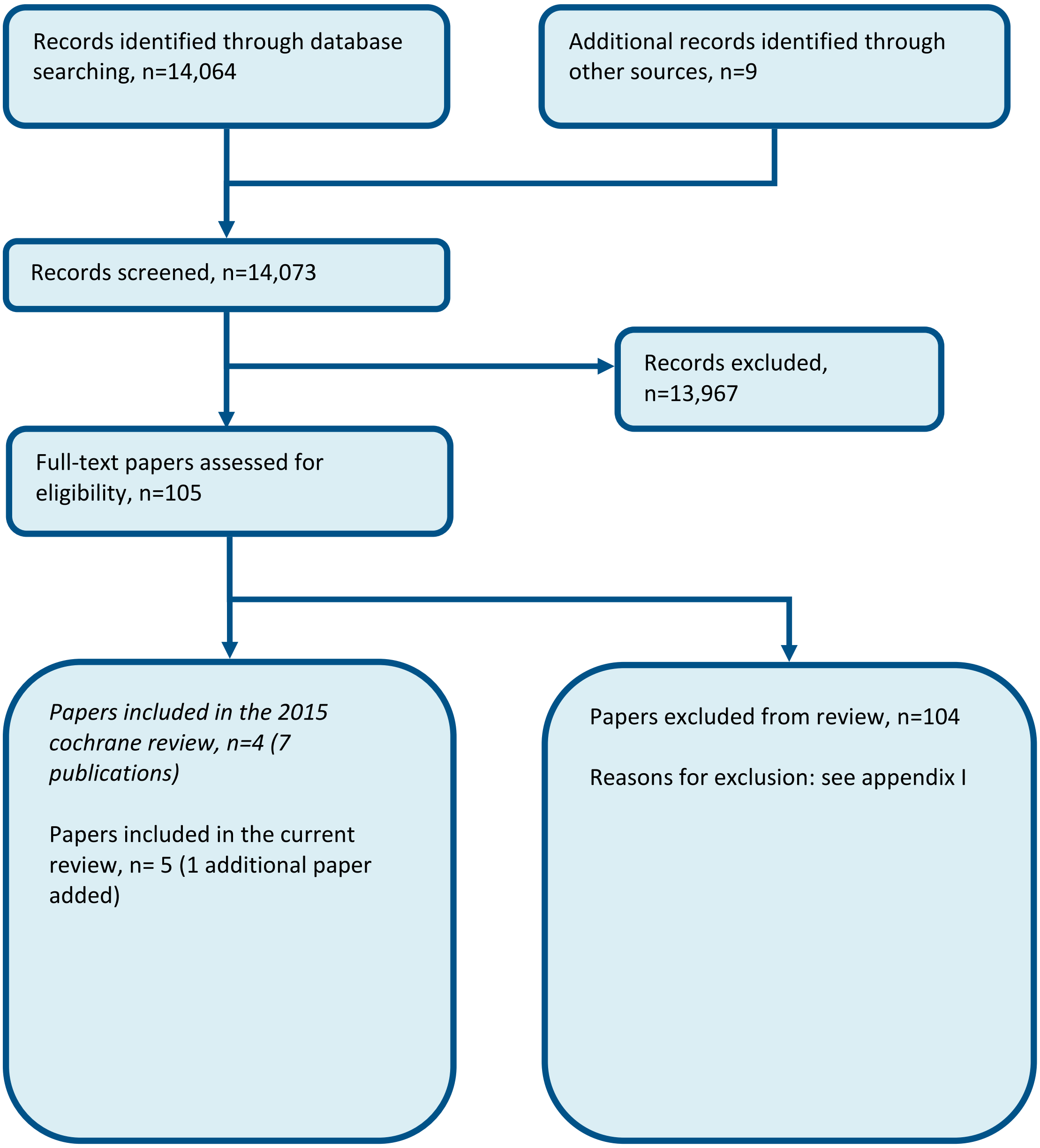


Figure 10: Flow chart of clinical study selection for the review of monitoring

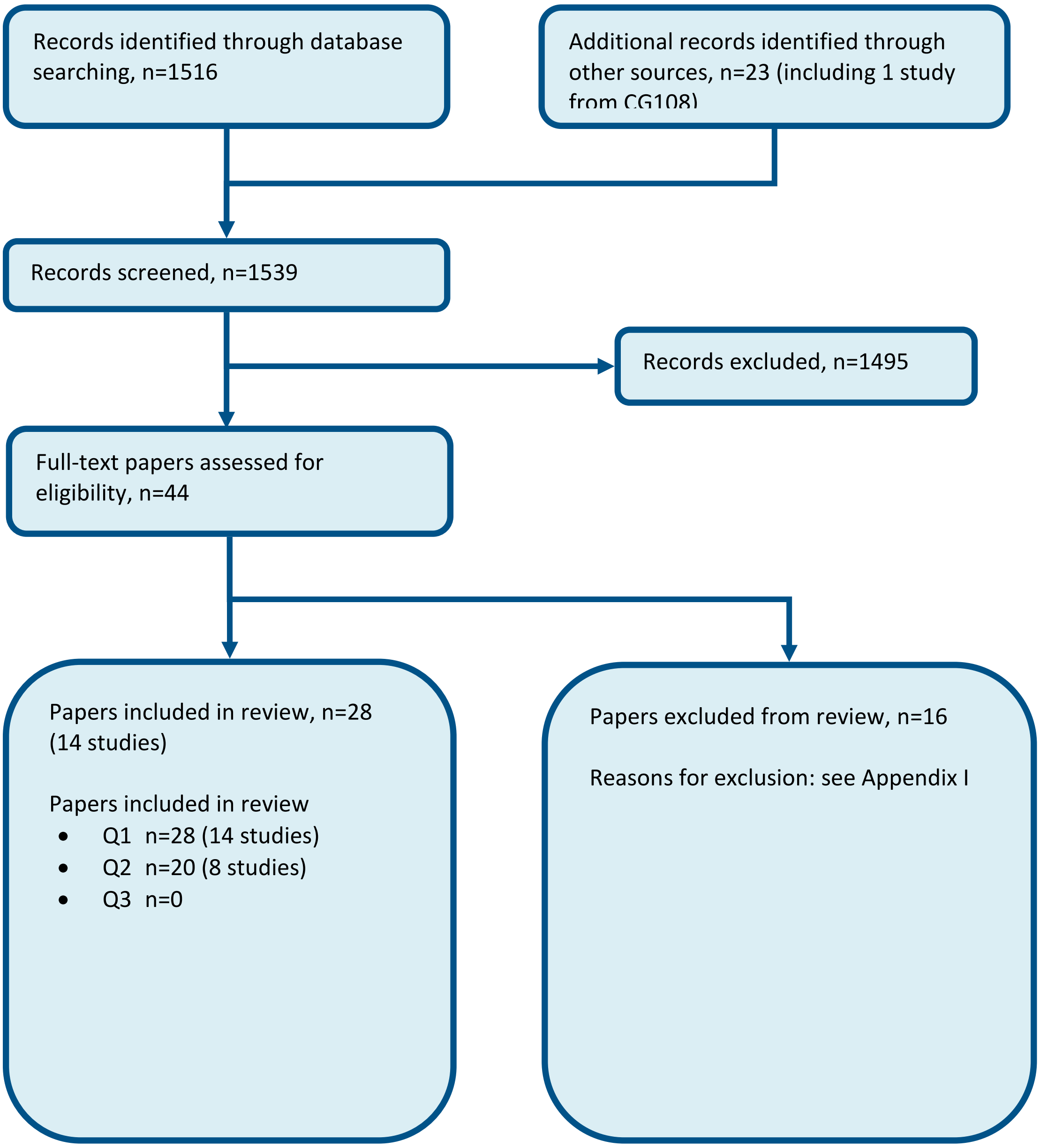


Figure 11: Flow chart of clinical study selection for the review of telemonitoring for chronic heart failure

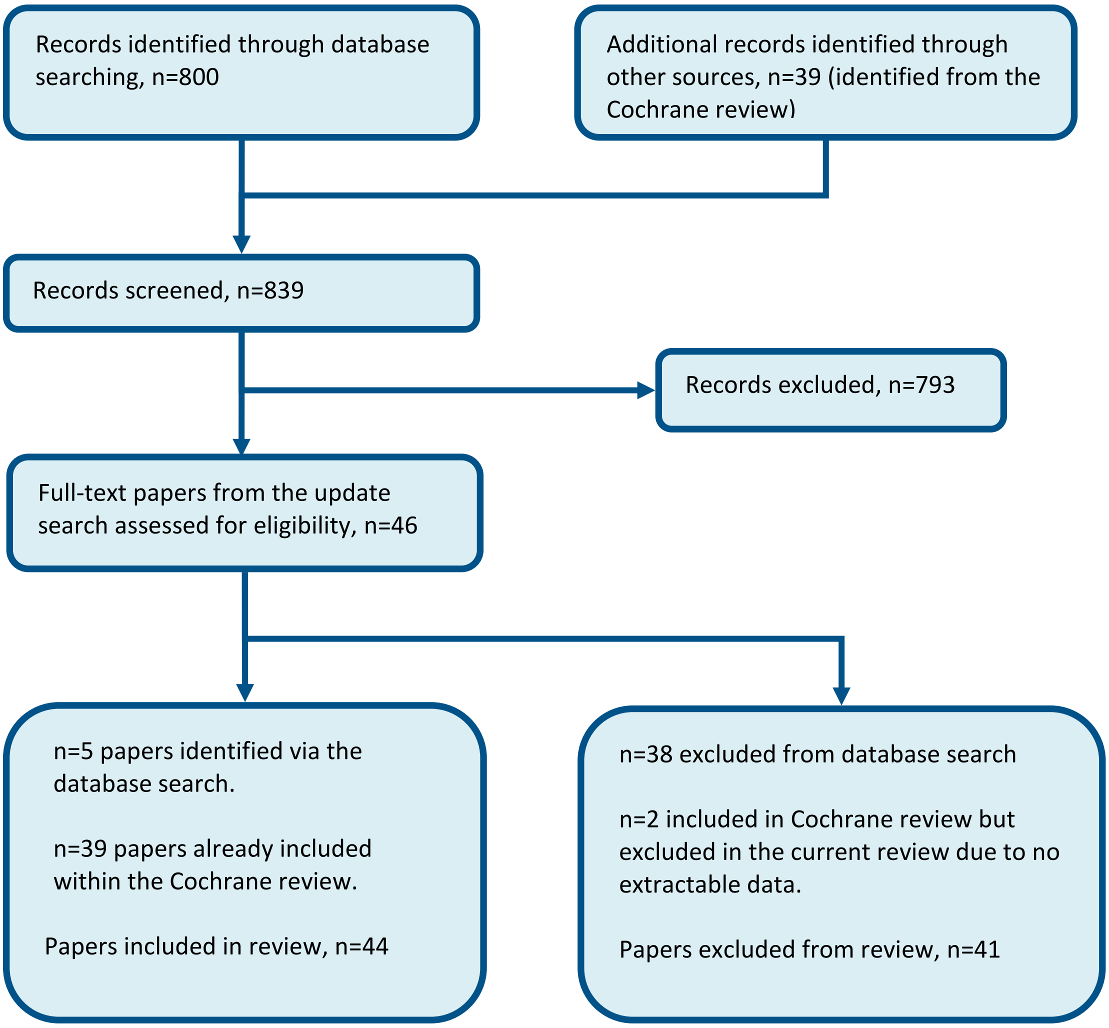


Figure 12: Flow chart of clinical study selection for the review of MDTs

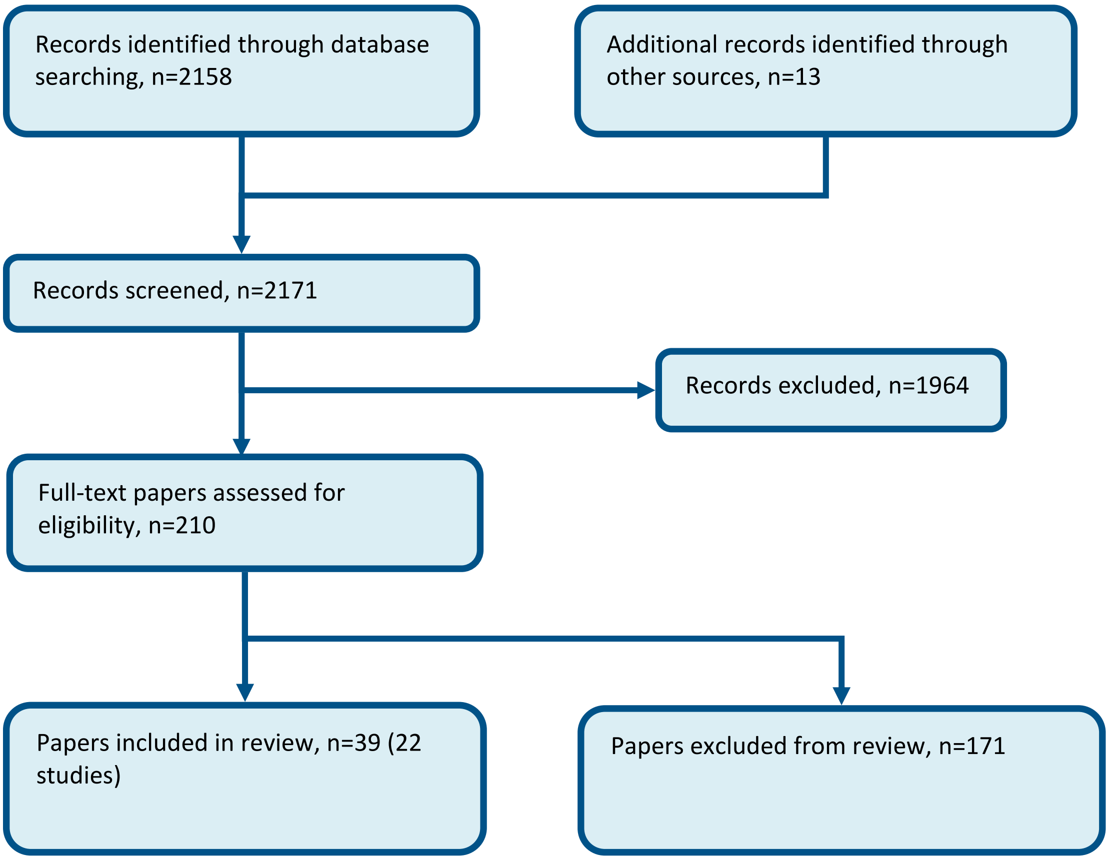


Figure 13: Flow chart of clinical article selection for the review of transition

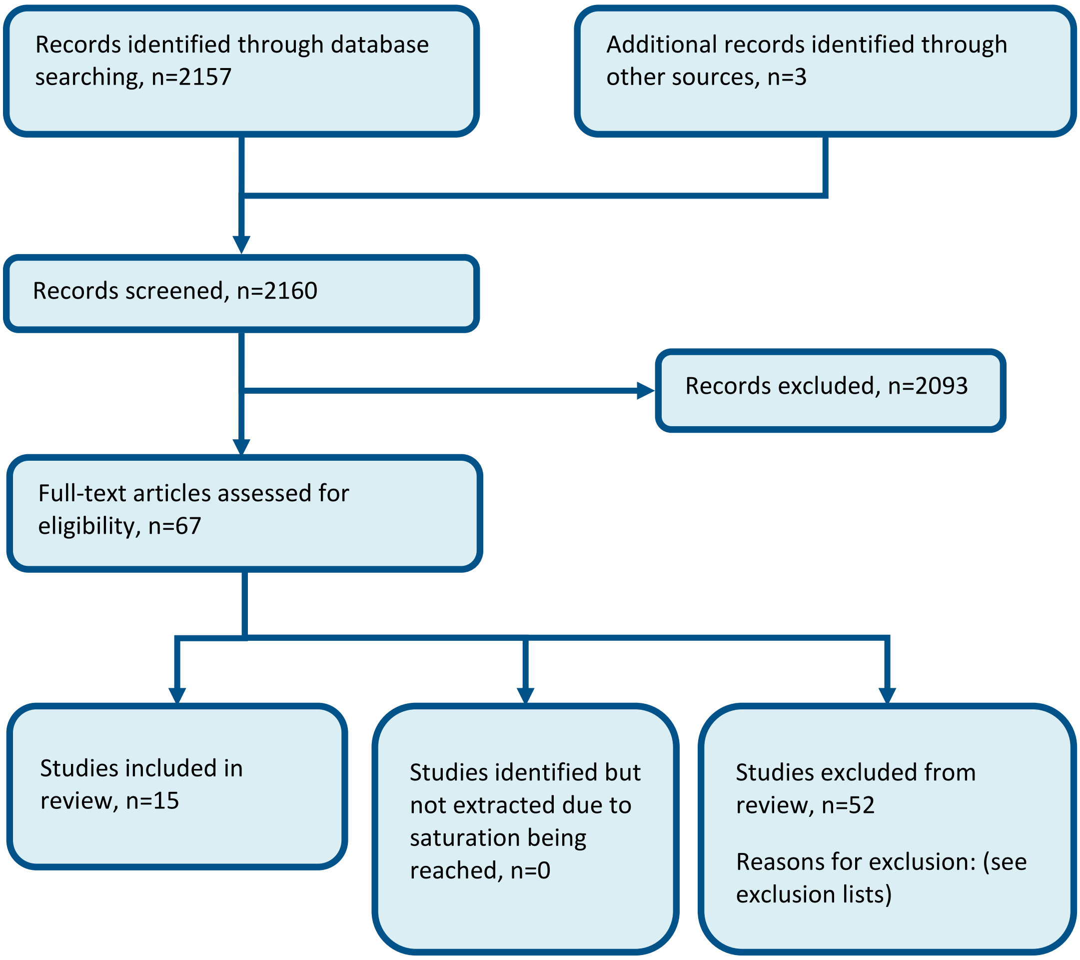


Figure 14: Flow chart of qualitative study selection for the review of communication needs

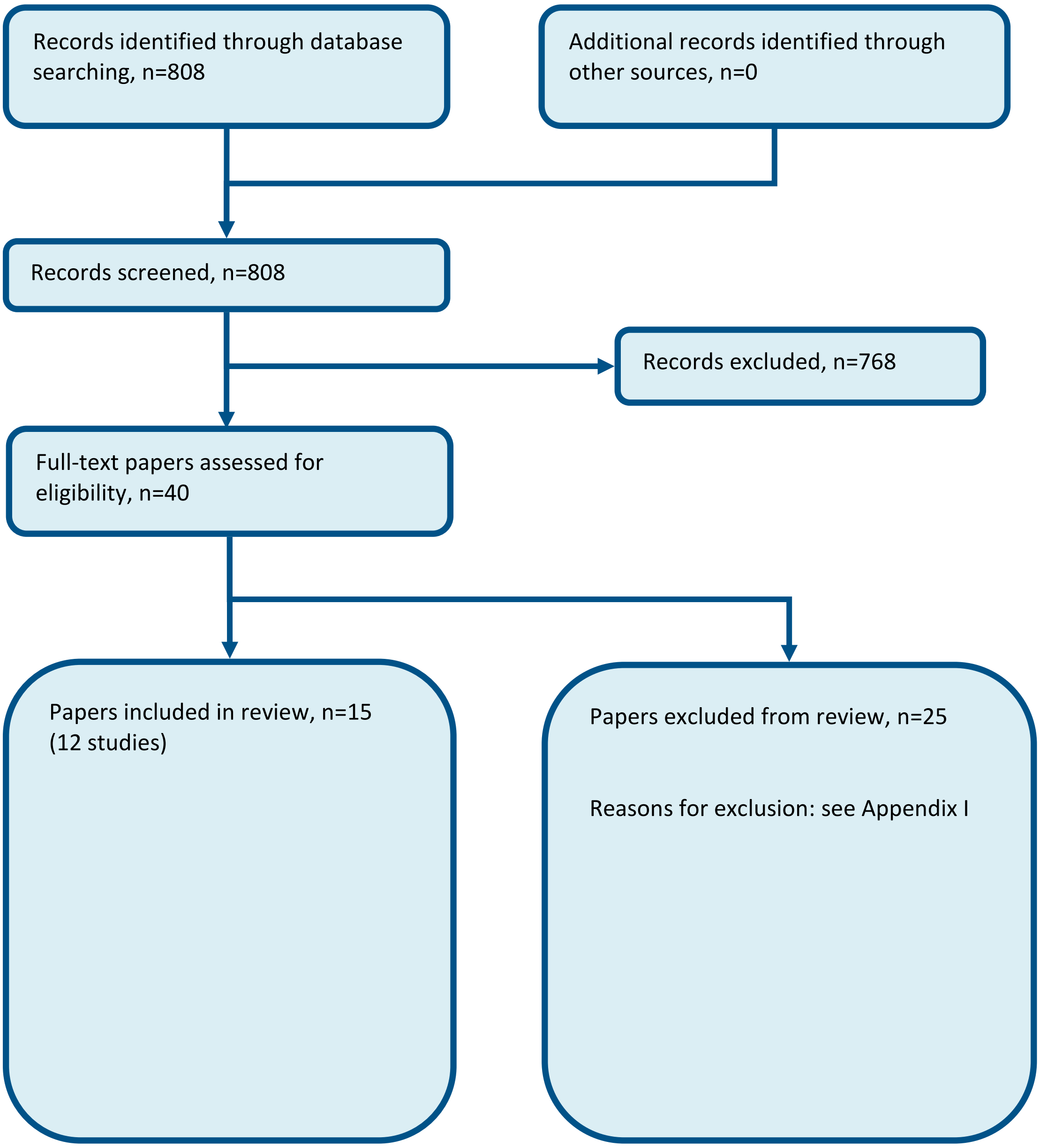


Figure 15: Flow chart of clinical study selection for the review of diuretics in advanced heart failure

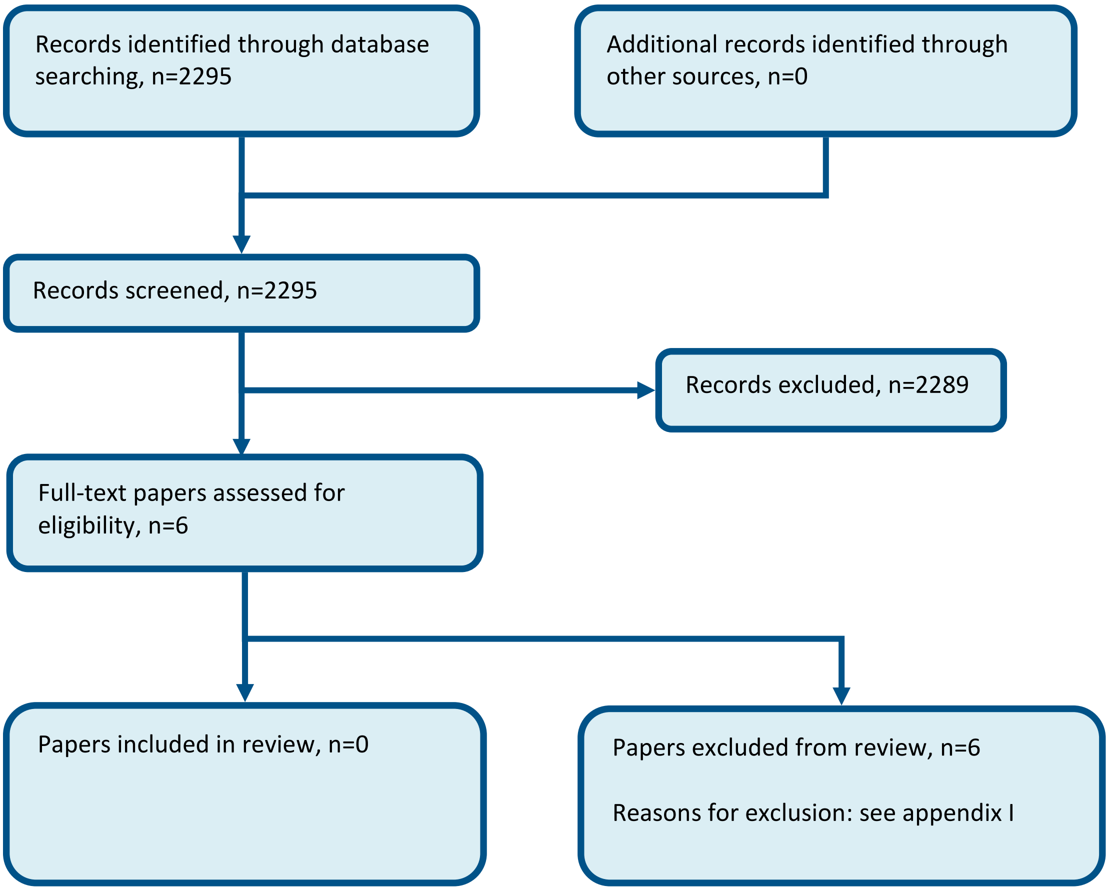


Figure 16: Flow chart of clinical study selection for the review of domiciliary oxygen therapy in advanced heart failure

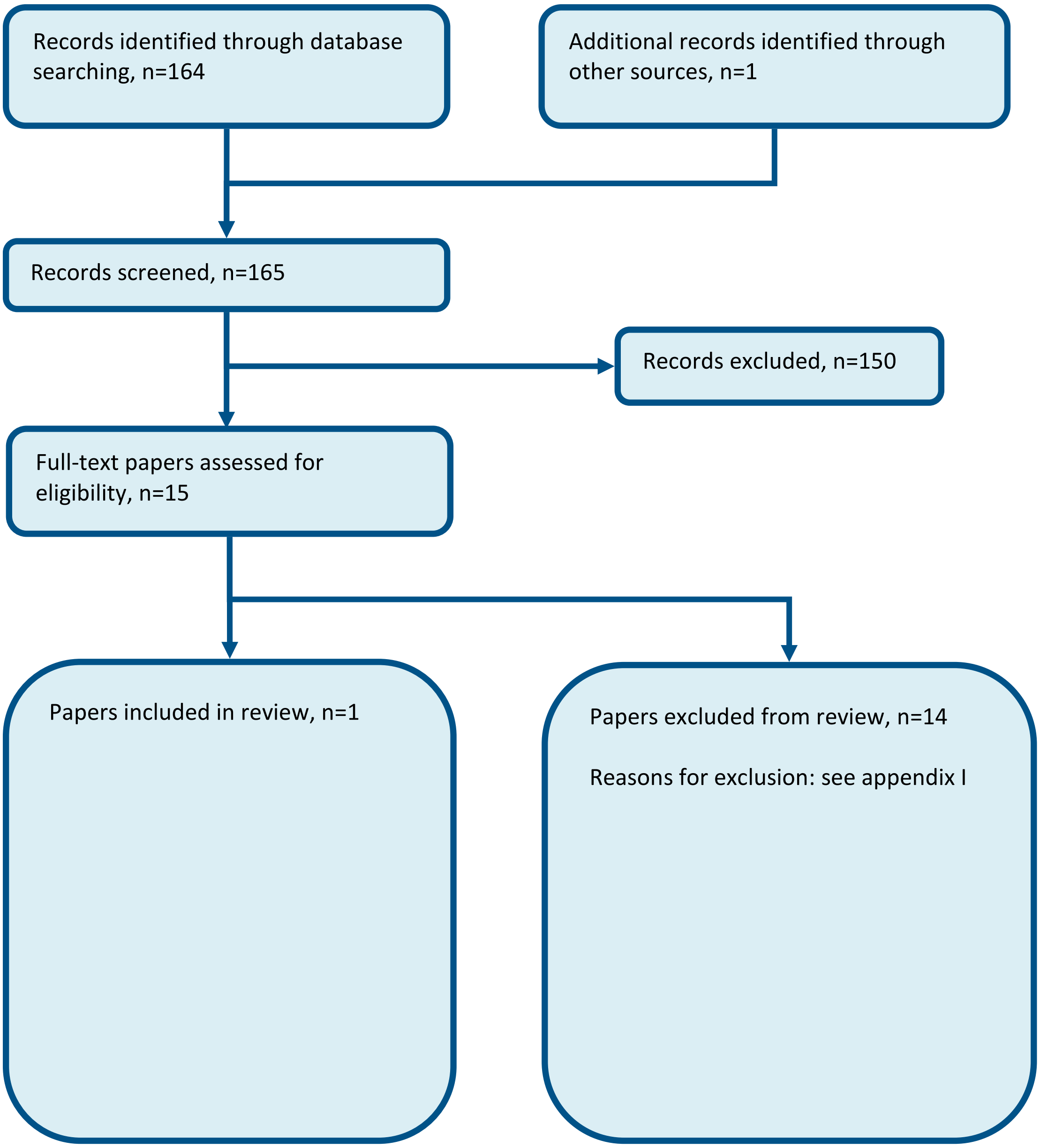


Figure 17: Flow chart of qualitative study selection for the review of discussing ICD deactivation

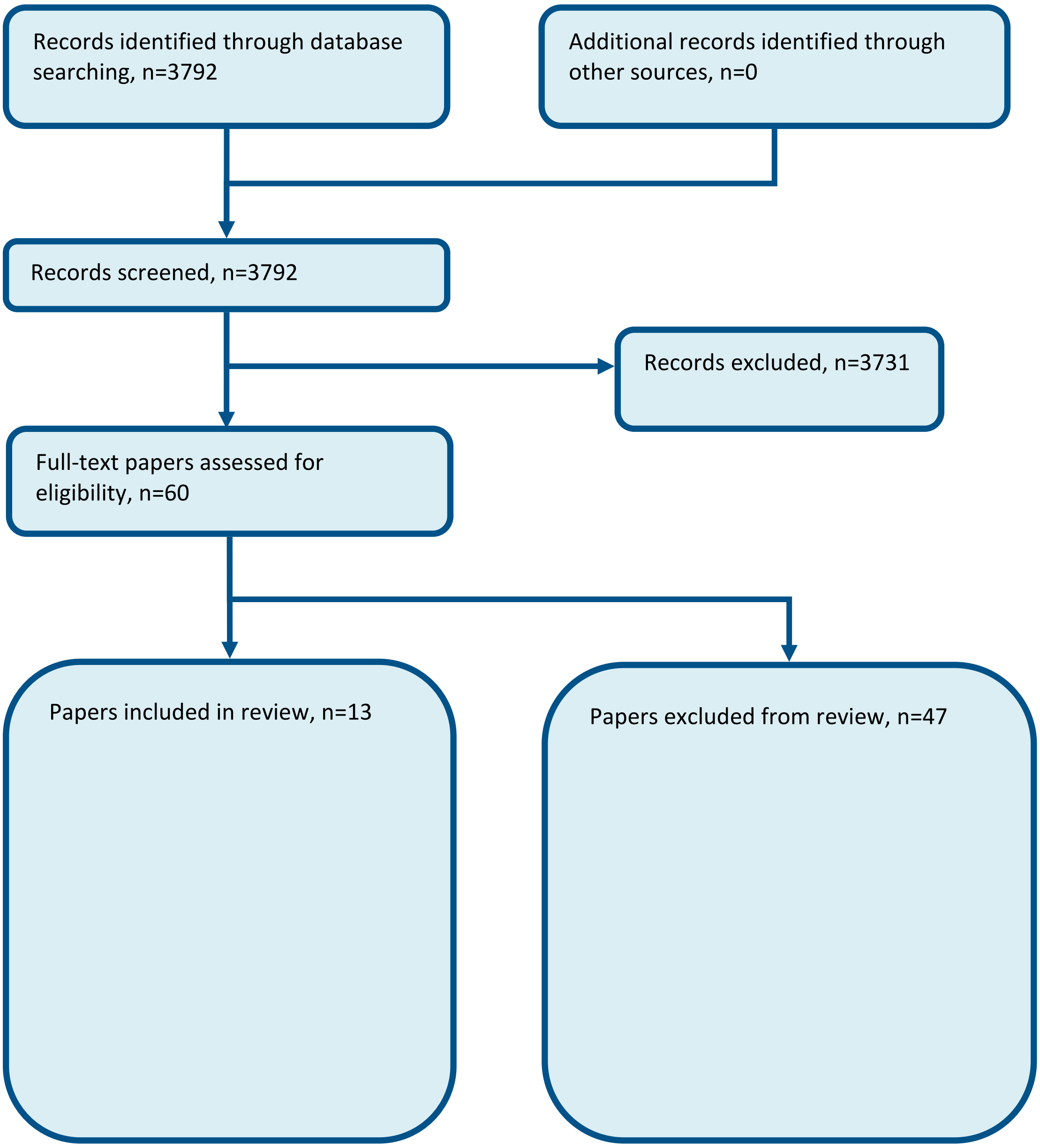
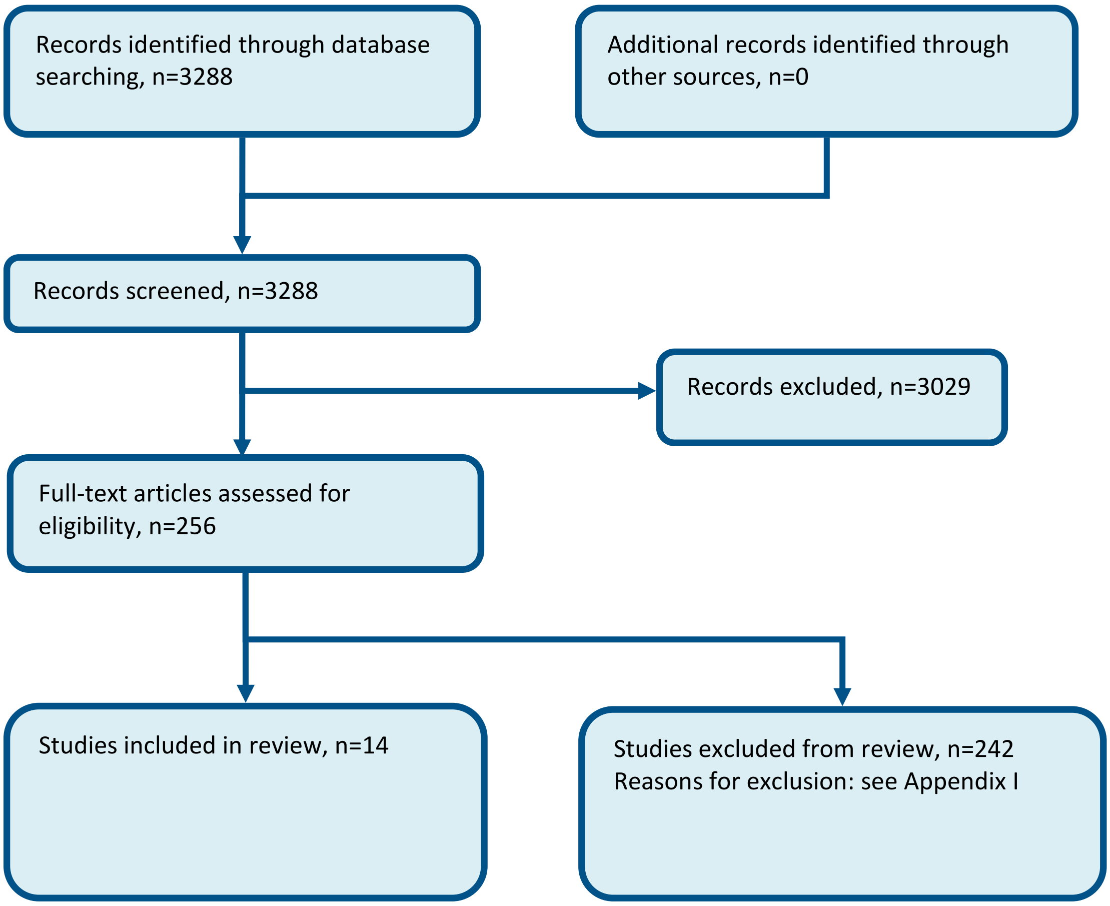
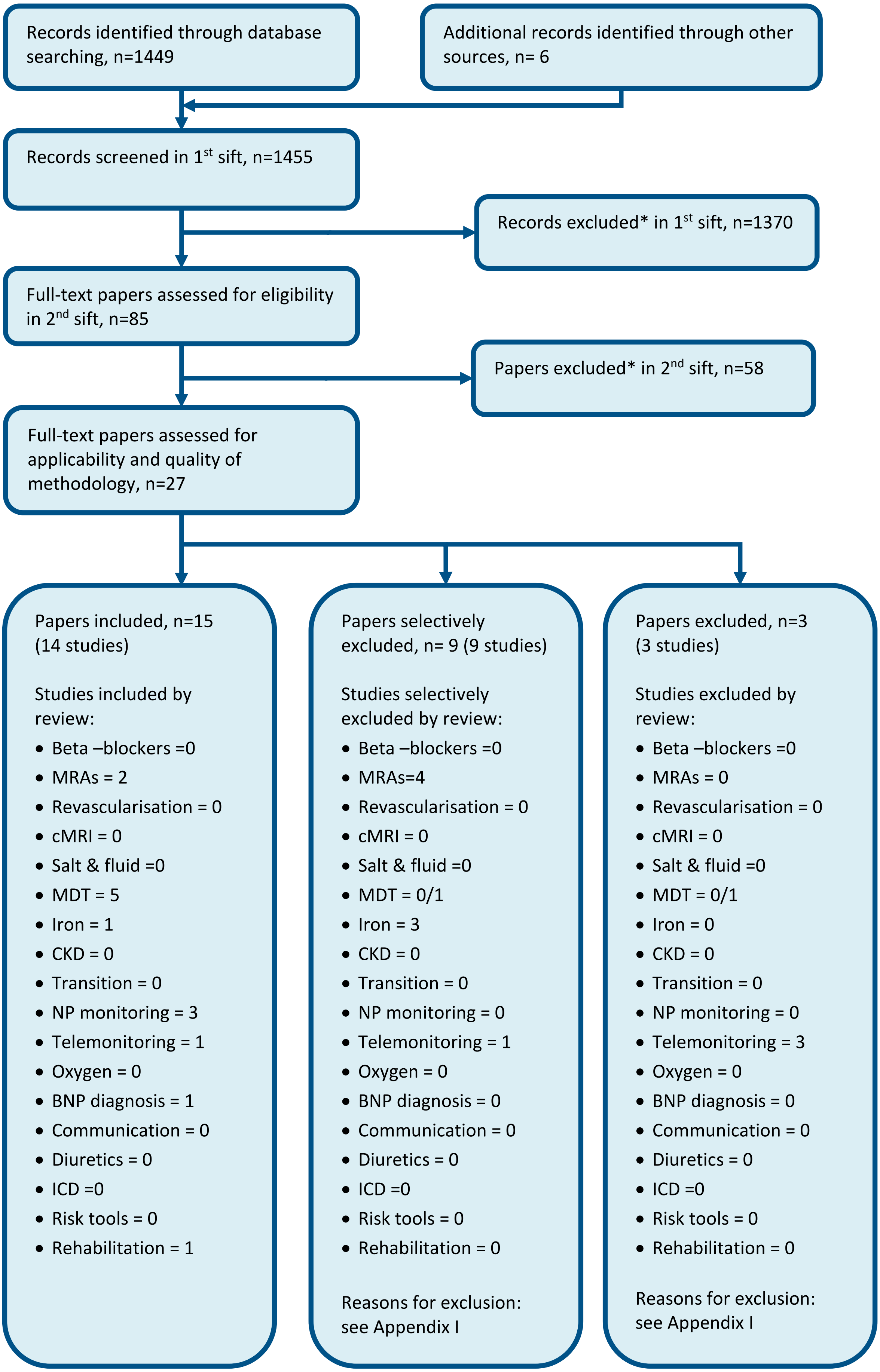


Figure 18: Flow chart of clinical article selection for the review of: In adults with heart failure, which validated risk tools best identify patients with heart failure who are at increased risk of mortality in the short term (up to 1 year)?



Appendix D: Health economic study selection

Figure 19: Flow chart of economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix E: Forest plots

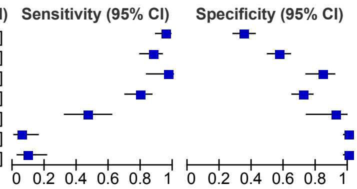
E.1 BNP and NT-proBNP in diagnosing heart failure

E.1.1 General population

E.1.1.1 BNP

Figure 20: Sensitivity and specificity of index test BNP in people with suspected heart failure

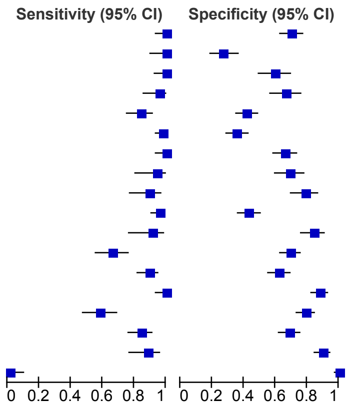
Study	TP	FP	FN	TN	Threshold (pg/mL)	Sensitivity (95% CI)	Specificity (95% CI)
Zaphiriou 2005 - 30	97	129	5	70	30.0	0.95 [0.89, 0.98]	0.35 [0.29, 0.42]
Zaphiriou 2005 - 65	89	85	13	113	65.0	0.87 [0.79, 0.93]	0.57 [0.50, 0.64]
Cowie 1997	30	12	1	63	77.0	0.97 [0.83, 1.00]	0.84 [0.74, 0.91]
Zaphiriou 2005 - 100	80	56	21	143	100.0	0.79 [0.70, 0.87]	0.72 [0.65, 0.78]
O'Shea 2012	23	2	26	23	178.0	0.47 [0.33, 0.62]	0.92 [0.74, 0.99]
Kelder 2011 - Centaur 400	3	0	48	121	400.0	0.06 [0.01, 0.16]	1.00 [0.97, 1.00]
Kelder 2011 - Axsym 400	5	0	46	121	400.0	0.10 [0.03, 0.21]	1.00 [0.97, 1.00]



E.1.1.2 NT-pro BNP (all thresholds)

Figure 21: Sensitivity and specificity of index test NT-pro BNP in people with suspected heart failure

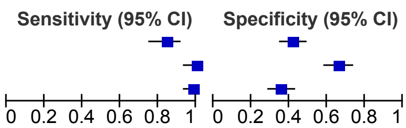
Study	TP	FP	FN	TN	Threshold (pg/mL)	Sensitivity (95% CI)	Specificity (95% CI)
Verdu 2012 - age specific	52	50	0	118		1.00 [0.93, 1.00]	0.70 [0.63, 0.77]
Nielsen 2004 - Women - 67	34	78	0	29	67.0	1.00 [0.90, 1.00]	0.27 [0.19, 0.37]
Nielsen 2004 - Men - 76	47	40	0	59	76.0	1.00 [0.92, 1.00]	0.60 [0.49, 0.69]
Nielsen 2004 - Men - 93	45	33	2	66	93.0	0.96 [0.85, 0.99]	0.67 [0.56, 0.76]
Taylor 2016 - 125	75	125	14	90	125.0	0.84 [0.75, 0.91]	0.42 [0.35, 0.49]
Zaphiriou 2005 - 125	101	128	2	71	125.0	0.98 [0.93, 1.00]	0.36 [0.29, 0.43]
Verdu 2012 - 125	52	57	0	111	125.0	1.00 [0.93, 1.00]	0.66 [0.58, 0.73]
Nielsen 2004 - Women 144	32	33	2	74	144.0	0.94 [0.80, 0.99]	0.69 [0.59, 0.78]
Nielsen 2004 - Men - 152	42	21	5	78	152.0	0.89 [0.77, 0.96]	0.79 [0.69, 0.86]
Zaphiriou 2005 - 166	99	113	4	86	166.0	0.96 [0.90, 0.99]	0.43 [0.36, 0.50]
Nielsen 2004 - Women 220	31	17	3	90	220.0	0.91 [0.76, 0.98]	0.84 [0.76, 0.90]
Taylor 2016 - 280	59	66	30	149	280.0	0.66 [0.55, 0.76]	0.69 [0.63, 0.75]
Zaphiriou 2005 - 280	92	75	11	124	280.0	0.89 [0.82, 0.95]	0.62 [0.55, 0.69]
Verdu 2012 - 280	52	20	0	148	280.0	1.00 [0.93, 1.00]	0.88 [0.82, 0.93]
Taylor 2016 - 400	52	45	37	170	400.0	0.58 [0.47, 0.69]	0.79 [0.73, 0.84]
Zaphiriou 2005 - 400	87	62	16	137	400.0	0.84 [0.76, 0.91]	0.69 [0.62, 0.75]
Verdu 2012 - 400	46	17	6	151	400.0	0.88 [0.77, 0.96]	0.90 [0.84, 0.94]
Kelder 2011 - NT 2000	1	0	50	121	2000.0	0.02 [0.00, 0.10]	1.00 [0.97, 1.00]



E.1.1.3 NT-pro BNP (at a threshold of 125 pg/ml)

Figure 22: Sensitivity and specificity of index test NT-pro BNP in people with suspected heart failure

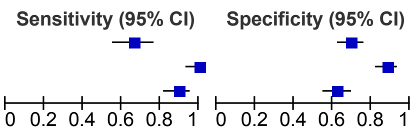
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Taylor 2016 - 125	75	125	14	90	0.84 [0.75, 0.91]	0.42 [0.35, 0.49]
Verdu 2012 - 125	52	57	0	111	1.00 [0.93, 1.00]	0.66 [0.58, 0.73]
Zaphiriou 2005 - 125	101	128	2	71	0.98 [0.93, 1.00]	0.36 [0.29, 0.43]



E.1.1.4 NT-pro BNP (at a threshold of 280 pg/ml)

Figure 23: Sensitivity and specificity of index test NT-pro BNP in people with suspected heart failure

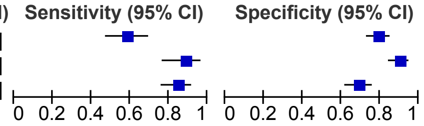
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Taylor 2016 - 280	59	66	30	149	0.66 [0.55, 0.76]	0.69 [0.63, 0.75]
Verdu 2012 - 280	52	20	0	148	1.00 [0.93, 1.00]	0.88 [0.82, 0.93]
Zaphiriou 2005 - 280	92	75	11	124	0.89 [0.82, 0.95]	0.62 [0.55, 0.69]



E.1.1.5 NT-pro BNP (at a threshold of 400 pg/ml)

Figure 24: Sensitivity and specificity of index test NT-pro BNP in people with suspected heart failure

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Taylor 2016 - 400	52	45	37	170	0.58 [0.47, 0.69]	0.79 [0.73, 0.84]
Verdu 2012 - 400	46	17	6	151	0.88 [0.77, 0.96]	0.90 [0.84, 0.94]
Zaphiriou 2005 - 400	87	62	16	137	0.84 [0.76, 0.91]	0.69 [0.62, 0.75]



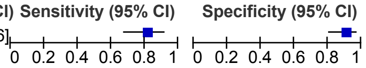
E.1.2 Atrial fibrillation

No included evidence.

E.1.3 Chronic kidney disease

Figure 25: Sensitivity and specificity of index test BNP in people with suspected heart failure and CKD

Study	TP	FP	FN	TN	Threshold (pg/mL)	Sensitivity (95% CI)	Specificity (95% CI)
Yang 2008 - CKD 3, 4	39	6	9	57	410.0	0.81 [0.67, 0.91]	0.90 [0.80, 0.96]

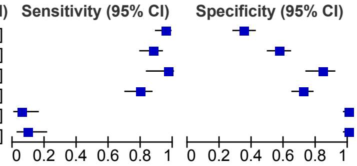


E.1.4 Sensitivity analysis for studies with a low risk of bias

E.1.4.1 BNP

Figure 26: Sensitivity and specificity of BNP in people with suspected heart failure

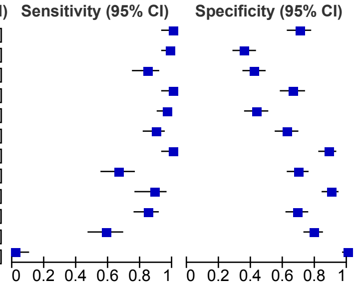
Study	TP	FP	FN	TN	Threshold (pg/mL)	Sensitivity (95% CI)	Specificity (95% CI)
Zaphiriou 2005 - 30	97	129	5	70	30.0	0.95 [0.89, 0.98]	0.35 [0.29, 0.42]
Zaphiriou 2005 - 65	89	85	13	113	65.0	0.87 [0.79, 0.93]	0.57 [0.50, 0.64]
Cowie 1997	30	12	1	63	77.0	0.97 [0.83, 1.00]	0.84 [0.74, 0.91]
Zaphiriou 2005 - 100	80	56	21	143	100.0	0.79 [0.70, 0.87]	0.72 [0.65, 0.78]
Kelder 2011 - Centaur 400	3	0	48	121	400.0	0.06 [0.01, 0.16]	1.00 [0.97, 1.00]
Kelder 2011 - Axsym 400	5	0	46	121	400.0	0.10 [0.03, 0.21]	1.00 [0.97, 1.00]



E.1.4.2 NT-pro BNP

Figure 27: Sensitivity and specificity of NT-pro BNP in people with suspected heart failure

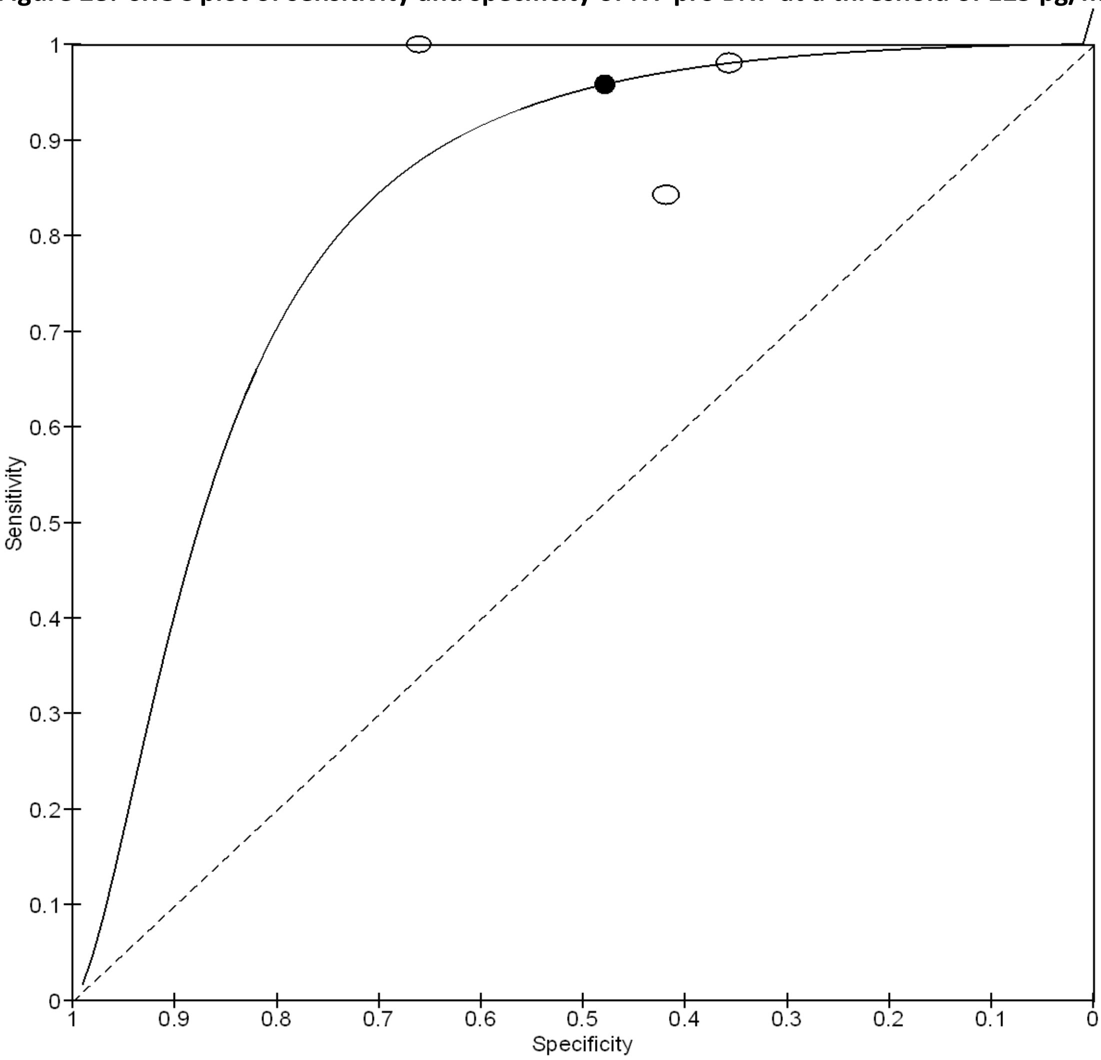
Study	TP	FP	FN	TN	Threshold (pg/mL)	Sensitivity (95% CI)	Specificity (95% CI)
Verdu 2012 - age specific	52	50	0	118		1.00 [0.93, 1.00]	0.70 [0.63, 0.77]
Zaphiriou 2005 - 125	101	128	2	71	125.0	0.98 [0.93, 1.00]	0.36 [0.29, 0.43]
Taylor 2016 - 125	75	125	14	90	125.0	0.84 [0.75, 0.91]	0.42 [0.35, 0.49]
Verdu 2012 - 125	52	57	0	111	125.0	1.00 [0.93, 1.00]	0.66 [0.58, 0.73]
Zaphiriou 2005 - 166	99	113	4	86	166.0	0.96 [0.90, 0.99]	0.43 [0.36, 0.50]
Zaphiriou 2005 - 280	92	75	11	124	280.0	0.89 [0.82, 0.95]	0.62 [0.55, 0.69]
Verdu 2012 - 280	52	20	0	148	280.0	1.00 [0.93, 1.00]	0.88 [0.82, 0.93]
Taylor 2016 - 280	59	66	30	149	280.0	0.66 [0.55, 0.76]	0.69 [0.63, 0.75]
Verdu 2012 - 400	46	17	6	151	400.0	0.88 [0.77, 0.96]	0.90 [0.84, 0.94]
Zaphiriou 2005 - 400	87	62	16	137	400.0	0.84 [0.76, 0.91]	0.69 [0.62, 0.75]
Taylor 2016 - 400	52	45	37	170	400.0	0.58 [0.47, 0.69]	0.79 [0.73, 0.84]
Kelder 2011 - NT 2000	1	0	50	121	2000.0	0.02 [0.00, 0.10]	1.00 [0.97, 1.00]



1 **E.1.5 ROC curve with study results by size**

2 **E.1.5.1 NT-pro BNP (at a threshold of 125 pg/ml)**

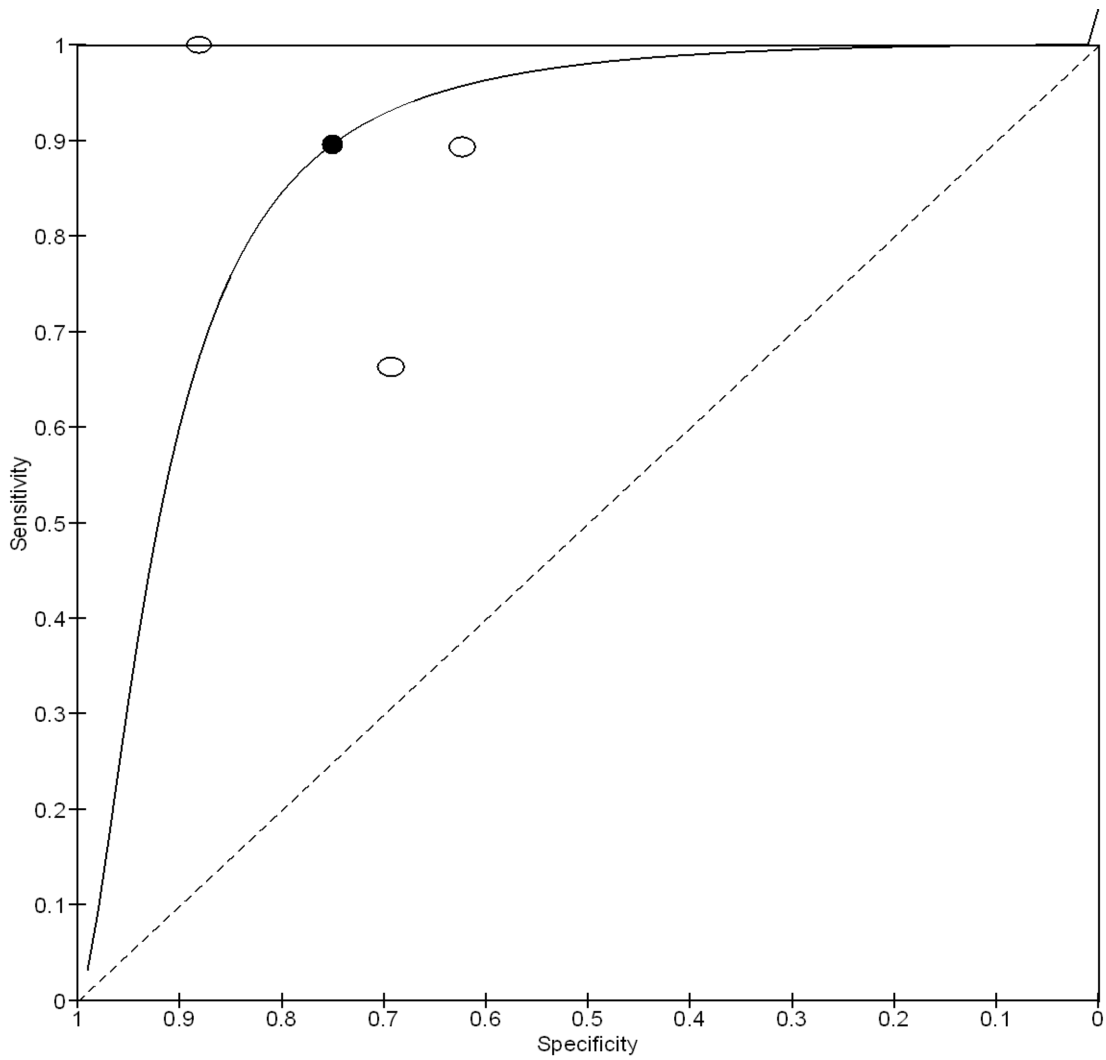
Figure 28: sROC plot of sensitivity and specificity of NT-pro BNP at a threshold of 125 pg/ml



The sROC plot is unable to display the 95% confidence regions due to their magnitude

3 **E.1.5.2 NT-pro BNP (at a threshold of 280 pg/ml)**

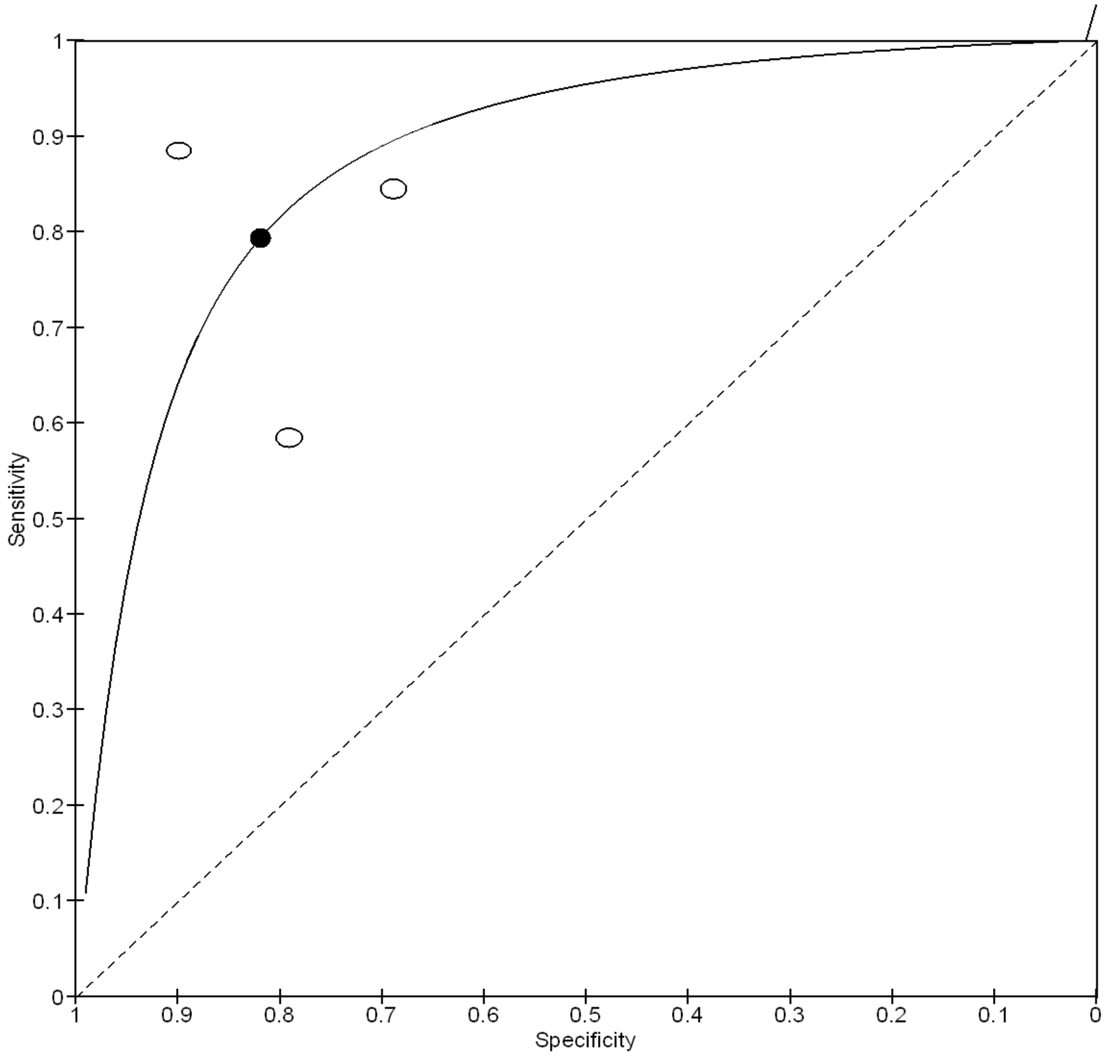
Figure 29: sROC plot of sensitivity and specificity of NT-pro BNP at a threshold of 280 pg/ml



The sROC plot is unable to display the 95% confidence regions due to their magnitude

1 **E.1.5.3 NT-pro BNP (at a threshold of 400 pg/ml)**

Figure 30: sROC plot of sensitivity and specificity of NT-pro BNP at a threshold of 400 pg/ml



The sROC plot is unable to display the 95% confidence regions due to their magnitude

E.2 Cardiac Magnetic Resonance Imaging in heart failure

No clinical evidence was identified.

E.3 Salt and fluid restriction

E.3.1 Programme for low sodium diet compared to Programme for moderate sodium diet for heart failure

Data unsuitable for forest plots.

E.3.2 Programme for fluid restriction compared to Advice on fluid restriction for heart failure

Figure 31: Quality of life (EQ-5D visual analogue scale)

Study or Subgroup	Programme Mean	Programme SD	Programme Total	Advice Mean	Advice SD	Advice Total	Mean Difference IV, Fixed, 95% CI
Miller Reilly 2015	61.82	19.27	11	70.5	18.77	10	-8.68 [-24.96, 7.60]

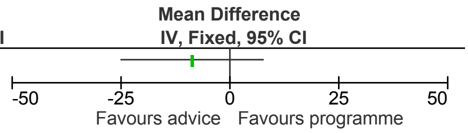
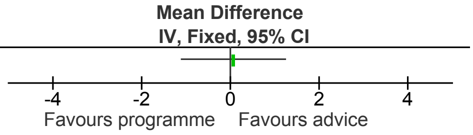


Figure 32: Congestion score (out of 5) at 3 months

Study or Subgroup	Programme Mean	Programme SD	Programme Total	Advice Mean	Advice SD	Advice Total	Mean Difference IV, Fixed, 95% CI
Miller Reilly 2015	1.25	1.6	12	1.18	1.25	11	0.07 [-1.10, 1.24]



E.4 Beta-blockers in people with heart failure and atrial fibrillation

E.4.1 Beta blockers versus placebo in people with CHF and atrial fibrillation

Figure 33: All-cause mortality at 3.3 years

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Bollano 1997 (ANZ)	-1.273	0.879	1.2%	0.28 [0.05, 1.57]
Dargie 1999 (CIBIS II)	-0.0202	0.2174	19.0%	0.98 [0.64, 1.50]
Dargie 2001 (CAPRICORN)	-0.1054	0.3424	7.6%	0.90 [0.46, 1.76]
Domanski 1994 (CIBIS I)	0.131	0.463	4.2%	1.14 [0.46, 2.82]
Flather 2005 (SENIORS)	0.131	0.1744	29.4%	1.14 [0.81, 1.60]
Packer 1996 (US-HF)	0.131	0.3627	6.8%	1.14 [0.56, 2.32]
Packer 2002 (COPERNICUS)	-0.0943	0.2663	12.6%	0.91 [0.54, 1.53]
Tepper 1999 (MERIT-HF)	0.0296	0.2349	16.2%	1.03 [0.65, 1.63]
Waagstein 1993 (MDC)	0	0.5504	3.0%	1.00 [0.34, 2.94]
Total (95% CI)			**100.0%**	**1.02 [0.85, 1.23]**

Heterogeneity: Chi² = 3.08, df = 8 (P = 0.93); I² = 0%
Test for overall effect: Z = 0.20 (P = 0.84)

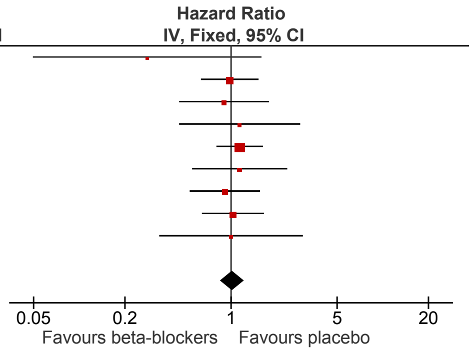


Figure 34: First heart-failure-related hospital admission at 3.3 years

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
Kotecha 2014	-0.0726	0.0948	0.93 [0.77, 1.12]

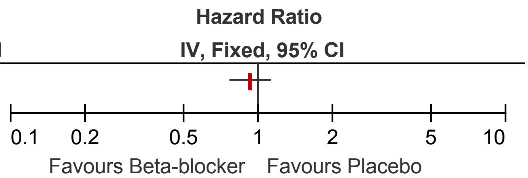
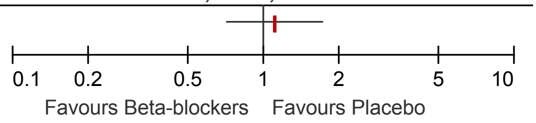


Figure 35: Fatal and non-fatal stroke at 3.3 years

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI
Kotecha 2014	0.1044	0.2231	1.11 [0.72, 1.72]	



E.5 Mineralocorticoid Receptor Antagonists

E.5.1 Mineralocorticoid receptor antagonists in heart failure with preserved ejection fraction

Figure 36: All-cause mortality (time to event)

Study or Subgroup	log[Hazard Ratio]	SE	MRA Total	Placebo Total	Weight	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI
Pitt 2014 (TOPCAT)	-0.0943	0.0852	1722	1723		0.91 [0.77, 1.08]	

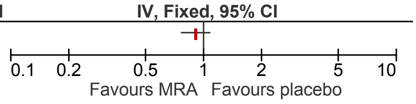


Figure 37: All-cause mortality at 1 year (dichotomous)

Study or Subgroup	MRA Events	MRA Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Edelmann 2013 (ALDO-DHF)	1	205	0	196		7.07 [0.14, 356.74]	

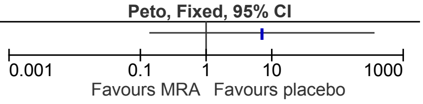


Figure 38: Quality of life (Kansas City) at 1 year

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
Pitt 2014 (TOPCAT)	1.35	0.58		1.35 [0.21, 2.49]	

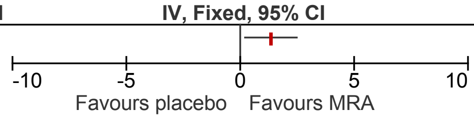


Figure 39: Quality of life (Minnesota) at 1 year

Study or Subgroup	MRA Mean	MRA SD	MRA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
Edelmann 2013 (ALDO-DHF)	21	18.22	204	21	17.86	196		0.00 [-3.54, 3.54]	

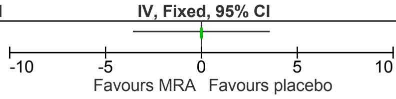


Figure 40: Quality of life (SF-36 Physical Functioning) at 1 year

Study or Subgroup	MRA Mean	MRA SD	MRA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
Edelmann 2013 (ALDO-DHF)	64	25.51	204	66	21.43	196		-2.00 [-6.61, 2.61]	

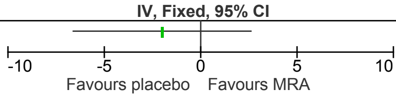


Figure 41: All-cause hospitalisation (count rate)

Study or Subgroup	log[Rate Ratio]	SE	MRA Total	Placebo Total	Weight	Rate Ratio IV, Fixed, 95% CI
Pitt 2014 (TOPCAT)	-0.0619	0.04	1722	1723		0.94 [0.87, 1.02]

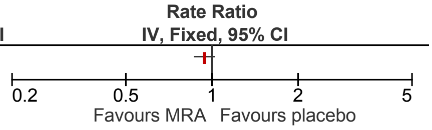


Figure 42: All cause hospitalisation at 1 year (dichotomous)

Study or Subgroup	MRA Events	MRA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Edelmann 2013 (ALDO-DHF)	60	204	50	204		1.20 [0.87, 1.65]

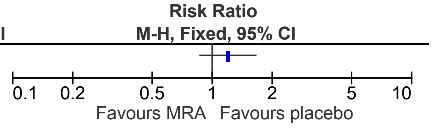


Figure 43: Participants with NYHA class I status at 1 year

Study or Subgroup	MRA Events	MRA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Edelmann 2013 (ALDO-DHF)	8	204	11	196		0.70 [0.29, 1.70]

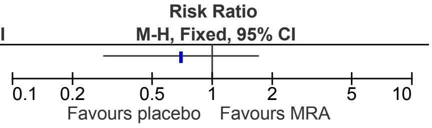


Figure 44: Hyperkalaemia (serum potassium > or ≥ 5.5mL) at 1-3.3 years

Study or Subgroup	MRA Events	MRA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Edelmann 2013 (ALDO-DHF)	4	204	3	196	1.9%	1.28 [0.29, 5.65]
Pitt 2014 (TOPCAT)	322	1722	157	1723	98.1%	2.05 [1.72, 2.45]
Total (95% CI)		**1926**		**1919**	**100.0%**	**2.04 [1.71, 2.43]**
Total events	326		160			
Heterogeneity: Chi² = 0.38, df = 1 (P = 0.54); I² = 0%						
Test for overall effect: Z = 7.86 (P < 0.00001)						

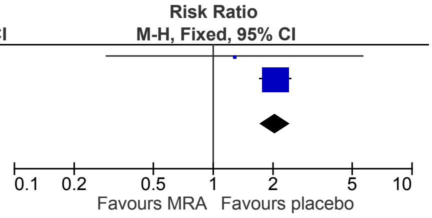


Figure 45: Worsening renal function at 1-3.3 years

Study or Subgroup	MRA Events	MRA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Edelmann 2013 (ALDO-DHF)	77	204	43	196	26.6%	1.72 [1.25, 2.36]
Pitt 2014 (TOPCAT)	176	1722	121	1723	73.4%	1.46 [1.17, 1.82]
Total (95% CI)		**1926**		**1919**	**100.0%**	**1.53 [1.27, 1.83]**
Total events	253		164			
Heterogeneity: Chi² = 0.72, df = 1 (P = 0.39); I² = 0%						
Test for overall effect: Z = 4.54 (P < 0.00001)						

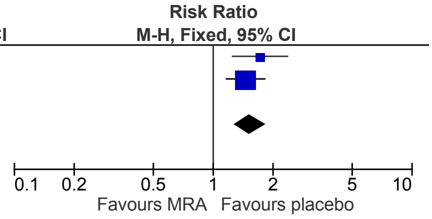
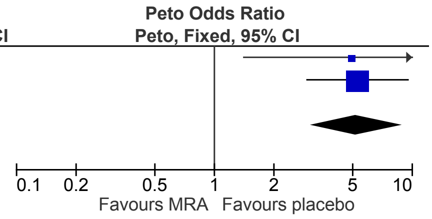


Figure 46: Gynaecomastia at 1-3.3 years

Study or Subgroup	MRA Events	MRA Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Edelmann 2013 (ALDO-DHF)	9	204	1	196	18.0%	4.94 [1.41, 17.30]
Pitt 2014 (TOPCAT)	41	1722	4	1723	82.0%	5.29 [2.94, 9.53]
Total (95% CI)		**1926**		**1919**	**100.0%**	**5.23 [3.07, 8.90]**
Total events	50		5			
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%						
Test for overall effect: Z = 6.09 (P < 0.00001)						



E.5.2 Mineralocorticoid receptor antagonists in heart failure with reduced ejection fraction

Figure 47: All-cause mortality

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Pitt 1999 (RALES)	-0.3567	0.0786	48.8%	0.70 [0.60, 0.82]
Tsutsui 2017 (J-EMPHASIS)	0.571	0.3988	8.5%	1.77 [0.81, 3.87]
Zannad 2011 (EMPHASIS-HF)	-0.2744	0.1039	42.7%	0.76 [0.62, 0.93]
Total (95% CI)			**100.0%**	**0.78 [0.61, 1.00]**

Heterogeneity: Tau² = 0.03; Chi² = 5.34, df = 2 (P = 0.07); I² = 63%
Test for overall effect: Z = 1.93 (P = 0.05)

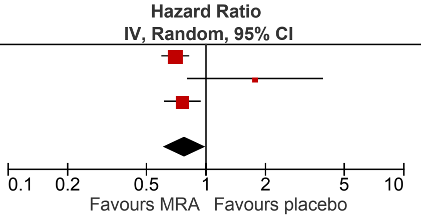


Figure 48: All-cause hospitalisation

Study or Subgroup	log[Rate Ratio]	SE	MRA Total	Placebo Total	Weight	Rate Ratio IV, Random, 95% CI
Pitt 1999 (RALES)	-0.1942	0.04	822	841	54.5%	0.82 [0.76, 0.89]
Zannad 2011 (EMPHASIS-HF)	-0.2942	0.05	1364	1373	45.5%	0.75 [0.68, 0.82]
Total (95% CI)			**2186**	**2214**	**100.0%**	**0.79 [0.71, 0.87]**

Heterogeneity: Tau² = 0.00; Chi² = 2.44, df = 1 (P = 0.12); I² = 59%
Test for overall effect: Z = 4.81 (P < 0.00001)

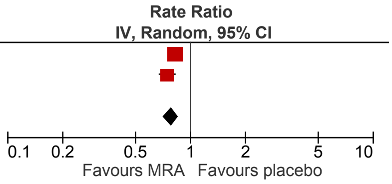


Figure 49: All-cause hospitalisation (dichotomous)

Study or Subgroup	MRA Events	MRA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Tsutsui 2017 (J-EMPHASIS)	45	111	58	110		0.77 [0.58, 1.02]

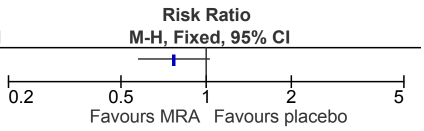


Figure 50: Change in NYHA class - Improved

Study or Subgroup	MRA Events	MRA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Pitt 1999 (RALES)	246	600	208	630	91.2%	1.24 [1.07, 1.44]
Udelson 2010	32	117	19	109	8.8%	1.57 [0.95, 2.60]
Total (95% CI)		**717**		**739**	**100.0%**	**1.27 [1.10, 1.46]**
Total events	278		227			

Heterogeneity: Chi² = 0.77, df = 1 (P = 0.38); I² = 0%
Test for overall effect: Z = 3.32 (P = 0.0009)

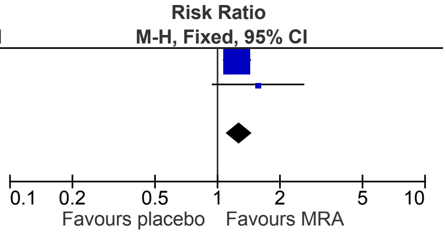


Figure 51: Hyperkalaemia

Study or Subgroup	MRA Events	MRA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Pitt 1999 (RALES)	156	822	47	841	32.2%	3.40 [2.49, 4.64]
Tsutsui 2017 (J-EMPHASIS)	8	111	6	110	14.7%	1.32 [0.47, 3.68]
Udelson 2010	14	117	9	109	19.3%	1.45 [0.65, 3.21]
Zannad 2011 (EMPHASIS-HF)	158	1336	96	1340	33.8%	1.65 [1.30, 2.10]
Total (95% CI)		**2386**		**2400**	**100.0%**	**1.97 [1.18, 3.27]**
Total events	336		158			

Heterogeneity: Tau² = 0.18; Chi² = 14.62, df = 3 (P = 0.002); I² = 79%
Test for overall effect: Z = 2.61 (P = 0.009)

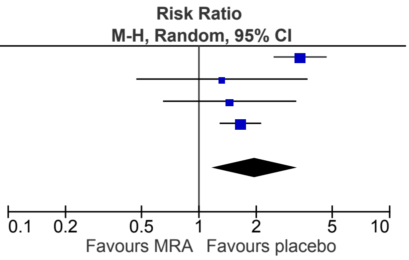


Figure 52: Renal function (change in creatinine (umol/L) – continuous)

Study or Subgroup	MRA Mean	MRA SD	MRA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Zannad 2011 (EMPHASIS-HF)	8	32.7	1360	3.5	35.4	1369		4.50 [1.94, 7.06]

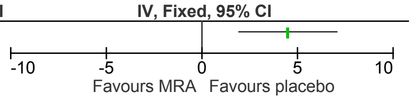


Figure 53: Renal function (change in eGFR (ml/min/173m^2) – continuous)

Study or Subgroup	MRA Mean	MRA SD	MRA Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Zannad 2011 (EMPHASIS-HF)	-3.18	18.4	1364	-1.29	18.2	1373		-1.89 [-3.26, -0.52]

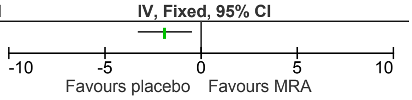


Figure 54: Renal function (creatinine increased - dichotomous)

Study or Subgroup	Experimental Events	Experimental Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Udelson 2010	11	117	6	109		1.71 [0.65, 4.46]

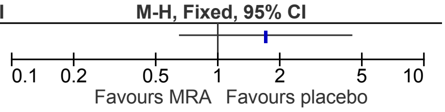


Figure 55 Renal function (30% reduction in eGFR from baseline - dichotomous)

Study or Subgroup	MRA Events	MRA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Pitt 1999 (RALES)	140	822	59	841		2.43 [1.82, 3.24]

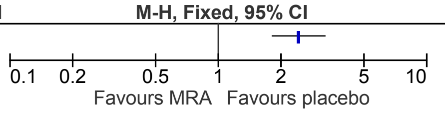


Figure 56: Renal impairment (undefined)

Study or Subgroup	MRA Events	MRA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Tsutsui 2017 (J-EMPHASIS)	5	111	10	110		0.50 [0.18, 1.40]

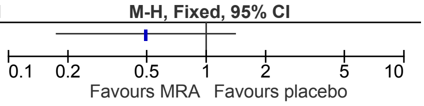


Figure 57: Renal failure

Study or Subgroup	MRA Events	MRA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Zannad 2011 (EMPHASIS-HF)	38	1360	41	1369		0.93 [0.60, 1.44]

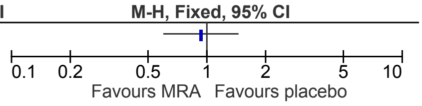


Figure 58: Gynaecomastia (spironolactone)

Study or Subgroup	MRA Events	MRA Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
1.11.1 Spironolactone					
Pitt 1999 (RALES)	55	603	8	614	7.00 [3.36, 14.57]

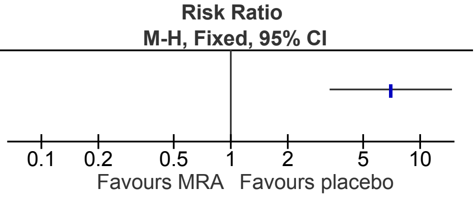


Figure 59: Gynaecomastia (eplerenone)

Study or Subgroup	Experimental Events	Experimental Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.10.1 Eplerenone						
Tsutsui 2017 (J-EMPHASIS)	0	111	0	110		Not estimable
Zannad 2011 (EMPHASIS-HF)	10	1360	14	1369	100.0%	0.72 [0.32, 1.61]
Subtotal (95% CI)		**1471**		**1479**	**100.0%**	**0.72 [0.32, 1.61]**
Total events	10		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.80 (P = 0.42)						

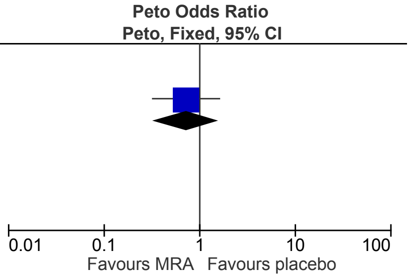
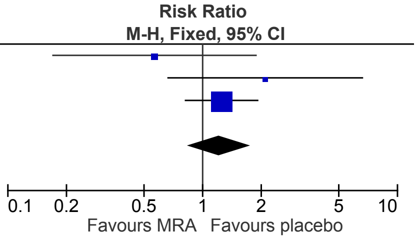


Figure 60: Hypotension

Study or Subgroup	MRA Events	MRA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Tsutsui 2017 (J-EMPHASIS)	4	111	7	110	14.6%	0.57 [0.17, 1.88]
Udelson 2010	9	117	4	109	8.6%	2.10 [0.66, 6.61]
Zannad 2011 (EMPHASIS-HF)	46	1360	37	1369	76.7%	1.25 [0.82, 1.92]
Total (95% CI)		**1588**		**1588**	**100.0%**	**1.22 [0.84, 1.78]**
Total events	59		48			
Heterogeneity: Chi² = 2.44, df = 2 (P = 0.30); I² = 18%						
Test for overall effect: Z = 1.06 (P = 0.29)						



E.6 Iron supplementation for iron deficiency in heart failure

E.6.1 IV iron versus placebo

Figure 61: Mortality

Study or Subgroup	Intravenous iron Events	Intravenous iron Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anker 2009 (FAIR-HF)	5	305	4	154	25.9%	0.63 [0.17, 2.32]
Beck-da-Silva 2013 (IRON-HF)	3	10	1	6	6.1%	1.80 [0.24, 13.63]
Ponikowski 2015 (CONFIRM-HF)	12	150	14	151	68.0%	0.86 [0.41, 1.80]
Toblli 2007	0	30	0	30		Not estimable
Total (95% CI)		**495**		**341**	**100.0%**	**0.86 [0.47, 1.58]**
Total events	20		19			
Heterogeneity: Chi² = 0.73, df = 2 (P = 0.69); I² = 0%						
Test for overall effect: Z = 0.49 (P = 0.63)						

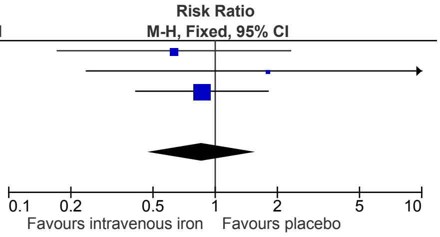


Figure 62: Quality of life – EQ-5D

Study or Subgroup	Intravenous iron Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Anker 2009 (FAIR-HF)	0.066	0.209	304	-0.01	0.224	155	0.08 [0.03, 0.12]

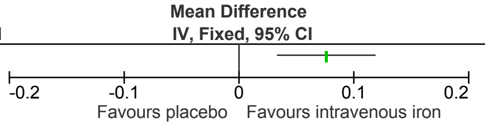


Figure 63: Quality of life – EQ-5D VAS

Study or Subgroup	Intravenous iron Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Anker 2009 (FAIR-HF)	9.1	17.44	304	3.4	19.92	155	45.8%	5.70 [2.00, 9.40]
Ponikowski 2015 (CONFIRM-HF)	7	12.8	114	4.4	12.9	106	54.2%	2.60 [-0.80, 6.00]
Total (95% CI)			**418**			**261**	**100.0%**	**4.02 [1.52, 6.52]**

Heterogeneity: Chi² = 1.46, df = 1 (P = 0.23); I² = 32%
Test for overall effect: Z = 3.15 (P = 0.002)

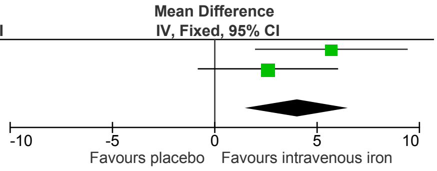


Figure 64: Quality of life – KCCQ

Study or Subgroup	Intravenous iron Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Anker 2009 (FAIR-HF)	12.8	22.67	304	6.2	18.67	155	44.2%	6.60 [2.71, 10.49]
Ponikowski 2015 (CONFIRM-HF)	6.8	13.07	114	2.3	13.13	106	55.8%	4.50 [1.04, 7.96]
Total (95% CI)			**418**			**261**	**100.0%**	**5.43 [2.84, 8.02]**

Heterogeneity: Chi² = 0.62, df = 1 (P = 0.43); I² = 0%
Test for overall effect: Z = 4.11 (P < 0.0001)

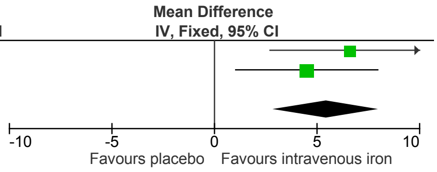


Figure 65: Quality of life – MLWHFQ

Study or Subgroup	Intravenous iron Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Toblli 2007	41	7	20	59	8	20		-18.00 [-22.66, -13.34]

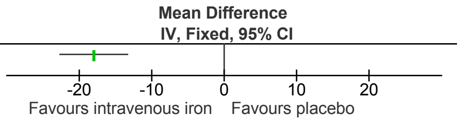


Figure 66: Improvement in NYHA class

Study or Subgroup	Intravenous iron Events	Total	Placebo Events	Total	Risk Ratio M-H, Fixed, 95% CI
Beck-da-Silva 2013 (IRON-HF)	2	10	1	6	1.20 [0.14, 10.58]

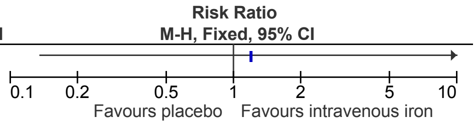


Figure 67: Hospitalisation due to HF

Study or Subgroup	Intravenous iron Events	Total	Placebo Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
Toblli 2007	0	20	5	20	0.11 [0.02, 0.69]

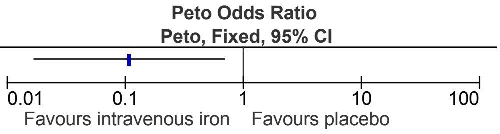


Figure 68: Hospitalisation (all-cause)

Study or Subgroup	log[Rate Ratio]	SE	IV iron Total	Placebo Total	Weight	Rate Ratio IV, Fixed, 95% CI
Anker 2009 (FAIR-HF)	-0.4422	0.1903	305	154	50.0%	0.64 [0.44, 0.93]
Ponikowski 2015 (CONFIRM-HF)	-0.3988	0.1903	150	151	50.0%	0.67 [0.46, 0.97]
Total (95% CI)			**455**	**305**	**100.0%**	**0.66 [0.50, 0.85]**

Heterogeneity: Chi² = 0.03, df = 1 (P = 0.87); I² = 0%
Test for overall effect: Z = 3.12 (P = 0.002)

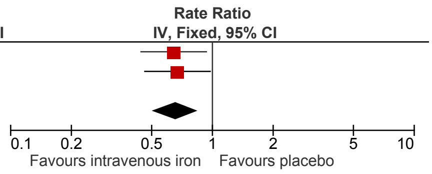


Figure 69: Exercise tolerance – 6MWT distance (m)

Study or Subgroup	Intravenous iron Mean	Intravenous iron SD	Intravenous iron Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Anker 2009 (FAIR-HF)	313	114.6	268	277	115.8	134	36.2%	36.00 [12.07, 59.93]
Ponikowski 2015 (CONFIRM-HF)	14	85.56	125	-22	84.18	121	46.0%	36.00 [14.79, 57.21]
Toblli 2007	240.1	51.2	20	184.5	58.5	20	17.8%	55.60 [21.53, 89.67]
Total (95% CI)			**413**			**275**	**100.0%**	**39.50 [25.11, 53.88]**

Heterogeneity: Chi² = 1.04, df = 2 (P = 0.59); I² = 0%
Test for overall effect: Z = 5.38 (P < 0.00001)

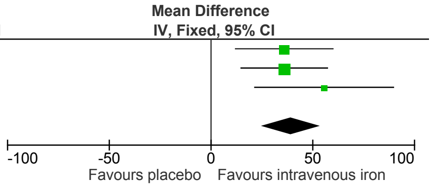


Figure 70: Haemoglobin in anaemic patients, g/dL

Study or Subgroup	Intravenous iron Mean	Intravenous iron SD	Intravenous iron Total	Placebo Mean	Placebo SD	Placebo Total	Mean Difference IV, Fixed, 95% CI
Toblli 2007	11.7	0.6	30	9.6	0.6	30	2.10 [1.80, 2.40]

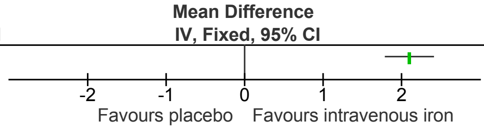


Figure 71: Discontinuation: adverse events

Study or Subgroup	Intravenous iron Events	Intravenous iron Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
Ponikowski 2015 (CONFIRM-HF)	14	152	19	152	0.74 [0.38, 1.42]

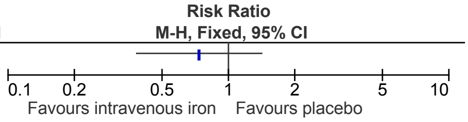


Figure 72: Ischaemic stroke

Study or Subgroup	Intravenous iron Events	Intravenous iron Total	Placebo Events	Placebo Total	Peto Odds Ratio Peto, Fixed, 95% CI
Anker 2009 (FAIR-HF)	2	305	0	154	4.52 [0.24, 85.34]

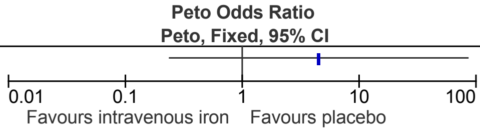


Figure 73: Drug related vascular disorders

Study or Subgroup	Intravenous iron Events	Intravenous iron Total	Placebo Events	Placebo Total	Peto Odds Ratio Peto, Fixed, 95% CI
Ponikowski 2015 (CONFIRM-HF)	1	152	1	152	1.00 [0.06, 16.06]

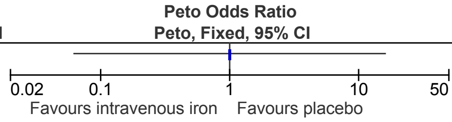


Figure 74: Gastrointestinal disorders

Study or Subgroup	Intravenous iron Events	Intravenous iron Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
Anker 2009 (FAIR-HF)	24	305	5	154	2.42 [0.94, 6.23]

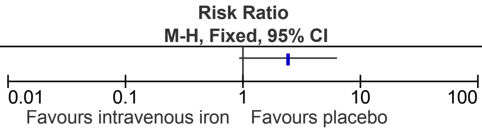


Figure 75: Drug related gastrointestinal disorders

Study or Subgroup	Intravenous iron Events	Intravenous iron Total	Placebo Events	Placebo Total	Peto Odds Ratio Peto, Fixed, 95% CI
Ponikowski 2015 (CONFIRM-HF)	2	152	0	152	7.44 [0.46, 119.46]

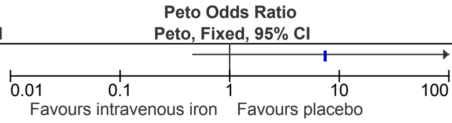


Figure 76: Nausea

Study or Subgroup	Intravenous iron Events	Intravenous iron Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
Toblli 2007	1	30	1	30	1.00 [0.07, 15.26]

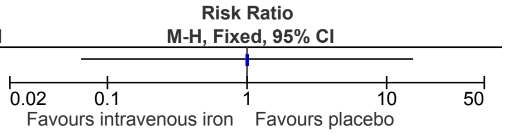


Figure 77: Abdominal pain

Study or Subgroup	Intravenous iron Events	Intravenous iron Total	Placebo Events	Placebo Total	Peto Odds Ratio Peto, Fixed, 95% CI
Toblli 2007	0	30	1	30	0.14 [0.00, 6.82]

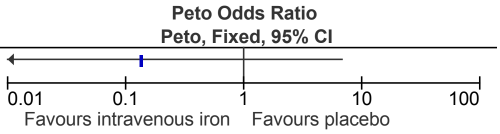
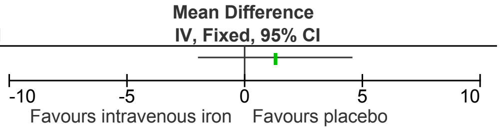


Figure 78: Systolic blood pressure, mmHg

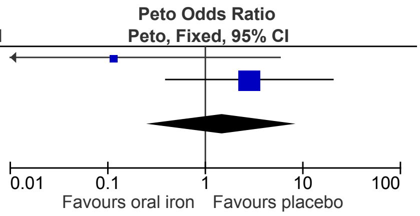
Study or Subgroup	Intravenous iron Mean	Intravenous iron SD	Intravenous iron Total	Placebo Mean	Placebo SD	Placebo Total	Mean Difference IV, Fixed, 95% CI
Toblli 2007	135.8	5.9	30	134.5	6.9	30	1.30 [-1.95, 4.55]



E.6.2 Oral iron versus placebo

Figure 20: Mortality

Study or Subgroup	Oral iron Events	Oral iron Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Beck-da-Silva 2013 (IRON-HF)	0	7	1	6	20.1%	0.11 [0.00, 5.84]
Lewis 2017 (IRONOUT HF)	3	111	1	114	79.9%	2.83 [0.39, 20.37]
Total (95% CI)		**118**		**120**	**100.0%**	**1.48 [0.25, 8.66]**
Total events	3		2			
Heterogeneity: Chi² = 2.04, df = 1 (P = 0.15); I² = 51%						
Test for overall effect: Z = 0.44 (P = 0.66)						



Unable to analyse using random effects model as peto odds method is being used.

Figure 21: Improvement in NYHA class

Study or Subgroup	Oral iron Events	Oral iron Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
Beck-da-Silva 2013 (IRON-HF)	6	7	1	6	5.14 [0.84, 31.57]

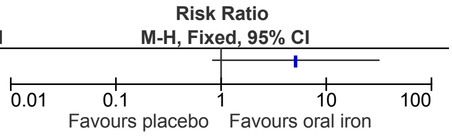


Figure 22: Permanent study drug discontinuation

Study or Subgroup	Oral iron Events	Oral iron Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
Lewis 2017 (IRONOUT HF)	15	111	17	114	0.91 [0.48, 1.72]

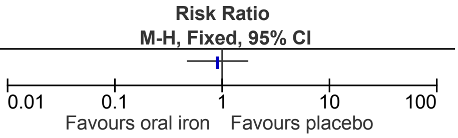


Figure 23: Adverse events (not described)

Study or Subgroup	Oral iron Events	Oral iron Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
Lewis 2017 (IRONOUT HF)	39	111	45	114	0.89 [0.63, 1.25]

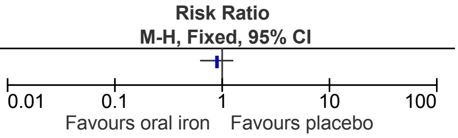
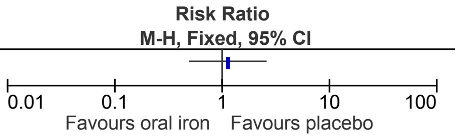


Figure 79: Serious adverse events (not described)

Study or Subgroup	Oral iron Events	Oral iron Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
Lewis 2017 (IRONOUT HF)	11	111	10	114	1.13 [0.50, 2.55]



E.6.3 Intravenous iron versus oral iron

Figure 23: Mortality

Study or Subgroup	Intravenous iron Events	Intravenous iron Total	Oral iron Events	Oral iron Total	Peto Odds Ratio Peto, Fixed, 95% CI
Beck-da-Silva 2013 (IRON-HF)	2	10	0	7	6.13 [0.33, 112.36]

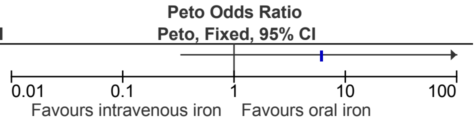
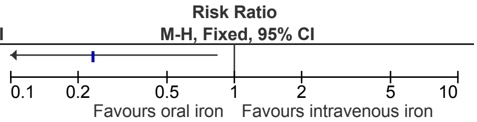


Figure 24: Improvement in NYHA class

Study or Subgroup	Intravenous iron Events	Intravenous iron Total	Oral iron Events	Oral iron Total	Risk Ratio M-H, Fixed, 95% CI
Beck-da-Silva 2013 (IRON-HF)	2	10	6	7	0.23 [0.07, 0.84]



E.7 Pharmacological treatment for heart failure in people with heart failure and chronic kidney disease

E.7.1 ACE inhibitors

E.7.1.1 ACE inhibitor versus placebo

Figure 80: All-cause Mortality (time to event)

Study or Subgroup	log[Hazard Ratio]	SE	ACE-I Total	Placebo Total	Hazard Ratio IV, Fixed, 95% CI
1.1.1 CKD stages 3-4					
Bowling 2013 (SOLVD-treat trial)	-0.1278	0.0953	498	538	0.88 [0.73, 1.06]
1.1.2 CKD stage 3b and 4 only					
Bowling 2013 (SOLVD-treat trial)	-0.2744	0.1744	134	134	0.76 [0.54, 1.07]

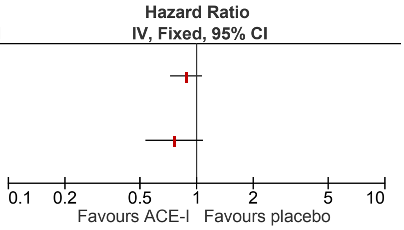


Figure 81: All-cause Hospitalisation (time to event)

Study or Subgroup	log[Hazard Ratio]	SE	ACE-I Total	Placebo Total	Hazard Ratio IV, Fixed, 95% CI
1.2.1 CKD stages 3-4					
Bowling 2013 (SOLVD-treat trial)	-0.1278	0.0953	498	538	0.88 [0.73, 1.06]

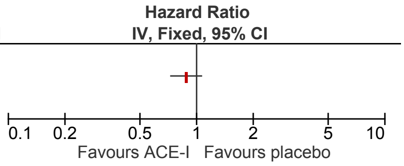


Figure 82: Renal function – change in serum creatinine umol/l (at 12 months)

Study or Subgroup	ACE-I Mean	ACE-I SD	ACE-I Total	Placebo Mean	Placebo SD	Placebo Total	Mean Difference IV, Fixed, 95% CI
1.3.1 CKD stages 3-4							
Bowling 2013 (SOLVD-treat trial)	0.04	0.28	466	-0.02	0.28	501	0.06 [0.02, 0.10]

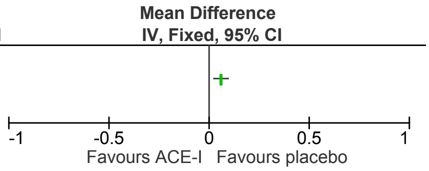
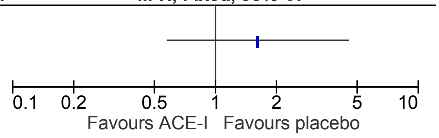


Figure 83: Adverse event – Hyperkalaemia, patients with K>5.5mmol/l (during study)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Risk Ratio M-H, Fixed, 95% CI
1.4.1 CKD stages 3-4					
Bowling 2013 (SOLVD-treat trial)	9	467	6	503	1.62 [0.58, 4.50]



E.7.1.2 ACE inhibitor dose comparison: High (Lisinopril 32.5-35mg) versus Low (Lisinopril 2.5-5mg)

Figure 84: All-cause Mortality (time to event)

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
2.1.1 CKD stages 3b-4			
Ryden 2000 (ATLAS trial)	0.0208	0.0876	1.02 [0.86, 1.21]

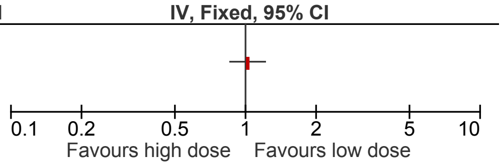


Figure 85: All-cause Mortality or All-cause Hospitalisation (time to event)

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
2.2.1 CKD stages 3b-4			
Ryden 2000 (ATLAS trial)	0.0178	0.0686	1.02 [0.89, 1.16]

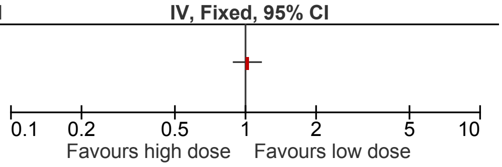
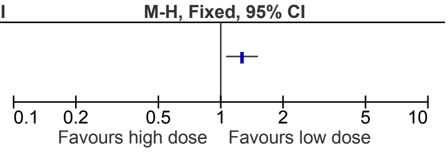


Figure 86: Adverse event – Renal dysfunction or hyperkalaemia (during study)

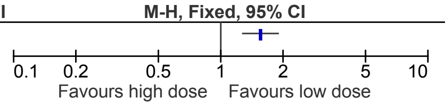
Study or Subgroup	High dose ACE-I Events	High dose ACE-I Total	Low dose ACE-I Events	Low dose ACE-I Total	Risk Ratio M-H, Fixed, 95% CI
2.3.1 CKD stages 3b-4					
Ryden 2000 (ATLAS trial)	199	494	157	494	1.27 [1.07, 1.50]



Nb Numbers in each arm estimated from total with CKD 3b-4

Figure 87: Adverse event – Hypotension or dizziness (during study)

Study or Subgroup	High dose ACE-I Events	High dose ACE-I Total	Low dose ACE-I Events	Low dose ACE-I Total	Risk Ratio M-H, Fixed, 95% CI
Ryden 2000 (ATLAS trial)	182	494	117	494	1.56 [1.28, 1.89]



Nb Numbers in each arm estimated from total with CKD 3b-4

E.7.2 Angiotensin Receptor Antagonist (ARB)

E.7.2.1 ARB versus placebo

Figure 88: All-cause Mortality (time to event)

Study or Subgroup	log[Hazard Ratio]	SE	ARB Total	Placebo Total	Hazard Ratio IV, Fixed, 95% CI
3.1.1 CKD class 3b-4					
Anand 2009 (Val-HeFT)	0.01	0.088	1478	1439	1.01 [0.85, 1.20]

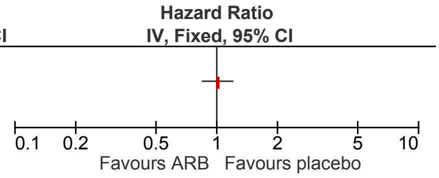


Figure 89: Cardiovascular Death or HF Admission (time to event)

Study or Subgroup	log[Hazard Ratio]	SE	ARB Total	Placebo Total	Hazard Ratio IV, Fixed, 95% CI
3.2.1 CKD class 3b-4					
Desai 2007 (CHARM-Overall trial)	-0.0834	0.0777	84	70	0.92 [0.79, 1.07]

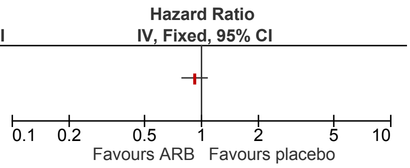


Figure 90: "Morbid Event" (time to event)

Study or Subgroup	log[Hazard Ratio]	SE	ARB Total	Placebo Total	Hazard Ratio IV, Fixed, 95% CI
3.3.1 CKD class 3b-4					
Anand 2009 (Val-HeFT)	-0.1508	0.0767	1476	1441	0.86 [0.74, 1.00]

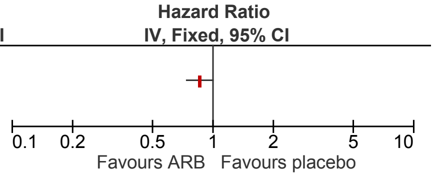


Figure 91: Renal function – change in eGFR (at 12 months)

Study or Subgroup	ARB Mean	ARB SD	ARB Total	Placebo Mean	Placebo SD	Placebo Total	Mean Difference IV, Fixed, 95% CI
3.4.1 CKD class 3b-4							
Anand 2009 (Val-HeFT)	-4.8	9.9725	1105	-1.2	6.5544	1074	-3.60 [-4.31, -2.89]

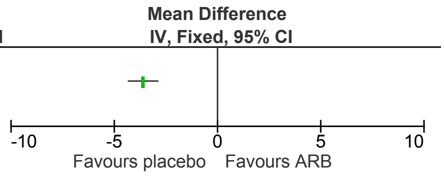


Figure 92: Adverse event – progression to dialysis (during study)

Study or Subgroup	ARB Events	ARB Total	Placebo Events	Placebo Total	Peto Odds Ratio Peto, Fixed, 95% CI
3.5.1 CKD class 3b-4					
Anand 2009 (Val-HeFT)	0	1476	0	1435	Not estimable

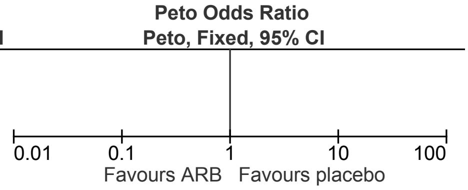
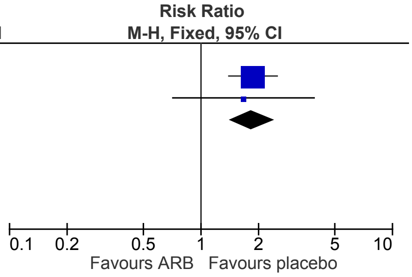


Figure 93: Adverse event – hyperkalaemia (during study)

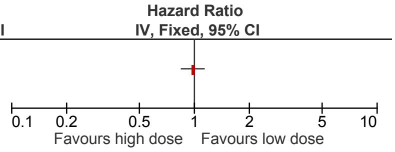
Study or Subgroup	ARB Events	ARB Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.6.1 CKD class 3b-4						
Anand 2009 (Val-HeFT)	125	1476	65	1435	89.6%	1.87 [1.40, 2.50]
Desai 2007 (CHARM-Overall trial)	14	84	7	70	10.4%	1.67 [0.71, 3.90]
Subtotal (95% CI)		**1560**		**1505**	**100.0%**	**1.85 [1.40, 2.43]**
Total events	139		72			
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.80); I² = 0%						
Test for overall effect: Z = 4.38 (P < 0.0001)						



E.7.2.2 ARB Dose Comparison: High (Losartan 150mg/day) versus Low (Losartan 50mg/day)

Figure 94: Death or HF hospitalisation (time to event)

Study or Subgroup	log[Hazard Ratio]	SE	ARB high dose Total	ARB low dose Total	Hazard Ratio IV, Fixed, 95% CI
4.1.1 CKD class 3a/b					
Konstam 2009 (HEAAL trial)	-0.0202	0.0726	495	450	0.98 [0.85, 1.13]



E.7.3 Beta-blockers

E.7.3.1 Beta-blockers versus placebo

Figure 95: All-Cause Mortality (time to event), strata CKD class 3a and class 3-4

Study or Subgroup	log[Hazard Ratio]	SE	Beta-blocker Total	Placebo Total	Weight	Hazard Ratio IV, Fixed, 95% CI
5.1.1 CKD class 3a						
Castagno 2010 (CIBIS-II) stratum 3a	-0.3711	0.2069	361	308	50.9%	0.69 [0.46, 1.04]
Ghali 2009 (MERIT-HF) stratum 3a	-0.3857	0.2106	466	510	49.1%	0.68 [0.45, 1.03]
Subtotal (95% CI)			**827**	**818**	**100.0%**	**0.69 [0.51, 0.91]**
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.96); I² = 0%						
Test for overall effect: Z = 2.56 (P = 0.01)						
5.1.3 CKD class 3-4						
Cohen-Solal 2009 (SENIORS trial)	-0.2744	0.1558	348	356	100.0%	0.76 [0.56, 1.03]
Subtotal (95% CI)			**348**	**356**	**100.0%**	**0.76 [0.56, 1.03]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.76 (P = 0.08)						

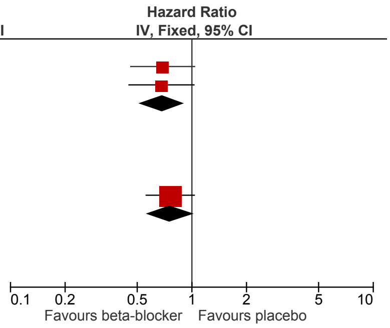


Figure 96: All-Cause Mortality (time to event), stratum CKD class 3b-4

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
5.2.2 CKD class 3b-4				
Castagno 2010 (CIBIS-II) stratum 3b/4	-0.3425	0.1997	54.0%	0.71 [0.48, 1.05]
Ghali 2009 (MERIT-HF) stratum 3b/4	-0.8916	0.2524	46.0%	0.41 [0.25, 0.67]
Subtotal (95% CI)			**100.0%**	**0.55 [0.32, 0.94]**
Heterogeneity: Tau² = 0.10; Chi² = 2.91, df = 1 (P = 0.09); I² = 66%				
Test for overall effect: Z = 2.18 (P = 0.03)				

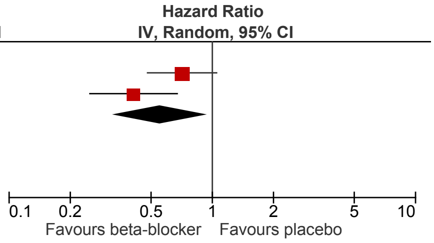


Figure 97: Death or Hospitalisation (time to event)

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
5.2.1 CKD class 3a			
Castagno 2010 (CIBIS-II) stratum 3a	-0.3285	0.1192	0.72 [0.57, 0.91]
5.2.2 CKD class 3b-4			
Castagno 2010 (CIBIS-II) stratum 3b/4	-0.1985	0.1264	0.82 [0.64, 1.05]

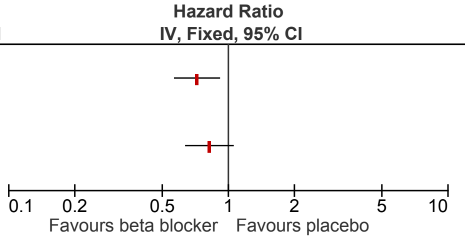


Figure 98: All-cause Hospitalisation (time to event)

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
5.3.1 CKD class 3a			
Ghali 2009 (MERIT-HF) stratum 3a	-0.1054	0.1068	0.90 [0.73, 1.11]
5.3.2 CKD class 3b-4			
Ghali 2009 (MERIT-HF) stratum 3b/4	-0.4943	0.133	0.61 [0.47, 0.79]

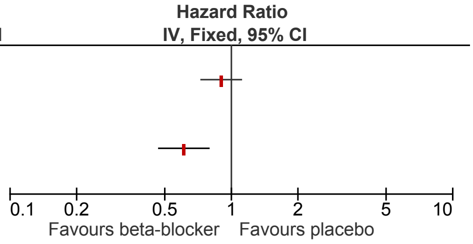


Figure 99: Hospitalisation for Cardiovascular dx (time to event)

Study or Subgroup	log[Hazard Ratio]	SE	Beta-blocker Total	Placebo Total	Hazard Ratio IV, Fixed, 95% CI
5.4.1 CKD class 3-4					
Cohen-Solal 2009 (SENIORS trial)	-0.0726	0.145	348	356	0.93 [0.70, 1.24]

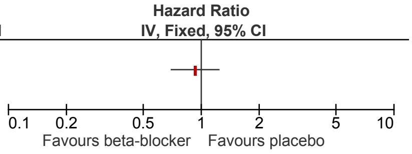


Figure 100: Hospitalisation for Heart Failure (time to event)

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
5.5.1 CKD class 3a			
Castagno 2010 (CIBIS-II) stratum 3a	-0.4155	0.1954	0.66 [0.45, 0.97]
5.5.2 CKD class 3b-4			
Castagno 2010 (CIBIS-II) stratum 3b/4	-0.2744	0.2035	0.76 [0.51, 1.13]

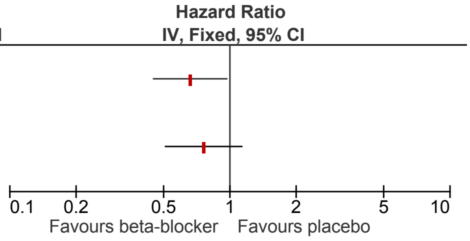


Figure 101: Adverse event – renal failure (not defined) (during study)

Study or Subgroup	Beta-blocker Events	Beta-blocker Total	Placebo Events	Placebo Total	Peto Odds Ratio Peto, Fixed, 95% CI
5.6.1 CKD class 3-4					
Cohen-Solal 2009 (SENIORS trial)	0	440	0	446	Not estimable

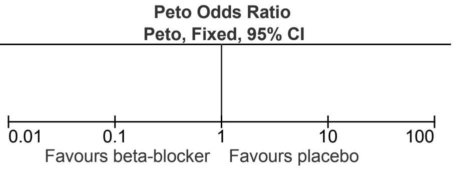


Figure 102: Adverse event – bradycardia (during study)

Study or Subgroup	Beta-blocker Events	Beta-blocker Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
5.8.1 CKD class 3-4					
Cohen-Solal 2009 (SENIORS trial)	12	440	9	446	1.35 [0.58, 3.18]

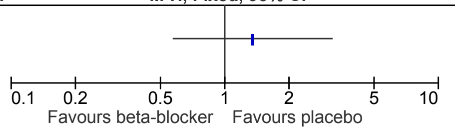
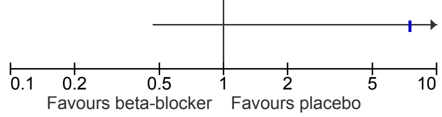


Figure 103: Adverse event – hypotension (during study)

Study or Subgroup	Beta-blocker Events	Beta-blocker Total	Placebo Events	Placebo Total	Peto Odds Ratio Peto, Fixed, 95% CI
5.9.1 CKD class 3-4					
Cohen-Solal 2009 (SENIORS trial)	2	440	0	446	7.51 [0.47, 120.22]



E.7.4 Digoxin

E.7.4.1 Digoxin vs placebo

Figure 104: All Cause Mortality (time to event)

Study or Subgroup	log[Hazard Ratio]	SE	Digoxin Total	Placebo Total	Hazard Ratio IV, Fixed, 95% CI
6.1.1 CKD class 3a/b					
Shlipak 2004 (DIG trial) stratum 3a	-0.0513	0.0567	1468	1471	0.95 [0.85, 1.06]
6.1.2 CKD class 4-5					
Shlipak 2004 (DIG trial) stratum 3b/4	-0.0726	0.1828	102	116	0.93 [0.65, 1.33]

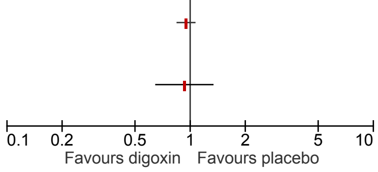
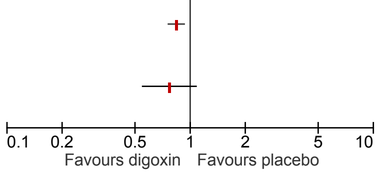


Figure 105: Death or Hospitalisation (time to event)

Study or Subgroup	log[Hazard Ratio]	SE	Digoxin Total	Placebo Total	Hazard Ratio IV, Fixed, 95% CI
6.2.1 CKD class 3a/b					
Shlipak 2004 (DIG trial) stratum 3a	-0.1744	0.0511	1468	1471	0.84 [0.76, 0.93]
6.2.2 CKD class 4-5					
Shlipak 2004 (DIG trial) stratum 3b/4	-0.2614	0.1717	102	116	0.77 [0.55, 1.08]



E.7.5 Ivabradine

E.7.5.1 Ivabradine vs Placebo

Figure 106: Renal function: change in eGFR (at 2 years)

Study or Subgroup	Ivabradine Mean	Ivabradine SD	Ivabradine Total	Placebo Mean	Placebo SD	Placebo Total	Mean Difference IV, Fixed, 95% CI
7.1.1 CKD class 3a/b							
Voors 2014 (SHIFT trial)	53.9	17.3	437	53.7	15.7	428	0.20 [-2.00, 2.40]

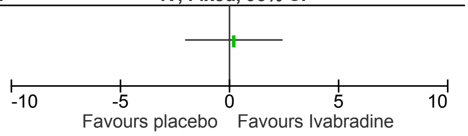


Figure 107: Adverse event – renal failure (not defined) (during study)

Study or Subgroup	Ivabradine Events	Ivabradine Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
7.2.1 CKD stage 3a/b					
Voors 2014 (SHIFT trial)	79	780	85	799	0.95 [0.71, 1.27]

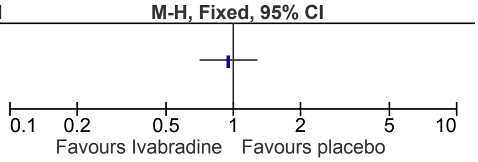


Figure 108: Adverse event – hyperkalaemia (during study)

Study or Subgroup	Ivabradine Events	Ivabradine Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
7.3.1 CKD class 3a/b					
Voors 2014 (SHIFT trial)	14	780	27	799	0.53 [0.28, 1.01]

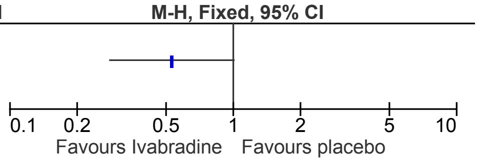
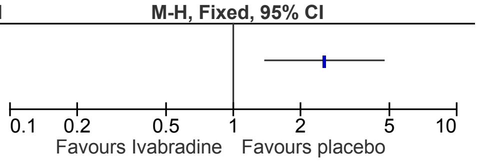


Figure 109: Adverse event – symptomatic bradycardia (during study)

Study or Subgroup	Ivabradine Events	Ivabradine Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
7.4.1 CKD class 3a/b					
Voors 2014 (SHIFT trial)	35	780	14	799	2.56 [1.39, 4.72]



E.7.6 Mineralocorticoid Receptor Antagonist (MRA)

E.7.6.1 MRA vs Placebo

Figure 110: All-cause Mortality (during study)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Risk Ratio M-H, Fixed, 95% CI
8.1.1 CKD class 3a/b					
Pitt 1999 (RALES trial)	32	390	48	402	0.69 [0.45, 1.05]

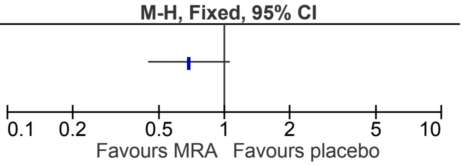


Figure 111: Cardiovascular Mortality or HF Hospitalisation (during study)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Risk Ratio M-H, Fixed, 95% CI
8.2.1 CKD class 3a/b					
Eschalier 2013 (EMPHASIS-HF)	107	439	163	473	0.71 [0.58, 0.87]

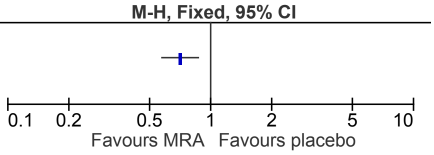


Figure 112: HF hospitalisation (during study)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Risk Ratio M-H, Fixed, 95% CI
8.3.1 CKD class 3a/b					
Pitt 1999 (RALES trial)	30	390	44	402	0.70 [0.45, 1.09]

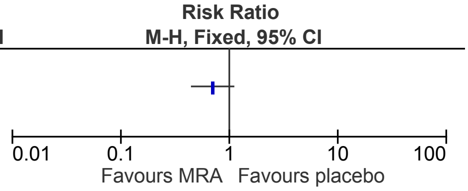


Figure 113: Renal function: change in eGFR (at 2 years)

Study or Subgroup	MRA Mean	MRA SD	MRA Total	Placebo Mean	Placebo SD	Placebo Total	Mean Difference IV, Fixed, 95% CI
8.4.1 CKD class 3a/b							
Eschalier 2013 (EMPHASIS-HF)	2.04	17	422	4.15	14.9	461	-2.11 [-4.23, 0.01]

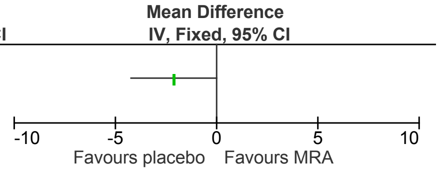
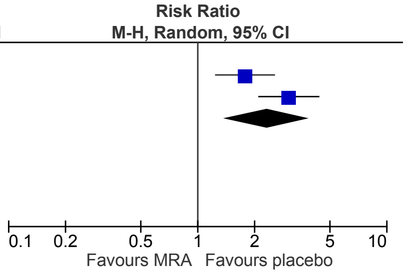


Figure 114: Adverse event – hyperkalaemia (during study)

Study or Subgroup	MRA Events	MRA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
8.5.1 CKD class 3a/b						
Eschalier 2013 (EMPHASIS-HF)	70	422	43	461	50.2%	1.78 [1.25, 2.54]
Pitt 1999 (RALES trial)	100	390	34	402	49.8%	3.03 [2.11, 4.36]
Subtotal (95% CI)		**812**		**863**	**100.0%**	**2.32 [1.37, 3.91]**
Total events	170		77			

Heterogeneity: Tau² = 0.11; Chi² = 4.23, df = 1 (P = 0.04); I² = 76%
Test for overall effect: Z = 3.15 (P = 0.002)



E.8 Coronary revascularisation

E.8.1 CABG + medical therapy versus medical therapy alone

Figure 115: All-cause mortality at 9.8 years

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
STICH 2011	-0.2231	0.0755	0.80 [0.69, 0.93]

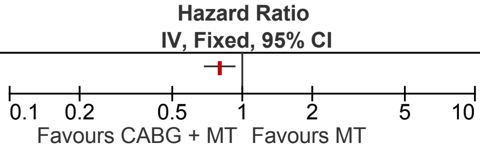


Figure 116: All-cause mortality at 30 days

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
STICH 2011	1.1378	0.435	3.12 [1.33, 7.32]

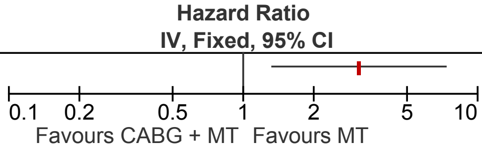


Figure 117: Quality of life – EQ-5D

Study or Subgroup	Mean Difference	SE	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
STICH 2011	0.052	0.0173	0.05 [0.02, 0.09]	

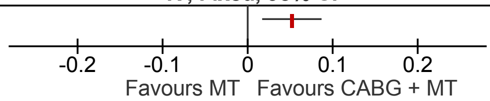


Figure 118: Quality of life – EQ-5D-VAS

Study or Subgroup	Mean Difference	SE	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
STICH 2011	5.9	1.3776	5.90 [3.20, 8.60]	

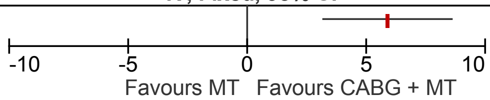


Figure 119: Quality of life – Kansas City Cardiomyopathy Questionnaire

Study or Subgroup	Mean Difference	SE	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
STICH 2011	8.8	1.7347	8.80 [5.40, 12.20]	

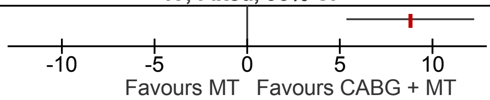


Figure 120: Quality of life – Short form – 12 (Physical component)

Study or Subgroup	Mean Difference	SE	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
STICH 2011	1.5	0.5102	1.50 [0.50, 2.50]	

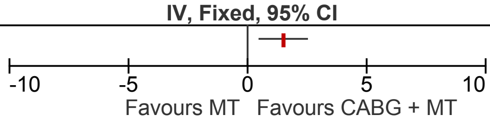


Figure 121: Quality of life – Short form – 12 (Mental component)

Study or Subgroup	Mean Difference	SE	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
STICH 2011	2.2	0.8674	2.20 [0.50, 3.90]	

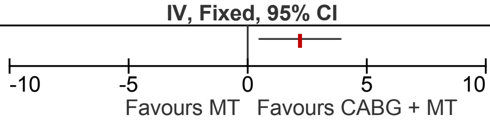


Figure 122: All-cause hospitalisations

Study or Subgroup	CABG + MT Events	CABG + MT Total	Medical therapy alone Events	Medical therapy alone Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
STICH 2011	290	610	340	602	0.84 [0.75, 0.94]	

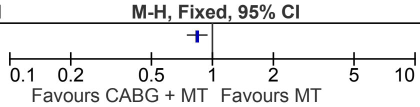


Figure 123: Subsequent procedures - CABG

Study or Subgroup	CABG + MT Events	CABG + MT Total	Medical therapy alone Events	Medical therapy alone Total	Peto Odds Ratio Peto, Fixed, 95% CI
STICH 2011	1	610	100	602	0.12 [0.08, 0.17]

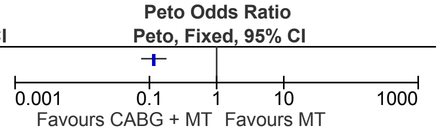


Figure 124: Subsequent procedures - PCI

Study or Subgroup	CABG + MT Events	CABG + MT Total	Medical therapy alone Events	Medical therapy alone Total	Risk Ratio M-H, Fixed, 95% CI
STICH 2011	26	610	37	602	0.69 [0.43, 1.13]

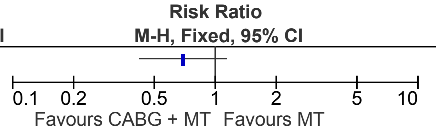


Figure 125: NYHA class I

Study or Subgroup	CABG + MT Events	CABG + MT Total	Medical therapy alone Events	Medical therapy alone Total	Risk Ratio M-H, Fixed, 95% CI
STICH 2011	255	610	206	602	1.22 [1.06, 1.41]

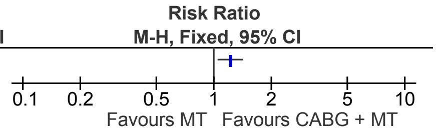
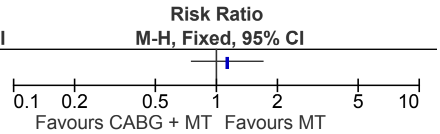


Figure 126: Stroke

Study or Subgroup	CABG + MT Events	CABG + MT Total	Medical therapy alone Events	Medical therapy alone Total	Risk Ratio M-H, Fixed, 95% CI
STICH 2011	47	610	41	602	1.13 [0.76, 1.69]



1 E.8.2 Invasive strategy + medical therapy versus medical therapy alone

Figure 127: All-cause mortality at 4.9 years

Study or Subgroup	Invasive strategy Events	Invasive strategy Total	Medical strategy Events	Medical strategy Total	Risk Ratio M-H, Fixed, 95% CI
HEART 2010	26	68	25	68	1.04 [0.67, 1.61]

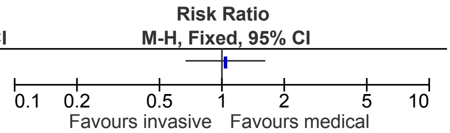


Figure 128: Quality of life – EQ-5D

Study or Subgroup	Mean Difference	SE	Mean Difference IV, Fixed, 95% CI
HEART 2010	-0.023	0.06148	-0.02 [-0.14, 0.10]

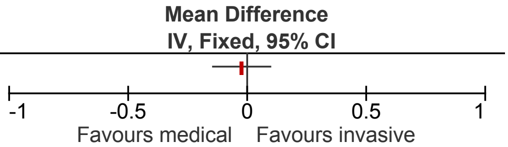
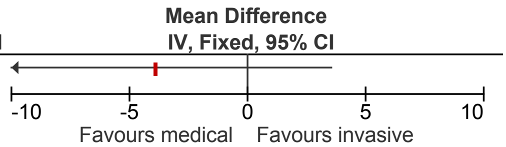


Figure 129: Quality of life – Minnesota Living with Heart Failure Questionnaire

Study or Subgroup	Mean Difference	SE	Mean Difference IV, Fixed, 95% CI
HEART 2010	-3.9	3.80102	-3.90 [-11.35, 3.55]



E.9 Home-based versus centre-based rehabilitation

E.9.1 Home-based versus centre-based rehabilitation programmes

Figure 130: All-cause mortality

Study or Subgroup	centre-based CR Events	centre-based CR Total	home-based CR Events	home-based CR Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Cowie 2012	3	15	3	15	71.3%	1.00 [0.17, 5.81]
Daskapan 2005	0	14	1	15	14.3%	0.14 [0.00, 7.31]
Hwang 2017	0	24	0	26		Not estimable
Karapolat 2009	0	37	0	37		Not estimable
Piotrowicz 2010	1	75	0	77	14.4%	7.59 [0.15, 382.58]
Total (95% CI)		**165**		**170**	**100.0%**	**1.01 [0.23, 4.48]**
Total events	4		4			

Heterogeneity: Chi² = 1.96, df = 2 (P = 0.38); I² = 0%
Test for overall effect: Z = 0.02 (P = 0.99)

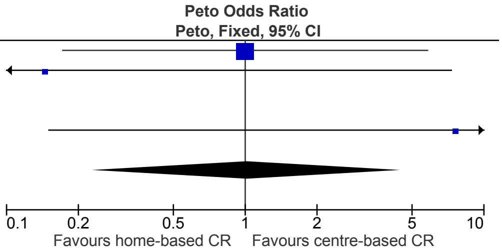


Figure 131: Health-related quality of life – SF-36 physical component

Study or Subgroup	home-based CR Mean	home-based CR SD	home-based CR Total	centre-based CR Mean	centre-based CR SD	centre-based CR Total	Weight	Mean Difference IV, Fixed, 95% CI
Cowie 2012	34.01	11.04	15	33.83	10	15	42.1%	0.18 [-7.36, 7.72]
Piotrowicz 2010	50.27	17.06	75	51.37	19.6	56	57.9%	-1.10 [-7.52, 5.32]
Total (95% CI)			**90**			**71**	**100.0%**	**-0.56 [-5.45, 4.33]**

Heterogeneity: Chi² = 0.06, df = 1 (P = 0.80); I² = 0%
Test for overall effect: Z = 0.23 (P = 0.82)

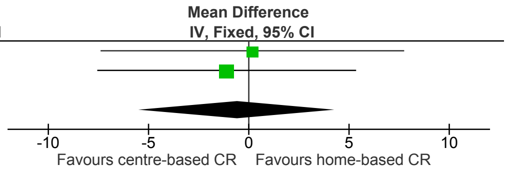


Figure 132: Health-related quality of life – SF-36 mental component

Study or Subgroup	home-based CR Mean	home-based CR SD	home-based CR Total	centre-based CR Mean	centre-based CR SD	centre-based CR Total	Weight	Mean Difference IV, Random, 95% CI
Cowie 2012	44.44	12.23	15	48.25	11.21	15	34.6%	-3.81 [-12.21, 4.59]
Piotrowicz 2010	21.68	12.46	75	18.56	9.18	56	65.4%	3.12 [-0.59, 6.83]
Total (95% CI)			**90**			**71**	**100.0%**	**0.72 [-5.74, 7.18]**

Heterogeneity: Tau² = 13.05; Chi² = 2.19, df = 1 (P = 0.14); I² = 54%
Test for overall effect: Z = 0.22 (P = 0.83)

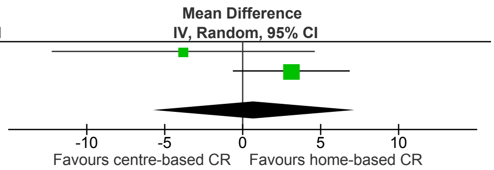


Figure 133: Health-related quality of life – EQ-5D utility

Study or Subgroup	Mean Difference	SE	Mean Difference IV, Fixed, 95% CI
Hwang 2017	-0.06	0.051	-0.06 [-0.16, 0.04]

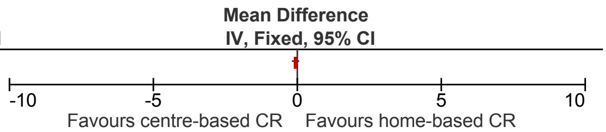


Figure 134: Health-related quality of life - MLWHFQ

Study or Subgroup	Mean Difference	SE	Mean Difference IV, Fixed, 95% CI
Hwang 2017	-4	6.6328	-4.00 [-17.00, 9.00]

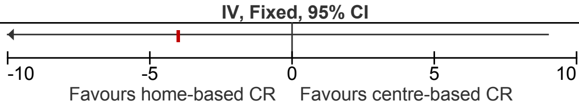


Figure 135: Exercise capacity – Incremental shuttle walking test

	home-based CR			centre-based CR			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Cowie 2012	318	153	15	312	155	15	6.00 [-104.22, 116.22]

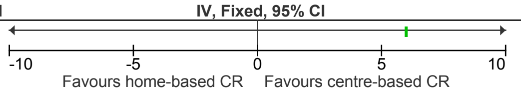


Figure 136: Exercise capacity – 6 minute walk distance

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
Hwang 2017	2	19.3881	41.0%	2.00 [-36.00, 40.00]
Piotrowicz 2010	0	16.1738	59.0%	0.00 [-31.70, 31.70]
Total (95% CI)			**100.0%**	**0.82 [-23.52, 25.16]**

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 0.07 (P = 0.95)

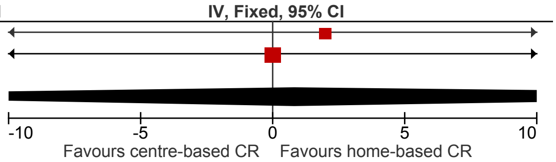


Figure 137: Exercise capacity – VO_2max

	home-based CR			centre-based CR				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Daskapan 2005	23.6	7.4	11	23.3	6.8	11	5.3%	0.30 [-5.64, 6.24]
Karapolat 2009	18.12	6	36	19.43	4.59	32	29.2%	-1.31 [-3.83, 1.21]
Piotrowicz 2010	19.7	5.2	75	19	4.6	56	65.5%	0.70 [-0.98, 2.38]
Total (95% CI)			**122**			**99**	**100.0%**	**0.09 [-1.27, 1.46]**

Heterogeneity: Chi² = 1.69, df = 2 (P = 0.43); I² = 0%
Test for overall effect: Z = 0.13 (P = 0.89)

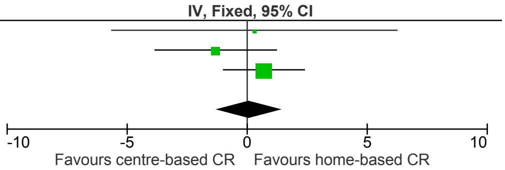


Figure 138: Exercise capacity – 10 metre walk test (fast)

Study or Subgroup	Mean Difference	SE	Mean Difference IV, Fixed, 95% CI
Hwang 2017	1	0.051	1.00 [0.90, 1.10]

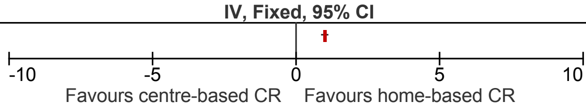


Figure 139: Exercise capacity – Grip strength (kg)

Study or Subgroup	Mean Difference	SE	Mean Difference IV, Fixed, 95% CI
Hwang 2017	1	1.5306	1.00 [-2.00, 4.00]

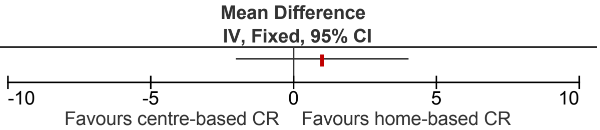


Figure 140: Study completers

Study or Subgroup	home-based CR Events	home-based CR Total	centre-based CR Events	centre-based CR Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cowie 2012	15	20	15	20	13.0%	1.00 [0.70, 1.43]
Daskapan 2005	11	15	11	14	9.9%	0.93 [0.62, 1.41]
Karapolat 2009	36	37	32	37	27.8%	1.13 [0.98, 1.29]
Piotrowicz 2010	75	77	56	75	49.3%	1.30 [1.14, 1.50]
Total (95% CI)		**149**		**146**	**100.0%**	**1.18 [1.07, 1.30]**
Total events	137		114			

Heterogeneity: Chi² = 4.61, df = 3 (P = 0.20); I² = 35%
Test for overall effect: Z = 3.28 (P = 0.001)

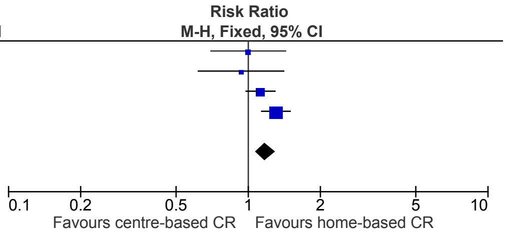
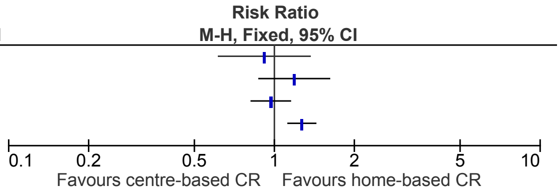


Figure 141: Adherence to intervention

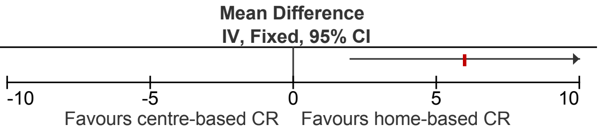
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Risk Ratio M-H, Fixed, 95% CI
Cowie 2012	11	15	12	15	0.92 [0.62, 1.36]
Daskapan 2005	14	15	11	14	1.19 [0.88, 1.61]
Karapolat 2009	32	37	33	37	0.97 [0.82, 1.15]
Piotrowicz 2010	77	77	59	75	1.27 [1.13, 1.43]



These outcomes have not been meta-analysed as there was a significant degree of variation in the methods of obtaining this information across studies.

Figure 142: Adherence to intervention (number of sessions attended)

Study or Subgroup	Mean Difference	SE	Mean Difference IV, Fixed, 95% CI
Hwang 2017	6	2.0409	6.00 [2.00, 10.00]



E.10 Monitoring

E.10.1 NP monitoring vs Clinical monitoring

Figure 143: Mortality in age <75/≥75 (Time to event)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
1.1.1 Age <75 years				
HTA Aggregate (7 studies)	-0.3711	0.1777	72.4%	0.69 [0.49, 0.98]
HTA IPD (Anguita)	0.27	0.9103	2.8%	1.31 [0.22, 7.80]
HTA IPD (NorthStar)	-0.1393	0.3034	24.8%	0.87 [0.48, 1.58]
Subtotal (95% CI)			**100.0%**	**0.74 [0.55, 1.00]**
Heterogeneity: Chi² = 0.83, df = 2 (P = 0.66); I² = 0%				
Test for overall effect: Z = 1.96 (P = 0.05)				
1.1.2 Age 75 and over				
HTA Aggregate (7 studies)	0.1044	0.289	53.8%	1.11 [0.63, 1.96]
HTA IPD (Anguita)	-0.3857	1.2387	2.9%	0.68 [0.06, 7.71]
HTA IPD (NorthStar)	0.3577	0.3225	43.2%	1.43 [0.76, 2.69]
Subtotal (95% CI)			**100.0%**	**1.22 [0.81, 1.85]**
Heterogeneity: Chi² = 0.57, df = 2 (P = 0.75); I² = 0%				
Test for overall effect: Z = 0.94 (P = 0.35)				

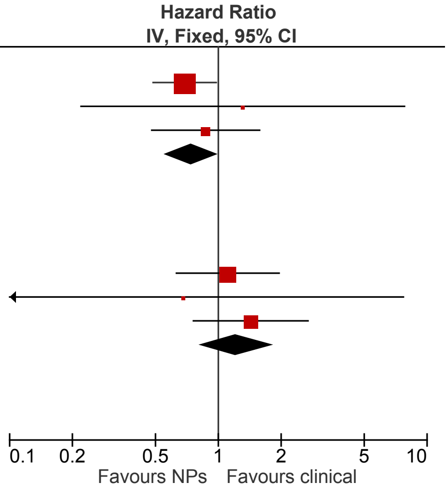


Figure 144: Mortality at 1-2 years

Study or Subgroup	NP monitoring Events	NP monitoring Total	Clinical monitoring Events	Clinical monitoring Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 All ages						
Felker 2017 (GUIDE-IT)	66	446	77	448	96.2%	0.86 [0.64, 1.16]
Krupicka 2010 (OPTIMA)	4	26	3	26	3.8%	1.33 [0.33, 5.38]
Subtotal (95% CI)		**472**		**474**	**100.0%**	**0.88 [0.65, 1.18]**
Total events	70		80			
Heterogeneity: Chi² = 0.36, df = 1 (P = 0.55); I² = 0%						
Test for overall effect: Z = 0.86 (P = 0.39)						

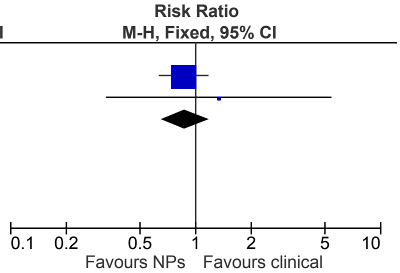


Figure 145: All-cause admission in age <75/≥75 (time to event)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
1.4.1 Age <75 years				
HTA Aggregate (Time-CHF)	-0.3567	0.182	31.9%	0.70 [0.49, 1.00]
HTA IPD (Anguita)	0.1044	0.4839	4.5%	1.11 [0.43, 2.87]
HTA IPD (NorthStar)	-0.1744	0.1717	35.9%	0.84 [0.60, 1.18]
HTA IPD (UPSTEP)	-0.1278	0.1954	27.7%	0.88 [0.60, 1.29]
Subtotal (95% CI)			**100.0%**	**0.81 [0.66, 0.99]**
Heterogeneity: Chi² = 1.29, df = 3 (P = 0.73); I² = 0%				
Test for overall effect: Z = 2.01 (P = 0.04)				
1.4.2 Age 75 and over				
HTA Aggregate (Time-CHF)	0.0953	0.1499	47.4%	1.10 [0.82, 1.48]
HTA IPD (Anguita)	-1.1712	1.0448	1.0%	0.31 [0.04, 2.40]
HTA IPD (NorthStar)	0.0198	0.1848	31.2%	1.02 [0.71, 1.47]
HTA IPD (UPSTEP)	-0.0305	0.2284	20.4%	0.97 [0.62, 1.52]
Subtotal (95% CI)			**100.0%**	**1.03 [0.84, 1.27]**
Heterogeneity: Chi² = 1.58, df = 3 (P = 0.66); I² = 0%				
Test for overall effect: Z = 0.33 (P = 0.74)				

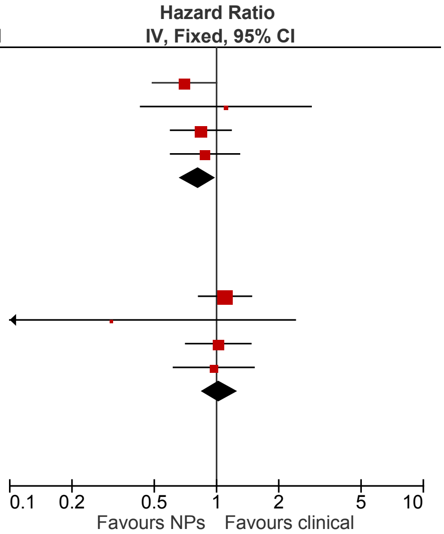


Figure 146: All-cause admissions at 15 months

Study or Subgroup	NP monitoring Events	NP monitoring Total	Clinical monitoring Events	Clinical monitoring Total	Risk Ratio M-H, Fixed, 95% CI
1.5.1 All ages					
Jourdain 2007 (STARS-BNP)	52	110	60	110	0.87 [0.67, 1.12]

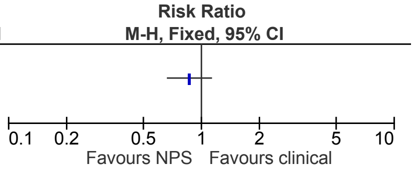


Figure 147: All-cause admissions at 6 months (count rate)

Study or Subgroup	log[Rate Ratio]	SE	Rate Ratio IV, Fixed, 95% CI
1.6.1 All ages			
Troughton 2000 (Christchurch)	-0.29865	0.314362	0.74 [0.40, 1.37]

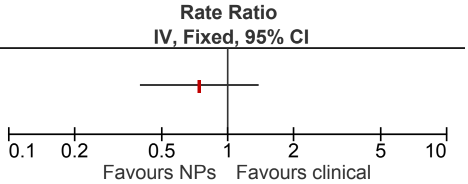


Figure 148: HF admission (time to event)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
1.7.1 All ages				
Troughton Rev IPD (BATTLESCARRED)	-0.2485	0.2477	23.8%	0.78 [0.48, 1.27]
Troughton Rev IPD (Berger)	-0.478	0.2498	23.4%	0.62 [0.38, 1.01]
Troughton Rev IPD (PRIMA)	0	0.1968	37.7%	1.00 [0.68, 1.47]
Troughton Rev IPD (PROTECT)	-0.4308	0.4118	8.6%	0.65 [0.29, 1.46]
Troughton Rev IPD (SIGNAL-HF)	-0.6349	0.4723	6.5%	0.53 [0.21, 1.34]
Subtotal (95% CI)			**100.0%**	**0.78 [0.61, 0.99]**
Heterogeneity: Chi² = 3.30, df = 4 (P = 0.51); I² = 0%				
Test for overall effect: Z = 2.07 (P = 0.04)				

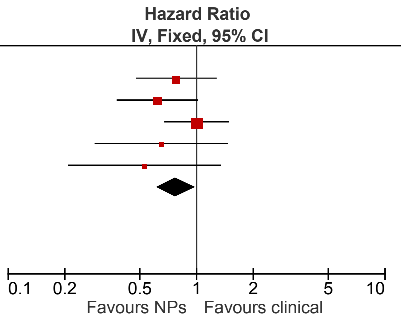


Figure 149: HF admissions at 2 years

Study or Subgroup	NP monitoring Events	NP monitoring Total	Clinical monitoring Events	Clinical monitoring Total	Risk Ratio M-H, Fixed, 95% CI
1.8.1 All ages					
Krupicka 2010 (OPTIMA)	6	26	13	26	0.46 [0.21, 1.03]

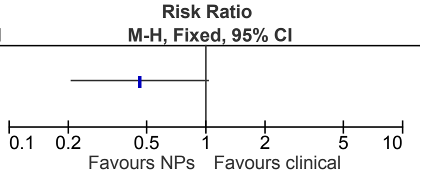


Figure 150: HF failure admissions at 1-2 years (count rate)

Study or Subgroup	log[Rate Ratio]	SE	Rate Ratio IV, Fixed, 95% CI
1.23.1 All ages			
Felker 2017 (GUIDE-IT)	0.2311	0.0804	1.26 [1.08, 1.48]

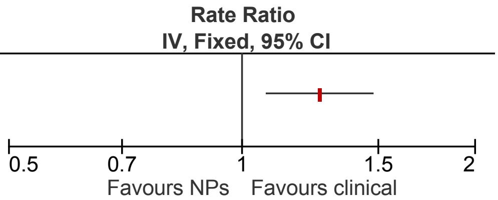


Figure 151: Quality of life by MLWHFQ score at 12 months (0-105)

Study or Subgroup	NP monitoring Mean	SD	Total	Clinical monitoring Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.9.1 MLWHFQ at 12 months (final value)								
Lainchbury 2009 (BATTLESCARRED)	28.8	21.6	121	26.5	22	121	43.5%	2.30 [-3.19, 7.79]
Maeder 2013 (TIME-CHF)	27.7	17.9	110	27	18.6	110	56.5%	0.70 [-4.12, 5.52]
Subtotal (95% CI)			**231**			**231**	**100.0%**	**1.40 [-2.23, 5.02]**
Heterogeneity: Chi² = 0.18, df = 1 (P = 0.67); I² = 0%								
Test for overall effect: Z = 0.76 (P = 0.45)								

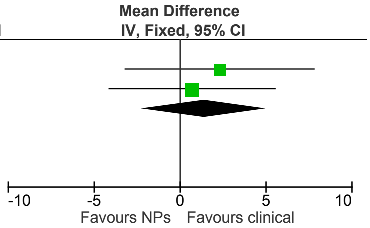


Figure 152: Quality of life by KCCQ change over 9 months (0-100)

Study or Subgroup	NP monitoring Mean	SD	Total	Clinical monitoring Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.10.1 Change in KCCQ at 9 months							
Persson 2010 (SIGNAL-HF)	3.6	18.5	126	6.2	18.5	124	-2.60 [-7.19, 1.99]

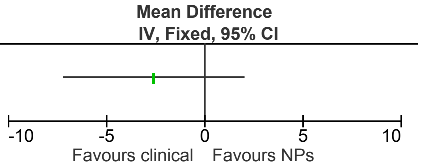


Figure 153: Quality of life (physical health) by SF36 PCS at 12 months (0-100)

Study or Subgroup	NP monitoring Mean	SD	Total	Clinical monitoring Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.11.1 SF36 physical at 12 months (final value)								
Karlstrom 2011 (UPSTEP)	37.8	12	100	35.6	11	98	48.4%	2.20 [-1.01, 5.41]
Maeder 2013 (TIME-CHF)	37.9	10.1	110	40.6	10.3	110	51.6%	-2.70 [-5.40, -0.00]
Subtotal (95% CI)			**210**			**208**	**100.0%**	**-0.33 [-5.13, 4.47]**
Heterogeneity: Tau² = 9.72; Chi² = 5.26, df = 1 (P = 0.02); I² = 81%								
Test for overall effect: Z = 0.13 (P = 0.89)								

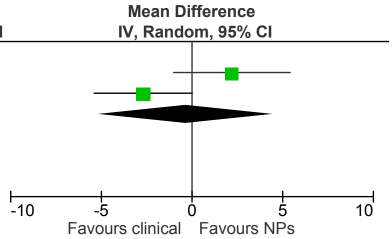


Figure 154: Quality of life (mental health) by SF36 MCS at 12 months (0-100)

Study or Subgroup	NP monitoring Mean	SD	Total	Clinical monitoring Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.12.1 SF36 mental at 12 months (final score)								
Karlstrom 2011 (UPSTEP)	46.5	10	100	46	11	98	44.7%	0.50 [-2.43, 3.43]
Maeder 2013 (TIME-CHF)	50.8	10.4	110	51.1	9.5	110	55.3%	-0.30 [-2.93, 2.33]
Subtotal (95% CI)			**210**			**208**	**100.0%**	**0.06 [-1.90, 2.02]**
Heterogeneity: Chi² = 0.16, df = 1 (P = 0.69); I² = 0%								
Test for overall effect: Z = 0.06 (P = 0.95)								

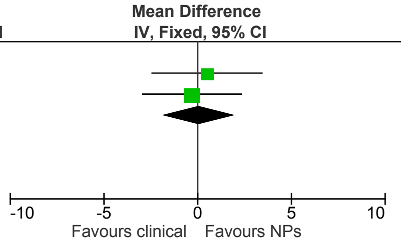
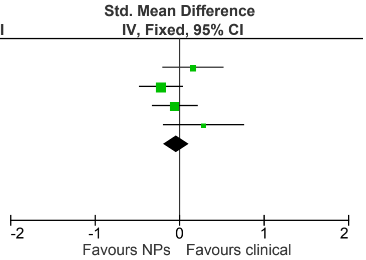


Figure 155: Renal function at 6-12 months (by GFR / creatinine clearance / serum creatinine, analysed using standardised mean difference)

Study or Subgroup	NP monitoring Mean	SD	Total	Clinical monitoring Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
1.14.1 All ages								
Januzzi 2011 (PROTECT)	49.7	24.4	65	46.1	20.5	58	18.8%	0.16 [-0.20, 0.51]
Lainchbury 2009 (BATTLESCARRED)	55	17	121	59	19	121	37.0%	-0.22 [-0.47, 0.03]
Maeder 2013 (TIME-CHF)	-1.44	0.5	110	-1.41	0.53	110	33.8%	-0.06 [-0.32, 0.21]
Troughton 2000 (Christchurch)	52.2	4.2	33	51	4.2	36	10.5%	0.28 [-0.19, 0.76]
Subtotal (95% CI)			**329**			**325**	**100.0%**	**-0.04 [-0.20, 0.11]**
Heterogeneity: Chi² = 4.96, df = 3 (P = 0.17); I² = 40%								
Test for overall effect: Z = 0.54 (P = 0.59)								



Note: *SMD of -0.04 (-0.2 to 0.11) is equivalent to a mean difference in eGFR of -0.76 (-3.8 to 2.09)*

Figure 156: Creatinine rise >30% at 3 months

Study or Subgroup	NP monitoring Events	NP monitoring Total	Clinical monitoring Events	Clinical monitoring Total	Risk Ratio M-H, Fixed, 95% CI
Jourdain 2007 (STARS-BNP)	7	110	9	110	0.78 [0.30, 2.01]

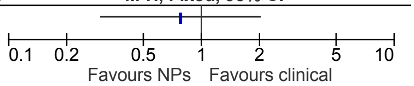


Figure 157: Worsening renal function at 12-24 months

Study or Subgroup	NP monitoring Events	NP monitoring Total	Clinical monitoring Events	Clinical monitoring Total	Risk Ratio M-H, Fixed, 95% CI
Felker 2017 (GUIDE-IT)	16	446	9	448	1.79 [0.80, 4.00]

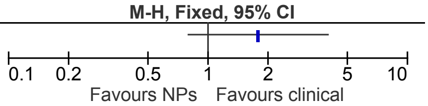


Figure 158: Acute Kidney Injury at 10-18 months

Study or Subgroup	NP monitoring Events	NP monitoring Total	Clinical monitoring Events	Clinical monitoring Total	Risk Ratio M-H, Fixed, 95% CI
1.16.1 Age <75 years					
Maeder 2013 (TIME-CHF)	32	108	28	102	1.08 [0.70, 1.66]
1.16.2 Age 75 and over					
Maeder 2013 (TIME-CHF)	42	146	47	143	0.88 [0.62, 1.24]
1.16.3 All ages					
Januzzi 2011 (PROTECT)	4	76	3	75	1.32 [0.30, 5.68]

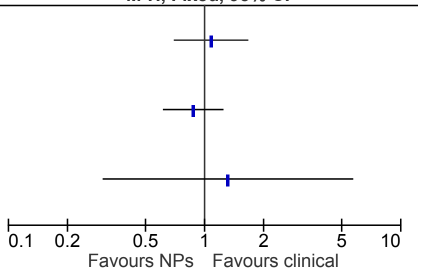


Figure 159: Hyperkalaemia at 18-24 months

Study or Subgroup	NP monitoring Events	NP monitoring Total	Clinical monitoring Events	Clinical monitoring Total	Risk Ratio M-H, Fixed, 95% CI
1.18.1 Age <75 years					
Maeder 2013 (TIME-CHF)	20	108	15	102	1.26 [0.68, 2.32]
1.18.2 Age 75 and over					
Maeder 2013 (TIME-CHF)	34	143	35	146	0.99 [0.66, 1.50]
1.18.3 All ages					
Felker 2017 (GUIDE-IT)	11	446	6	448	1.84 [0.69, 4.94]

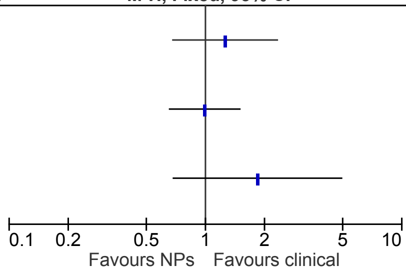


Figure 160: Hypotension at 10-24 months (age <75 years and age ≥75 years)

Study or Subgroup	NP monitoring Events	NP monitoring Total	Clinical monitoring Events	Clinical monitoring Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.20.1 Age <75 years						
Maeder 2013 (TIME-CHF)	48	108	38	102	100.0%	1.19 [0.86, 1.66]
Subtotal (95% CI)		**108**		**102**	**100.0%**	**1.19 [0.86, 1.66]**
Total events	48		38			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.29)						
1.20.2 Age 75 and over						
Maeder 2013 (TIME-CHF)	68	143	44	146	100.0%	1.58 [1.17, 2.13]
Subtotal (95% CI)		**143**		**146**	**100.0%**	**1.58 [1.17, 2.13]**
Total events	68		44			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.97 (P = 0.003)						

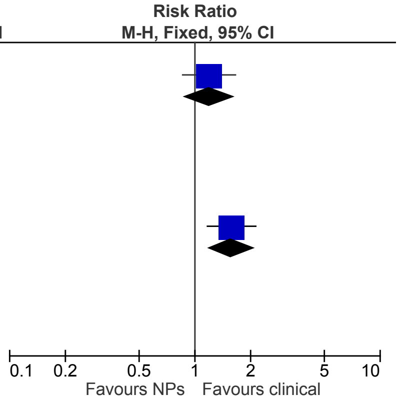


Figure 161: Hypotension at 10-24 months (all ages)

Study or Subgroup	NP monitoring Events	NP monitoring Total	Clinical monitoring Events	Clinical monitoring Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.26.3 All ages						
Felker 2017 (GUIDE-IT)	7	446	2	448	40.2%	3.08 [0.83, 11.45]
Januzzi 2011 (PROTECT)	4	76	0	75	17.7%	7.59 [1.05, 55.00]
Troughton 2000 (Christchurch)	7	33	4	36	42.2%	2.10 [0.58, 7.57]
Subtotal (95% CI)		**555**		**559**	**100.0%**	**3.08 [1.34, 7.07]**
Total events	18		6			
Heterogeneity: Chi² = 1.14, df = 2 (P = 0.57); I² = 0%						
Test for overall effect: Z = 2.65 (P = 0.008)						

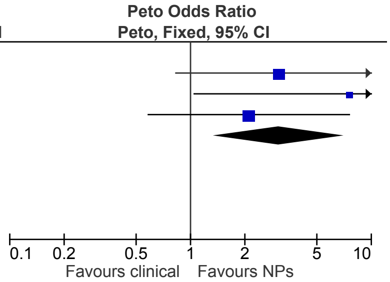


Figure 162: Bradycardia at 18 month

Study or Subgroup	NP monitoring Events	NP monitoring Total	Clinical monitoring Events	Clinical monitoring Total	Risk Ratio M-H, Fixed, 95% CI
1.20.1 Age <75 years					
Maeder 2013 (TIME-CHF)	13	108	8	102	1.53 [0.66, 3.55]
1.20.2 Age 75 and over					
Maeder 2013 (TIME-CHF)	21	143	18	146	1.19 [0.66, 2.14]

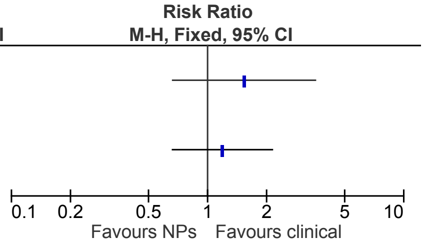


Figure 163: Symptomatic bradycardia at 12-24 months

Study or Subgroup	NP monitoring Events	NP monitoring Total	Clinical monitoring Events	Clinical monitoring Total	Risk Difference M-H, Fixed, 95% CI
1.24.1 All ages					
Felker 2017 (GUIDE-IT)	0	446	0	448	0.00 [-0.00, 0.00]

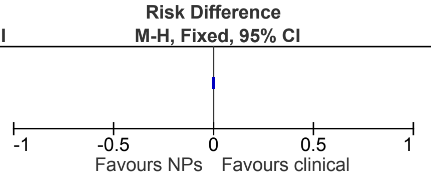


Figure 164: Significant ventricular arrhythmia at10 months

Study or Subgroup	NP monitoring Events	NP monitoring Total	Clinical monitoring Events	Clinical monitoring Total	Risk Ratio M-H, Fixed, 95% CI
1.21.1 All ages					
Januzzi 2011 (PROTECT)	7	76	4	75	1.73 [0.53, 5.66]

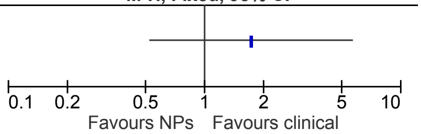
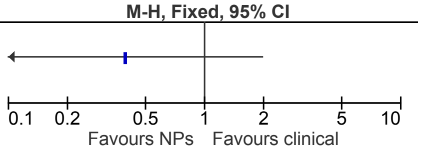


Figure 165: New atrial fibrillation at 10 months

Study or Subgroup	NP monitoring Events	NP monitoring Total	Clinical monitoring Events	Clinical monitoring Total	Risk Ratio M-H, Fixed, 95% CI
1.22.1 All ages					
Januzzi 2011 (PROTECT)	2	76	5	75	0.39 [0.08, 1.97]



E.10.2 NP monitoring vs No monitoring protocol

Figure 166: Mortality in age <75/≥75 (Time to event)

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
2.1.1 Age <75 years			
HTA IPD (Shochat)	-2.2073	1.0492	0.11 [0.01, 0.86]
2.1.2 Age 75 and over			
HTA IPD (Shochat)	0.392	0.7357	1.48 [0.35, 6.26]

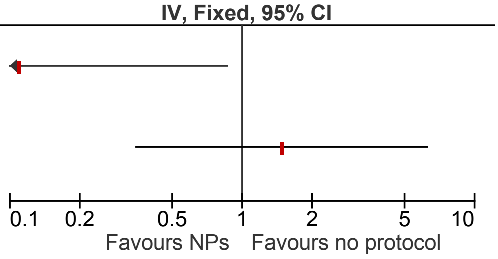


Figure 167: Mortality at 15 months – 3 years

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Risk Ratio M-H, Fixed, 95% CI
2.2.1 Age <75 years at 15 months					
Lainchbury 2009 (BATTLESCARRED)	9	58	20	64	0.50 [0.25, 1.00]
2.2.2 Age 75 and over at 15 months					
Lainchbury 2009 (BATTLESCARRED)	31	63	20	58	1.43 [0.92, 2.20]
2.2.3 All ages at 3 years					
Berger 2010	20	92	35	90	0.56 [0.35, 0.89]

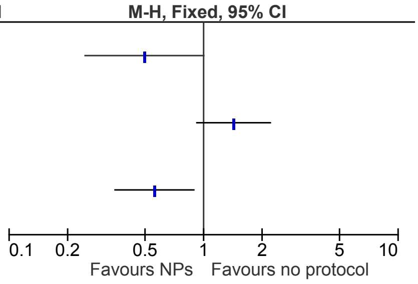


Figure 168: All-cause admissions in age <75/≥75 (time to event)

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
2.3.1 Age <75 years			
HTA IPD (Shochat)	0.077	0.3443	1.08 [0.55, 2.12]
2.3.2 Age 75 and over			
HTA IPD (Shochat)	0.5068	0.3661	1.66 [0.81, 3.40]

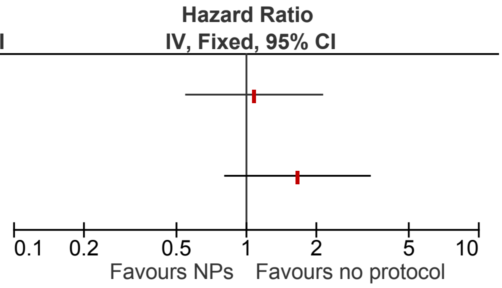
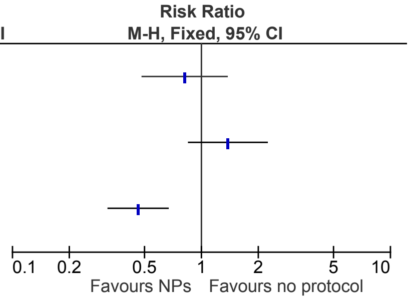


Figure 169: HF admissions at 15 months – 3 years

Study or Subgroup	NP monitoring Events	NP monitoring Total	No monitoring Events	No monitoring Total	Risk Ratio M-H, Fixed, 95% CI
2.4.1 Age <75 years					
Lainchbury 2009 (BATTLESCARRED)	17	58	23	64	0.82 [0.49, 1.37]
2.4.2 Age 75 and over					
Lainchbury 2009 (BATTLESCARRED)	27	63	18	58	1.38 [0.86, 2.23]
2.4.3 All ages					
Berger 2010	26	92	55	90	0.46 [0.32, 0.67]



E.10.3 CKD: NP monitoring vs Clinical monitoring

Figure 170: Mortality at 9.5 to 36 months

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
3.1.1 All ages				
Troughton Rev IPD (HFpEF)	0.3853	0.2795	41.3%	1.47 [0.85, 2.54]
Troughton Rev IPD (HFrEF)	-0.2107	0.1282	58.7%	0.81 [0.63, 1.04]
Subtotal (95% CI)			**100.0%**	**1.04 [0.58, 1.84]**

Heterogeneity: Tau² = 0.13; Chi² = 3.76, df = 1 (P = 0.05); I² = 73%
Test for overall effect: Z = 0.12 (P = 0.90)

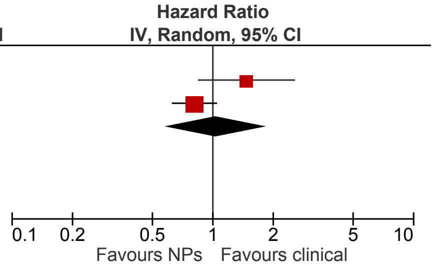
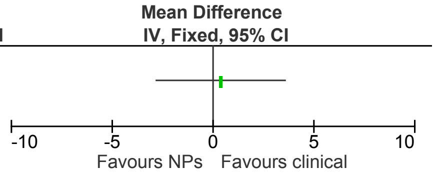


Figure 171: All-cause hospitalisation (days in hospital)at 24 months

Study or Subgroup	NP monitoring Mean	NP monitoring SD	NP monitoring Total	Clinical monitoring Mean	Clinical monitoring SD	Clinical monitoring Total	Mean Difference IV, Fixed, 95% CI
3.2.1 All ages							
Eurlings 2010 (PRIMA)	6.92	10.2	81	6.54	10.6	82	0.38 [-2.81, 3.57]



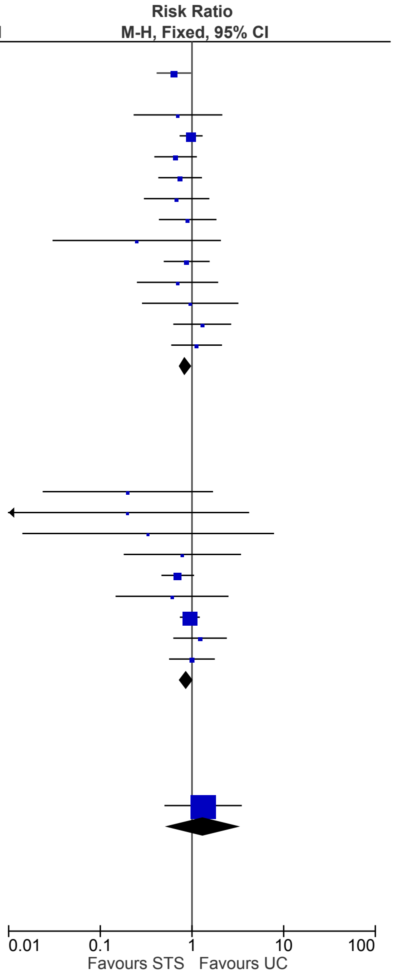
E.11 Telemonitoring and self-monitoring

E.11.1 Structured telephone support

E.11.1.1 All-cause mortality

Figure 172: Structured telephone support versus usual care

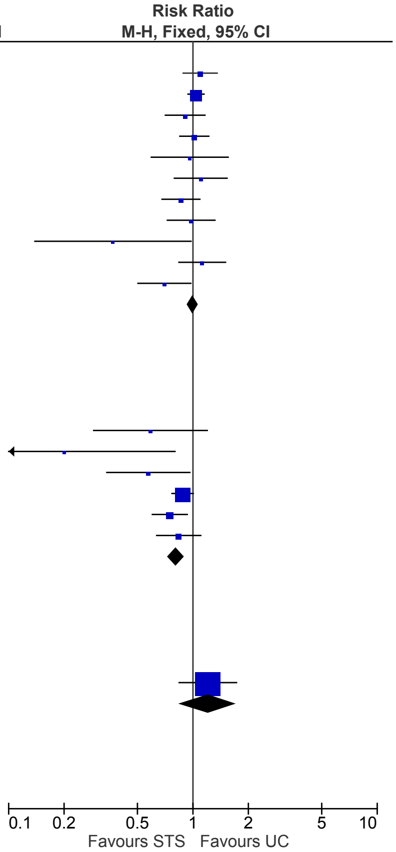
Study or Subgroup	STS Events	STS Total	Usual Care Events	Usual Care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Recent admission						
Angermann 2012 (INH)	32	352	52	363	16.9%	0.63 [0.42, 0.96]
Barth 2001	0	17	0	17		Not estimable
Capomolla 2004	5	67	7	66	2.3%	0.70 [0.24, 2.11]
Chaudhry 2010 (Tele-HF)	92	826	94	827	31.1%	0.98 [0.75, 1.28]
Cleland 2005 (Struct Tele) (TENS-HMS)	27	173	20	85	8.9%	0.66 [0.40, 1.11]
DeBusk 2004	21	228	29	234	9.5%	0.74 [0.44, 1.26]
Domingues 2011	8	57	13	63	4.1%	0.68 [0.30, 1.52]
Laramee 2003	13	141	15	146	4.9%	0.90 [0.44, 1.82]
Rainville 1999	1	19	4	19	1.3%	0.25 [0.03, 2.04]
Riegel 2002	16	130	32	228	7.7%	0.88 [0.50, 1.54]
Riegel 2006	6	70	8	65	2.7%	0.70 [0.26, 1.90]
Sales 2014	5	70	5	67	1.7%	0.96 [0.29, 3.16]
Tsuyuki 2004	16	140	12	136	4.0%	1.30 [0.64, 2.64]
Wakefield 2008	25	99	11	49	4.9%	1.12 [0.60, 2.09]
Subtotal (95% CI)		**2389**		**2365**	**100.0%**	**0.84 [0.72, 0.98]**
Total events	267		302			
Heterogeneity: Chi² = 8.16, df = 12 (P = 0.77); I² = 0%						
Test for overall effect: Z = 2.16 (P = 0.03)						
1.1.2 Community						
Al Sutari 2017	1	72	5	72	2.2%	0.20 [0.02, 1.67]
Baker 2011	0	303	2	302	1.1%	0.20 [0.01, 4.13]
Bento 2009	0	20	1	20	0.7%	0.33 [0.01, 7.72]
DeWalt 2006	3	62	4	65	1.7%	0.79 [0.18, 3.37]
Galbreath 2004	54	710	39	359	22.7%	0.70 [0.47, 1.04]
Gattis 1999 (PHARM)	3	90	5	91	2.2%	0.61 [0.15, 2.46]
GESICA 2005 (DIAL)	116	760	122	758	53.4%	0.95 [0.75, 1.20]
Krum 2013 (CHAT)	17	188	16	217	6.5%	1.23 [0.64, 2.36]
Sisk 2006	22	203	22	203	9.6%	1.00 [0.57, 1.75]
Subtotal (95% CI)		**2408**		**2087**	**100.0%**	**0.88 [0.73, 1.05]**
Total events	216		216			
Heterogeneity: Chi² = 6.36, df = 8 (P = 0.61); I² = 0%						
Test for overall effect: Z = 1.47 (P = 0.14)						
1.1.3 Mixed						
Mortara 2009 (Struct Tele) (HHH)	7	94	9	160	100.0%	1.32 [0.51, 3.44]
Subtotal (95% CI)		**94**		**160**	**100.0%**	**1.32 [0.51, 3.44]**
Total events	7		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						



E.11.1.2 All-cause hospitalisation

Figure 173: Structured telephone support versus usual care

Study or Subgroup	STS Events	STS Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Recent admission						
Angermann 2012 (INH)	119	352	112	363	11.4%	1.10 [0.89, 1.35]
Chaudhry 2010 (Tele-HF)	407	826	392	827	40.3%	1.04 [0.94, 1.15]
Cleland 2005 (Struct Tele) (TENS-HMS)	85	173	46	85	6.4%	0.91 [0.71, 1.16]
DeBusk 2004	116	228	117	234	11.9%	1.02 [0.85, 1.22]
Domingues 2011	20	57	23	63	2.2%	0.96 [0.59, 1.55]
Laramee 2003	49	141	46	146	4.7%	1.10 [0.79, 1.53]
Riegel 2002	56	130	114	228	8.5%	0.86 [0.68, 1.09]
Riegel 2006	39	70	37	65	4.0%	0.98 [0.73, 1.32]
Sales 2014	5	70	13	67	1.4%	0.37 [0.14, 0.98]
Tsuyuki 2004	59	140	51	136	5.3%	1.12 [0.84, 1.50]
Wakefield 2008	41	99	29	49	4.0%	0.70 [0.50, 0.97]
Subtotal (95% CI)		**2286**		**2263**	**100.0%**	**1.00 [0.94, 1.07]**
Total events	996		980			
Heterogeneity: Chi² = 12.97, df = 10 (P = 0.23); I² = 23%						
Test for overall effect: Z = 0.01 (P = 0.99)						
2.1.2 Community						
Al Sutari 2017	10	72	17	72	3.2%	0.59 [0.29, 1.20]
Bento 2009	2	20	10	20	1.9%	0.20 [0.05, 0.80]
Gattis 1999 (PHARM)	17	90	30	91	5.6%	0.57 [0.34, 0.96]
GESICA 2005 (DIAL)	261	760	296	758	55.6%	0.88 [0.77, 1.00]
Krum 2013 (CHAT)	74	188	114	217	19.9%	0.75 [0.60, 0.93]
Sisk 2006	62	203	74	203	13.9%	0.84 [0.64, 1.10]
Subtotal (95% CI)		**1333**		**1361**	**100.0%**	**0.81 [0.73, 0.89]**
Total events	426		541			
Heterogeneity: Chi² = 8.44, df = 5 (P = 0.13); I² = 41%						
Test for overall effect: Z = 4.10 (P < 0.0001)						
2.1.3 Mixed						
Mortara 2009 (Struct Tele) (HHH)	34	94	48	160	100.0%	1.21 [0.84, 1.72]
Subtotal (95% CI)		**94**		**160**	**100.0%**	**1.21 [0.84, 1.72]**
Total events	34		48			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.02 (P = 0.31)						



1 E.11.1.3 Quality of life

2 *E.11.1.3.1 Recent admission*

Figure 174: SF-36 Physical health component

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
3.1.1 Recent admission							
Angermann 2012 (INH)	2.8	10	352	1.3	9.9	363	1.50 [0.04, 2.96]

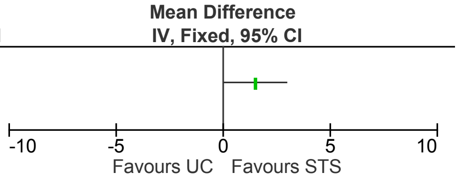


Figure 175: SF-36 Physical functioning component

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
3.2.1 Recent admission							
Angermann 2012 (INH)	5.9	25.8	352	1.8	24.7	363	4.10 [0.40, 7.80]

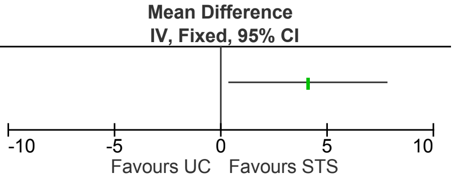


Figure 176: MLWHFQ

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
3.5.1 Recent admission							
Riegel 2006	12.1	21.3	69	12.9	10.9	65	-0.80 [-6.48, 4.88]

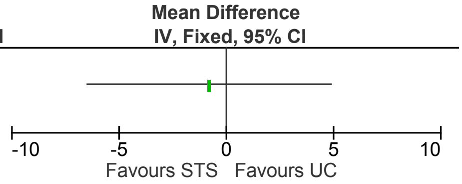


Figure 177: EQ-5D

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
3.10.1 Recent admission							
Riegel 2006	0.82	0.2	69	0.78	0.2	65	0.04 [-0.03, 0.11]

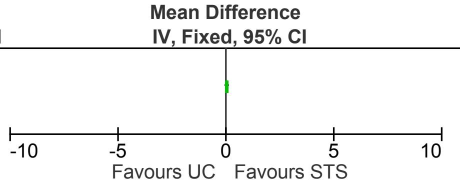
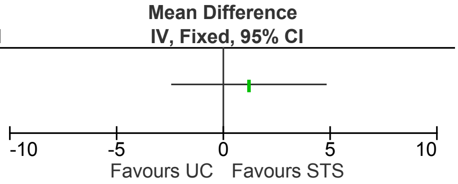


Figure 178: HFSS

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
3.11.1 Recent admission							
Baker 2011	65.3	22.4	303	64.1	22.8	302	1.20 [-2.40, 4.80]



1E.11.1.3.2 *Community*

Figure 179: MLWHFQ

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
3.3.2 Community				
Dang 2017	-4.69	5.9338	3.4%	-4.69 [-16.32, 6.94]
DeWalt 2006	2	3.57	9.4%	2.00 [-5.00, 9.00]
GESICA 2005 (DIAL)	-4.4	1.3	70.8%	-4.40 [-6.95, -1.85]
Sisk 2006	-7.3	2.7	16.4%	-7.30 [-12.59, -2.01]
Subtotal (95% CI)			**100.0%**	**-4.28 [-6.43, -2.14]**

Heterogeneity: Chi² = 4.36, df = 3 (P = 0.23); I² = 31%
Test for overall effect: Z = 3.92 (P < 0.0001)

Test for subgroup differences: Not applicable

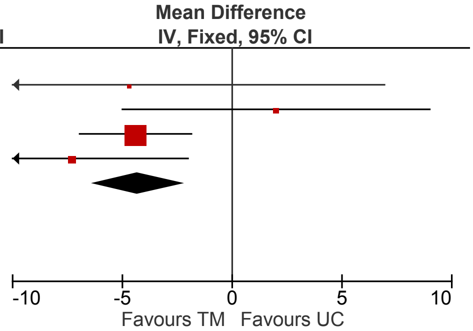
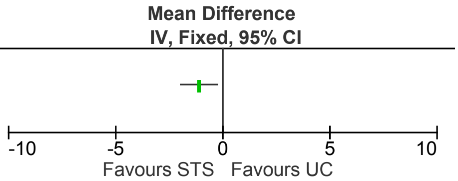


Figure 180: Health distress score

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
3.9.1 Community							
Dang 2017	-0.08	1.49	36	1.03	1.44	16	-1.11 [-1.97, -0.25]



E.11.1.3.3 *Mixed*

Figure 181: MLWHFQ

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
3.7.3 Mixed							
Stavrianopoulos 2016	-19.36	7.251	25	1.4	2.582	25	-20.76 [-23.78, -17.74]

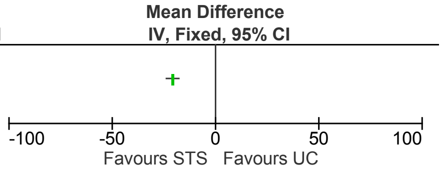
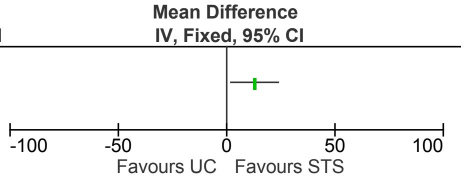


Figure 182: KCCQ HRQoL

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
3.8.1 Mixed							
Ramachandran 2007	76.3	17.3	25	63.4	21.9	25	12.90 [1.96, 23.84]



E.11.1.4 Adherence to intervention

E.11.1.4.1 *Recent admission*

Figure 183: Weight self daily

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
4.1.1 Recent admisssion							
Laramee 2003	4.7	3.8112	141	3.2	3.8112	146	1.50 [0.62, 2.38]

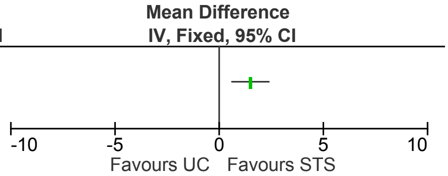


Figure 184: Check ankles and feet for swelling

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
4.2.1 Recent admission							
Laramee 2003	4.9	1.101	141	4.5	1.101	146	0.40 [0.15, 0.65]

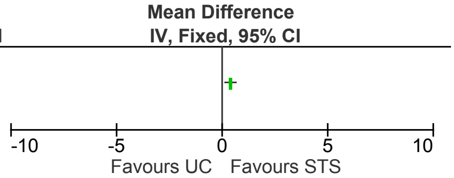


Figure 185: Follow fluid recommendations

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
4.3.1 Recent admission							
Laramee 2003	5	1.1857	141	4.6	1.1857	146	0.40 [0.13, 0.67]

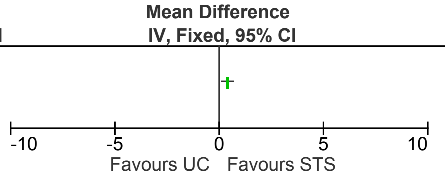


Figure 186: Follow low-salt diet

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
4.4.1 Recent admission							
Laramee 2003	4.9	0.7622	141	4.6	0.7622	146	0.30 [0.12, 0.48]

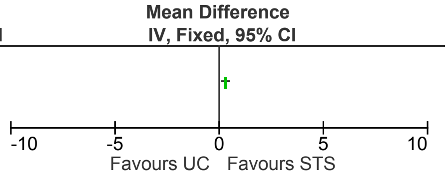
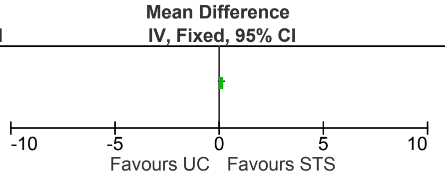


Figure 187: Take medication

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
4.5.1 Recent admission							
Laramee 2003	5	0.5928	141	4.9	0.5928	146	0.10 [-0.04, 0.24]

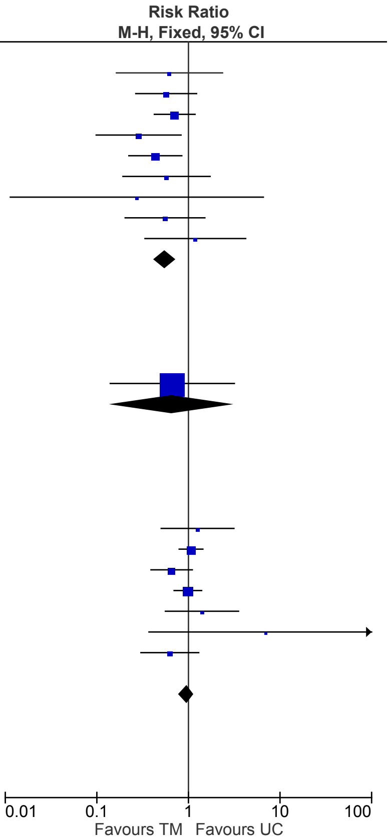


E.11.2 Telemonitoring

E.11.2.1 All-cause mortality

Figure 188: Telemonitoring versus usual care

Study or Subgroup	Telemonitoring Events	Telemonitoring Total	Usual Care Events	Usual Care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Recent admission						
Antonicelli 2008	3	28	5	29	4.5%	0.62 [0.16, 2.36]
Biannic 2012 (SEDIC)	8	45	14	45	12.9%	0.57 [0.27, 1.23]
Cleland 2005 (Telemon) (TENS-HMS)	28	168	20	85	24.6%	0.71 [0.42, 1.18]
Dendale 2012 (TEMA-HF1)	4	80	14	80	12.9%	0.29 [0.10, 0.83]
Goldberg 2003 (WHARF)	11	138	26	142	23.7%	0.44 [0.22, 0.85]
Lyngå 2012 (WISH)	5	166	8	153	7.7%	0.58 [0.19, 1.72]
Scherr 2009 (MOBITEL)	0	66	1	54	1.5%	0.27 [0.01, 6.58]
Villani 2014 (ICAROS)	5	40	9	40	8.3%	0.56 [0.20, 1.51]
Woodend 2008	5	62	4	59	3.8%	1.19 [0.34, 4.22]
Subtotal (95% CI)		**793**		**687**	**100.0%**	**0.56 [0.42, 0.74]**
Total events	69		101			
Heterogeneity: Chi² = 4.49, df = 8 (P = 0.81); I² = 0%						
Test for overall effect: Z = 3.97 (P < 0.0001)						
1.2.2 Community						
De Lusignan 2001	2	10	3	10	100.0%	0.67 [0.14, 3.17]
Subtotal (95% CI)		**10**		**10**	**100.0%**	**0.67 [0.14, 3.17]**
Total events	2		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.51 (P = 0.61)						
1.2.3 Mixed						
Balk 2008	9	101	8	113	4.6%	1.26 [0.50, 3.14]
Blum 2014 (MCCD)	49	104	45	102	27.6%	1.07 [0.79, 1.44]
Giordano 2009	21	230	32	230	19.4%	0.66 [0.39, 1.10]
Koehler 2011 (TIM-HF)	54	354	55	356	33.3%	0.99 [0.70, 1.39]
Mortara 2009 (Telemon) (HHH)	8	101	9	160	4.2%	1.41 [0.56, 3.53]
Seto 2012	3	50	0	50	0.3%	7.00 [0.37, 132.10]
Soran 2008	11	160	17	155	10.5%	0.63 [0.30, 1.29]
Vuorinen 2014	0	47	0	47		Not estimable
Subtotal (95% CI)		**1147**		**1213**	**100.0%**	**0.96 [0.79, 1.16]**
Total events	155		166			
Heterogeneity: Chi² = 6.67, df = 6 (P = 0.35); I² = 10%						
Test for overall effect: Z = 0.46 (P = 0.65)						

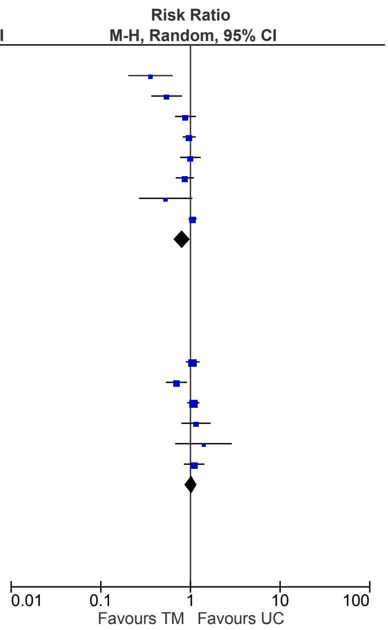


E.11.2.2 All-cause hospitalisation

Figure 189: Telemonitoring versus usual care

Study or Subgroup	Telemonitoring Events	Telemonitoring Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Recent admission						
Antonicelli 2008	9	28	26	29	7.5%	0.36 [0.21, 0.62]
Biannic 2012 (SEDIC)	19	45	35	45	10.9%	0.54 [0.37, 0.79]
Cleland 2005 (Telemon) (TENS-HMS)	80	168	46	85	13.8%	0.88 [0.68, 1.13]
Dendale 2012 (TEMA-HF1)	64	80	66	80	16.1%	0.97 [0.84, 1.13]
Goldberg 2003 (WHARF)	65	138	67	142	13.9%	1.00 [0.78, 1.28]
Lyngå 2012 (WISH)	79	166	84	153	14.7%	0.87 [0.70, 1.07]
Scherr 2009 (MOBITEL)	11	66	17	54	5.9%	0.53 [0.27, 1.03]
Woodend 2008	60	62	54	59	17.1%	1.06 [0.97, 1.16]
Subtotal (95% CI)		**753**		**647**	**100.0%**	**0.81 [0.66, 0.98]**
Total events	387		395			
Heterogeneity: Tau² = 0.06; Chi² = 42.18, df = 7 (P < 0.00001); I² = 83%						
Test for overall effect: Z = 2.12 (P = 0.03)						
2.2.2 Mixed						
Blum 2014 (MCCD)	80	104	74	102	24.4%	1.06 [0.90, 1.24]
Giordano 2009	67	230	96	230	17.0%	0.70 [0.54, 0.90]
Koehler 2011 (TIM-HF)	192	354	179	356	26.0%	1.08 [0.94, 1.24]
Mortara 2009 (Telemon) (HHH)	35	101	48	160	11.4%	1.16 [0.81, 1.65]
Seto 2012	14	50	10	50	3.8%	1.40 [0.69, 2.85]
Soran 2008	75	160	66	155	17.5%	1.10 [0.86, 1.41]
Subtotal (95% CI)		**999**		**1053**	**100.0%**	**1.02 [0.88, 1.18]**
Total events	463		473			
Heterogeneity: Tau² = 0.02; Chi² = 11.17, df = 5 (P = 0.05); I² = 55%						
Test for overall effect: Z = 0.25 (P = 0.80)						

Test for subgroup differences: Chi² = 3.43, df = 1 (P = 0.06), I² = 70.8%



E.11.2.3 Quality of life

E.11.2.3.1 Recent admission

Figure 190: SF-12 Physical

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
3.12.1 Recent admission							
Goldberg 2003 (WHARF)	6.7	10.4	138	4.3	11.4	142	2.40 [-0.15, 4.95]

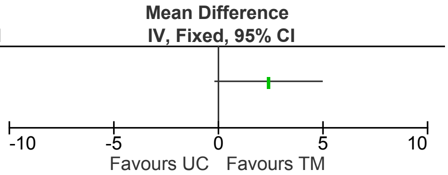


Figure 191: SF-12 Mental

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
3.13.1 Recent admission							
Goldberg 2003 (WHARF)	5.9	10.6	138	5.2	13.2	142	0.70 [-2.10, 3.50]

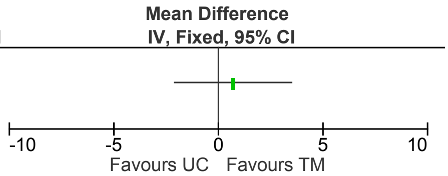


Figure 192: Health distress score

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
3.14.1 Recent admission							
Goldberg 2003 (WHARF)	4.8	8.3	138	5.5	8.8	142	-0.70 [-2.70, 1.30]

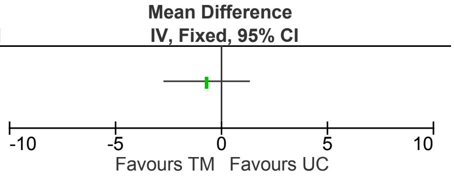


Figure 193: MLWHFQ

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
3.16.1 Recent admission				
Biannic 2012 (SEDIC)	-1.9	2.61	57.5%	-1.90 [-7.02, 3.22]
Goldberg 2003 (WHARF)	-4.5	3.0358	42.5%	-4.50 [-10.45, 1.45]
Subtotal (95% CI)			**100.0%**	**-3.01 [-6.88, 0.87]**

Heterogeneity: Chi² = 0.42, df = 1 (P = 0.52); I² = 0%
Test for overall effect: Z = 1.52 (P = 0.13)

Test for subgroup differences: Not applicable

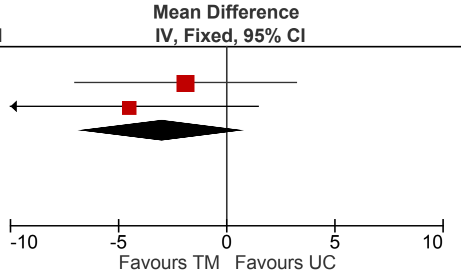


Figure 194: SF-36 Mental component summary

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
3.19.1 Recent admission							
Antonicelli 2008	53	12	28	48	9	29	5.00 [-0.52, 10.52]

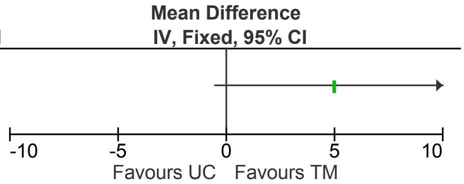
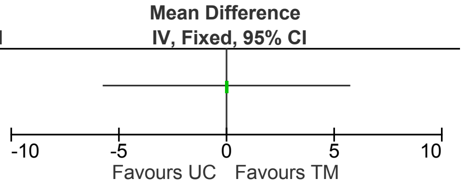


Figure 195: SF-36 Physical component summary

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
3.21.1 Recent admission							
Antonicelli 2008	39	11	28	39	11	29	0.00 [-5.71, 5.71]



1E.11.2.3.2 *Mixed*

Figure 196: SF-36 Physical functioning component

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
3.15.1 Mixed							
Koehler 2011 (TIM-HF)	53.8	1.4	354	51.7	1.4	356	2.10 [1.89, 2.31]

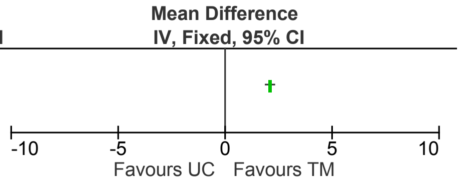


Figure 197: MLWHFQ

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
3.18.1 Mixed								
Blum 2014 (MCCD)	-24	24	102	-18	21	101	75.7%	-6.00 [-12.20, 0.20]
Seto 2012	41.4	26.7	38	47.3	23.4	44	24.3%	-5.90 [-16.85, 5.05]
Subtotal (95% CI)			**140**			**145**	**100.0%**	**-5.98 [-11.37, -0.58]**
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); I² = 0%								
Test for overall effect: Z = 2.17 (P = 0.03)								

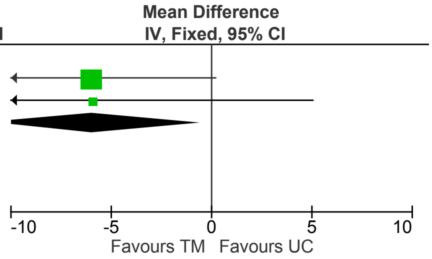


Figure 198: SF-36 Mental component summary

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
3.20.2 Mixed							
Blum 2014 (MCCD)	52	11	102	55	9	101	-3.00 [-5.76, -0.24]

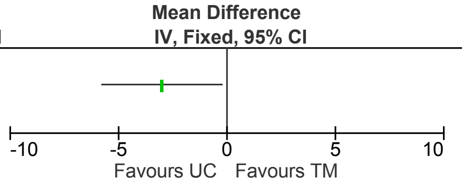
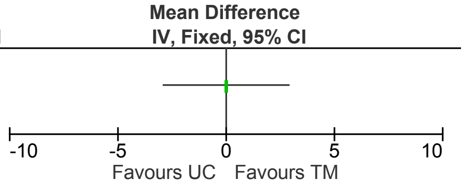


Figure 199: SF-36 Physical component summary

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
3.22.2 Mixed							
Blum 2014 (MCCD)	38	10	102	38	11	101	0.00 [-2.89, 2.89]



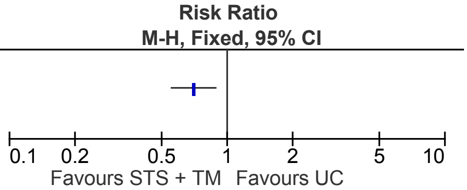
E.11.3 Structured telephone support + telemonitoring

E.11.3.1 All-cause mortality

E.11.3.1.1 Recent admission

Figure 200: Structured telephone support + telemonitoring versus usual care

Study or Subgroup	Experimental Events	Experimental Total	Usual Care Events	Usual Care Total	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Recent admission					
Ong 2016	100	715	144	722	0.70 [0.56, 0.89]

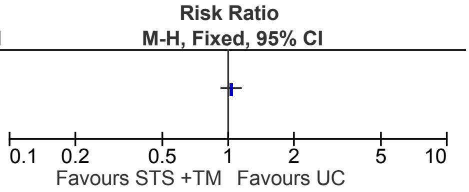


E.11.3.2 All-cause hospitalisation

E.11.3.2.1 Recent admission

Figure 201: Structured telephone support + telemonitoring versus usual care

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Risk Ratio M-H, Fixed, 95% CI
2.4.1 Recent admission					
Ong 2016	363	715	355	722	1.03 [0.93, 1.15]

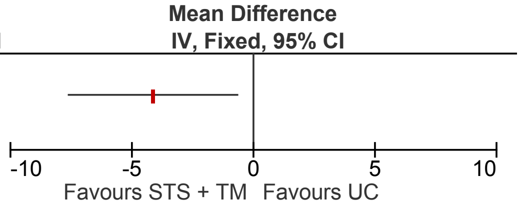


E.11.3.3 Quality of life

E.11.3.3.1 Recent admission

Figure 202: MLHWFQ

Study or Subgroup	Mean Difference	SE	Mean Difference IV, Fixed, 95% CI
3.23.1 Recent admission			
Ong 2016	-4.13	1.77	-4.13 [-7.60, -0.66]



E.11.4 Funnel plots

E.11.4.1 Telemonitoring versus usual care

Figure 203: All-cause mortality

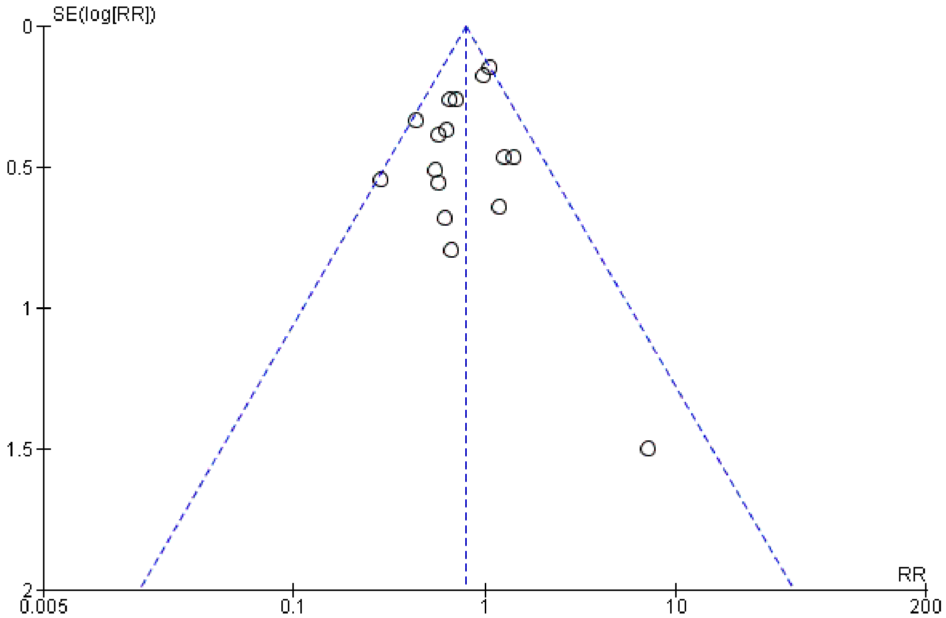
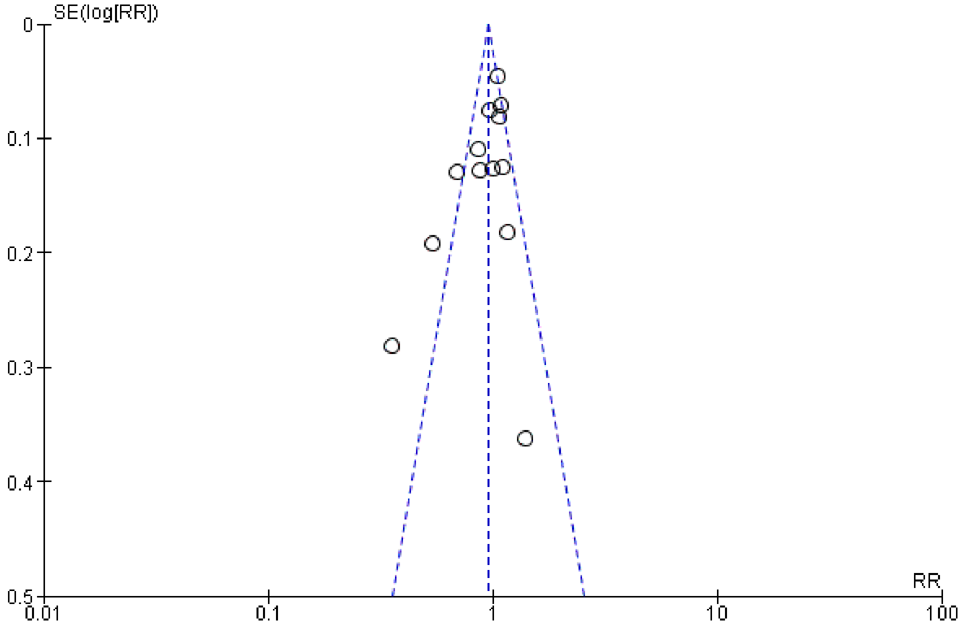


Figure 204: All-cause hospitalisation



E.11.4.2 Structured telephone support versus usual care

Figure 205: All-cause mortality

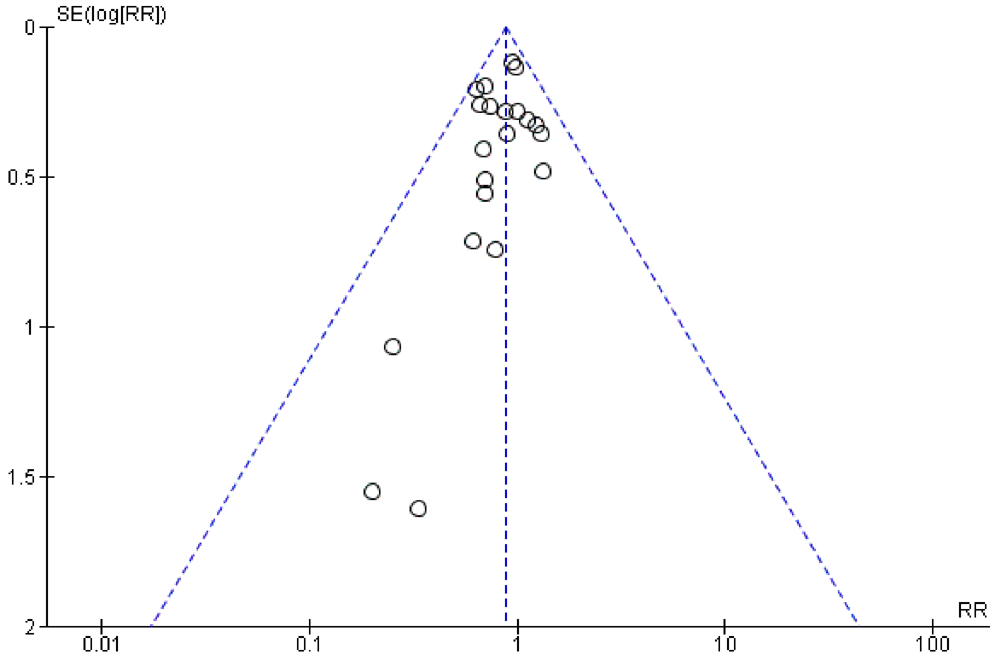
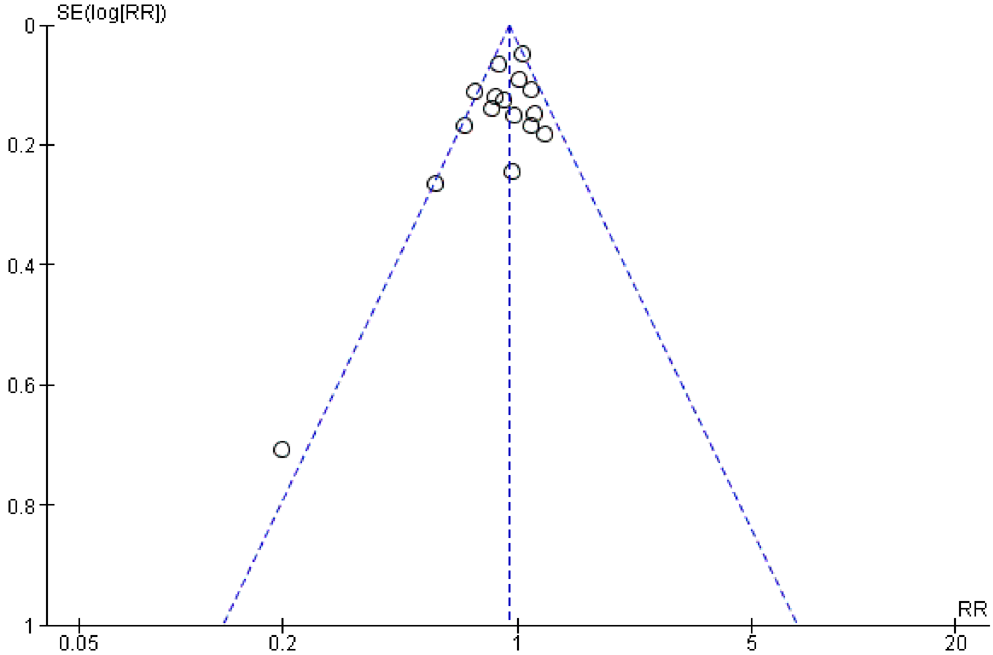


Figure 206: All-cause hospitalisation



E.12 Multi-Disciplinary Teams

E.12.1 Short MDT clinic vs usual care for high risk

Figure 207: Admissions to hospital during study

Study or Subgroup	log[Rate Ratio]	SE	MDT Total	Usual care Total	Rate Ratio IV, Fixed, 95% CI
Ledwidge 2003	-1.8971	0.76376262	51	47	0.15 [0.03, 0.67]
Rao 2007	0.463299	0.346989	59	53	1.59 [0.81, 3.14]

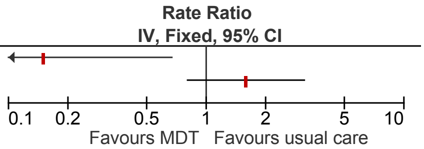


Figure 208: Deaths during study

Study or Subgroup	MDT Events	MDT Total	Usual care Events	Usual care Total	Risk Ratio M-H, Fixed, 95% CI
Ledwidge 2003	3	51	3	47	0.92 [0.20, 4.34]
Rao 2007	1	59	2	53	0.45 [0.04, 4.81]

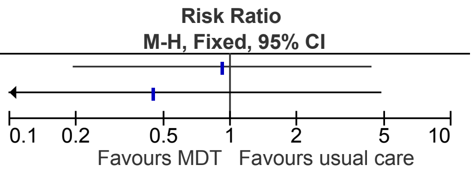


Figure 209: Proportion prescribed ACE-I

Study or Subgroup	MDT Events	MDT Total	Usual care Events	Usual care Total	Risk Ratio M-H, Fixed, 95% CI
Rao 2007	50	59	34	53	1.32 [1.05, 1.66]

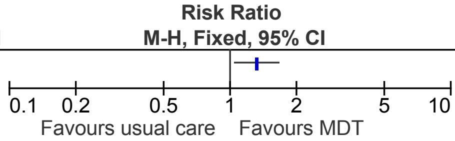
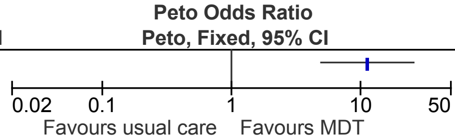


Figure 210: Proportion prescribed beta-blockers

Study or Subgroup	MDT Events	MDT Total	Usual care Events	Usual care Total	Peto Odds Ratio Peto, Fixed, 95% CI
Rao 2007	30	59	1	53	11.29 [4.95, 25.77]



E.12.2 Mid-length home-based MDT vs usual care for high risk

Figure 211: Admissions during study

Study or Subgroup	log[Rate Ratio]	SE	MDT Total	Usual care Total	Rate Ratio IV, Fixed, 95% CI
Brannstrom 2014 (PREFER study)	-1.26224	0.292463	36	36	0.28 [0.16, 0.50]

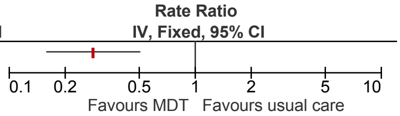


Figure 212: Deaths during study

Study or Subgroup	MDT Events	MDT Total	Usual care Events	Usual care Total	Risk Ratio M-H, Fixed, 95% CI
Brannstrom 2014 (PREFER study)	8	36	4	36	2.00 [0.66, 6.06]

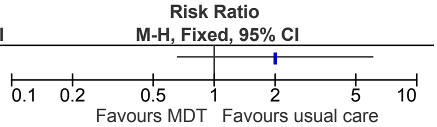
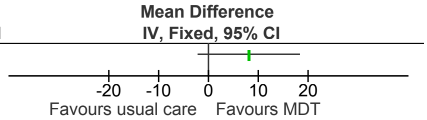


Figure 213: QoL: EQ5D final score (higher = better)

Study or Subgroup	MDT Mean	MDT SD	MDT Total	Usual care Mean	Usual care SD	Usual care Total	Mean Difference IV, Fixed, 95% CI
Brannstrom 2014 (PREFER study)	60.4	20.6	36	52.3	23.2	36	8.10 [-2.03, 18.23]



E.12.3 Mid-length MDT clinic vs usual care for high risk

Figure 214: Admissions during study

Study or Subgroup	log[Rate Ratio]	SE	MDT Total	Usual care Total	Rate Ratio IV, Fixed, 95% CI
Ducharme 2005	-0.38358	0.147772	115	115	0.68 [0.51, 0.91]
Gonzalez-Guerrero 2014	-0.08609	0.21455	59	58	0.92 [0.60, 1.40]
Nucifora 2006	-0	0.158122	99	101	1.00 [0.73, 1.36]

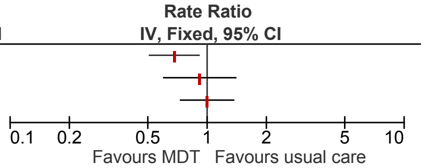


Figure 215: Deaths during study

Study or Subgroup	MDT Events	MDT Total	Usual care Events	Usual care Total	Risk Ratio M-H, Fixed, 95% CI
Ducharme 2005	12	115	19	115	0.63 [0.32, 1.24]
Gonzalez-Guerrero 2014	13	59	22	58	0.58 [0.32, 1.04]
Nucifora 2006	14	99	8	101	1.79 [0.78, 4.07]

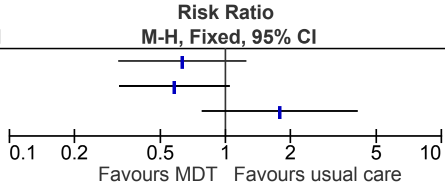


Figure 216: QoL: MLWHFQ final score (lower = better)

	MDT			Usual care			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Nucifora 2006	14	20	74	10	16	75	4.00 [-1.82, 9.82]	

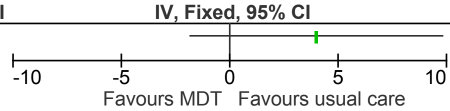


Figure 217: Proportion prescribed ACE inhibitor

	MDT		Usual care		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Nucifora 2006	68	85	75	93	0.99 [0.86, 1.15]	

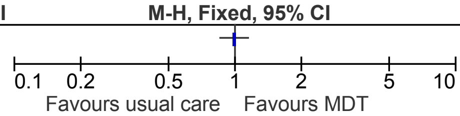


Figure 218: Proportion prescribed beta-blockers

	MDT		Usual care		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Nucifora 2006	12	85	18	93	0.73 [0.37, 1.42]	

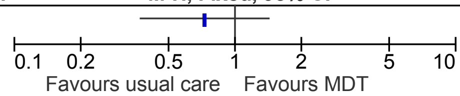
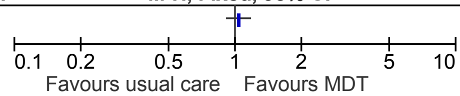


Figure 219: Proportion taking medication as prescribed

	MDT		Usual care		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Nucifora 2006	74	85	78	93	1.04 [0.92, 1.17]	



1 ## E.12.4 Mid-length nurse-led clinic vs usual care for high risk

Figure 220: Admissions during study

			MDT	Usual care	Rate Ratio	Rate Ratio
Study or Subgroup	log[Rate Ratio]	SE	Total	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Ekman 1998	-0.08797	0.148393	79	79	0.92 [0.68, 1.22]	

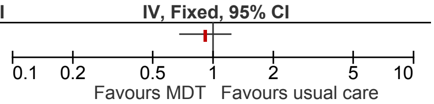


Figure 221: Admissions and emergency department attendances during study

			Rate Ratio	Rate Ratio
Study or Subgroup	log[Rate Ratio]	SE	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Driscoll 2014	-0.4056	1.1547	0.67 [0.07, 6.41]	

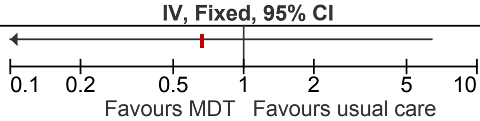


Figure 222: Deaths during study

	MDT		Usual care		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Ekman 1998	21	79	17	79	1.24 [0.71, 2.16]	

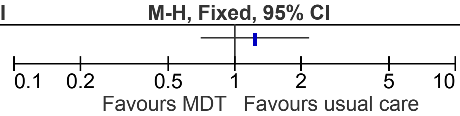


Figure 223: Deaths during study (Peto Odds ratio)

Study or Subgroup	MDT Events	MDT Total	Usual care Events	Usual care Total	Peto Odds Ratio Peto, Fixed, 95% CI
Driscoll 2014	1	12	0	13	8.03 [0.16, 406.02]

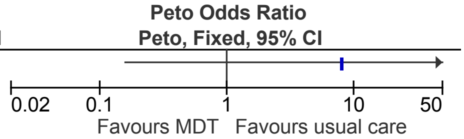


Figure 224: Symptoms: Change in NYHA class during study (lower = better)

Study or Subgroup	MDT Mean	MDT SD	MDT Total	Usual care Mean	Usual care SD	Usual care Total	Mean Difference IV, Fixed, 95% CI
Ekman 1998	-0.2	0.9	79	-0.3	0.7	79	0.10 [-0.15, 0.35]

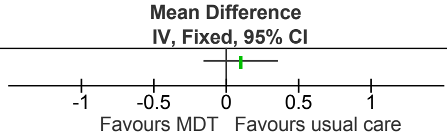


Figure 225: QoL: Change in score on MLWHFQ (lower = better)

Study or Subgroup	MDT Mean	MDT SD	MDT Total	Usual care Mean	Usual care SD	Usual care Total	Mean Difference IV, Fixed, 95% CI
Driscoll 2014	6.7	16.2	12	9.5	10.8	13	-2.80 [-13.68, 8.08]

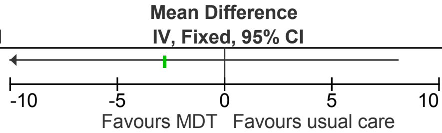


Figure 226: Proportion prescribed ACE-inhibitor

Study or Subgroup	MDT Events	MDT Total	Usual care Events	Usual care Total	Risk Ratio M-H, Fixed, 95% CI
Ekman 1998	49	70	47	75	1.12 [0.89, 1.41]

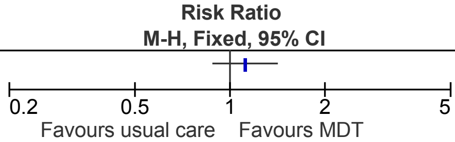
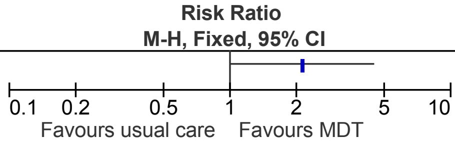


Figure 227: Proportion prescribed beta-blocker at optimal dose

Study or Subgroup	MDT Events	MDT Total	Usual care Events	Usual care Total	Risk Ratio M-H, Fixed, 95% CI
Driscoll 2014	9	11	5	13	2.13 [1.01, 4.47]



E.12.5 Mid-length case management vs usual care for high risk

Figure 228: Time to first hospital admission (hazard ratio)

Study or Subgroup	log[Hazard Ratio]	SE	MDT Total	Usual care Total	Hazard Ratio IV, Fixed, 95% CI
Tsuchihashi-Makaya 2013 (J-HOMECARE trial)	-0.6539	0.325	71	74	0.52 [0.28, 0.98]

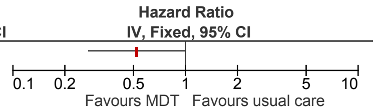


Figure 229: Deaths during study

Study or Subgroup	MDT Events	MDT Total	Usual care Events	Usual care Total	Risk Ratio M-H, Fixed, 95% CI
Tsuchihashi-Makaya 2013 (J-HOMECARE trial)	8	79	8	82	1.04 [0.41, 2.63]

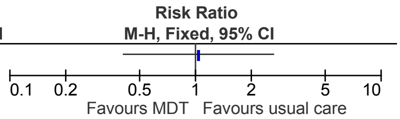


Figure 230: QoL: SF-8 physical component final score (higher = better)

Study or Subgroup	MDT Mean	MDT SD	MDT Total	Usual care Mean	Usual care SD	Usual care Total	Mean Difference IV, Fixed, 95% CI
Tsuchihashi-Makaya 2013 (J-HOMECARE trial)	44	9	70	42	10	68	2.00 [-1.18, 5.18]

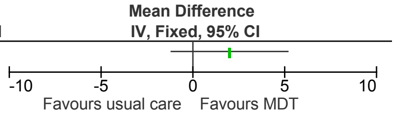
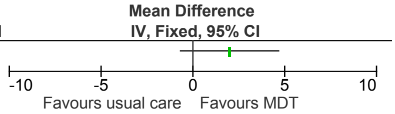


Figure 231: QoL: SF-8 mental health component final score (higher = better)

Study or Subgroup	MDT Mean	MDT SD	MDT Total	Usual care Mean	Usual care SD	Usual care Total	Mean Difference IV, Fixed, 95% CI
Tsuchihashi-Makaya 2013 (J-HOMECARE trial)	49	8	70	47	8	68	2.00 [-0.67, 4.67]



E.12.6 Long home-based MDT vs usual care for high risk

Figure 232: Admissions during study (rate ratio)

Study or Subgroup	log[Rate Ratio]	SE	MDT Total	Usual care Total	Rate Ratio IV, Fixed, 95% CI
Jaarsma 2008 (Intensive - COACH study)	0.09632	0.071488	339	344	1.10 [0.96, 1.27]

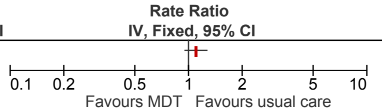
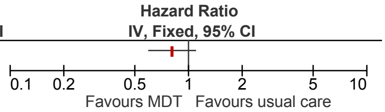


Figure 233: Deaths (time to event – hazard ratio)

Study or Subgroup	log[Hazard Ratio]	SE	MDT Total	Usual care Total	Hazard Ratio IV, Fixed, 95% CI
Jaarsma 2008 (Intensive - COACH study)	-0.2107	0.1531	340	339	0.81 [0.60, 1.09]



E.12.7 Long MDT clinic vs usual care for high risk

Figure 234: Admissions during study (rate ratio)

Study or Subgroup	log[Rate Ratio]	SE	MDT Total	Usual care Total	Rate Ratio IV, Fixed, 95% CI
8.3.1 All-cause hospitalisation					
Atienza 2004 (PRICE trial)	-0.39783	0.113849	164	174	0.67 [0.54, 0.84]
Doughty 2002 (Aukland-HF study)	-0.27992	0.121766	100	97	0.76 [0.60, 0.96]
8.3.2 HF hospitalisation					
Capomolla 2002	-1.70624	0.299572	112	122	0.18 [0.10, 0.33]

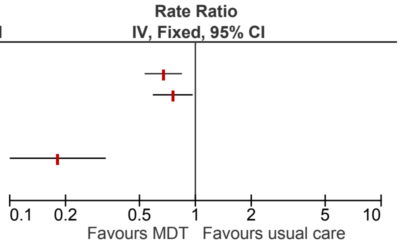


Figure 235: Proportion admitted during study

Study or Subgroup	MDT Events	MDT Total	Usual care Events	Usual care Total	Risk Ratio M-H, Fixed, 95% CI
Del Sindaco 2007	48	86	65	87	0.75 [0.60, 0.93]

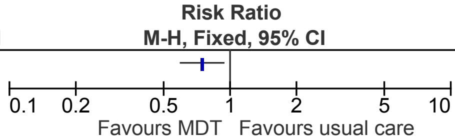


Figure 236: Days in hospital during study

Study or Subgroup	log[Rate Ratio]	SE	MDT Total	Usual care Total	Rate Ratio IV, Fixed, 95% CI
de la Porte 2007 (DEAL-HF study)	-0.5798	0.0681	118	122	0.56 [0.49, 0.64]

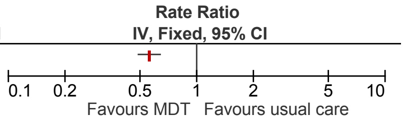


Figure 237: Deaths during study

Study or Subgroup	MDT Events	MDT Total	Usual care Events	Usual care Total	Risk Ratio M-H, Fixed, 95% CI
8.1.1 All-cause mortality					
Atienza 2004 (PRICE trial)	51	164	30	174	1.80 [1.21, 2.68]
de la Porte 2007 (DEAL-HF study)	12	118	23	122	0.54 [0.28, 1.03]
Del Sindaco 2007	27	86	32	87	0.85 [0.56, 1.29]
Doughty 2002 (Aukland-HF study)	19	100	24	97	0.77 [0.45, 1.31]
8.1.2 Cardiac death					
Capomolla 2002	3	112	21	122	0.16 [0.05, 0.51]

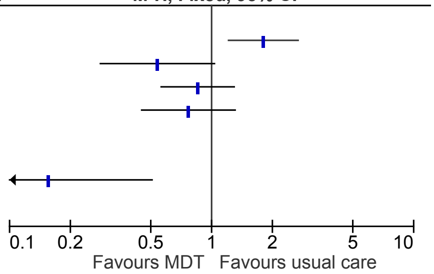


Figure 238: QoL: MLWHFQ final score (lower = better)

Study or Subgroup	MDT Mean	MDT SD	MDT Total	Usual care Mean	Usual care SD	Usual care Total	Mean Difference IV, Fixed, 95% CI
Atienza 2004 (PRICE trial)	28.9	6.1	110	35.5	7.9	110	-6.60 [-8.47, -4.73]

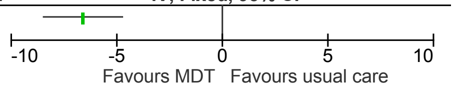


Figure 239: QoL: MLWHFQ change score (negative = better)

Study or Subgroup	MDT Mean	MDT SD	MDT Total	Usual care Mean	Usual care SD	Usual care Total	Mean Difference IV, Fixed, 95% CI
Doughty 2002 (Aukland-HF study)	-19.5	2.7	81	-12.5	2.5	73	-7.00 [-7.82, -6.18]

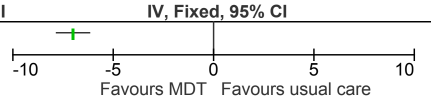


Figure 240: Utility: Time trade-off (higher = better)

Study or Subgroup	MDT Mean	MDT SD	MDT Total	Usual care Mean	Usual care SD	Usual care Total	Mean Difference IV, Fixed, 95% CI
Capomolla 2002	0.72	0.17	109	0.63	0.22	101	0.09 [0.04, 0.14]

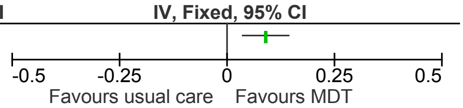


Figure 241: Proportion prescribed ACE-inhibitor

Study or Subgroup	MDT Events	MDT Total	Usual care Events	Usual care Total	Risk Ratio M-H, Fixed, 95% CI
Atienza 2004 (PRICE trial)	51	76	53	77	0.97 [0.78, 1.21]
Doughty 2002 (Aukland-HF study)	67	81	53	73	1.14 [0.96, 1.35]

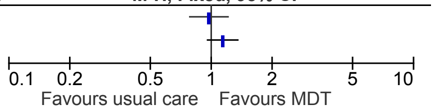


Figure 242: Average (?) dose ACE-inhibitor prescribed

Study or Subgroup	MDT Mean	MDT SD	MDT Total	Usual care Mean	Usual care SD	Usual care Total	Mean Difference IV, Fixed, 95% CI
Capomolla 2002	20	8	109	12	10	101	8.00 [5.54, 10.46]

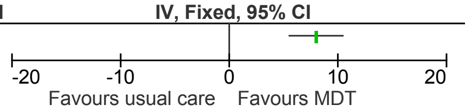


Figure 243: Proportion prescribed beta-blocker

Study or Subgroup	MDT Events	MDT Total	Usual care Events	Usual care Total	Risk Ratio M-H, Fixed, 95% CI
Atienza 2004 (PRICE trial)	48	76	30	77	1.62 [1.17, 2.25]

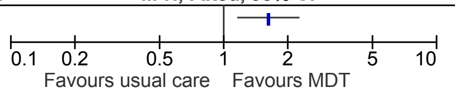
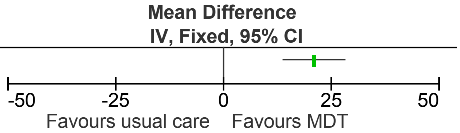


Figure 244: Average (?) dose beta-blocker prescribed

Study or Subgroup	MDT Mean	MDT SD	MDT Total	Usual care Mean	Usual care SD	Usual care Total	Mean Difference IV, Fixed, 95% CI
Capomolla 2002	34	23	109	13	29	101	21.00 [13.88, 28.12]



E.12.8 Long nurse-led clinic vs usual care for high risk

Figure 245: Admissions during study

Study or Subgroup	log[Rate Ratio]	SE	MDT Total	Usual care Total	Rate Ratio IV, Fixed, 95% CI
Jaarsma 2008 (Basic - COACH study)	0.014352	0.072884	340	344	1.01 [0.88, 1.17]
Mejhert 2004 OPTIMAL	-0.10763	0.064422	103	105	0.90 [0.79, 1.02]

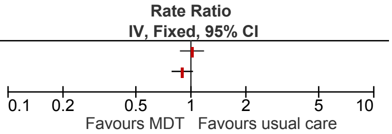


Figure 246: Deaths – time to event

Study or Subgroup	log[Hazard Ratio]	SE	MDT Total	Usual care Total	Hazard Ratio IV, Fixed, 95% CI
Jaarsma 2008 (Basic - COACH study)	-0.1278	0.1468	377	376	0.88 [0.66, 1.17]

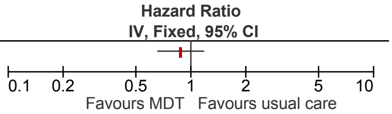


Figure 247: Deaths during study - count

Study or Subgroup	MDT Events	MDT Total	Usual care Events	Usual care Total	Risk Ratio M-H, Fixed, 95% CI
Mejhert 2004 OPTIMAL	40	103	34	105	1.20 [0.83, 1.73]

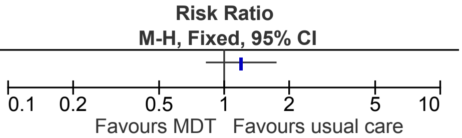


Figure 248: QoL: Nottingham Profile final score (lower = better)

Study or Subgroup	MDT Mean	MDT SD	MDT Total	Usual care Mean	Usual care SD	Usual care Total	Mean Difference IV, Fixed, 95% CI
Mejhert 2004 OPTIMAL	136	107	103	127	115	105	9.00 [-21.18, 39.18]

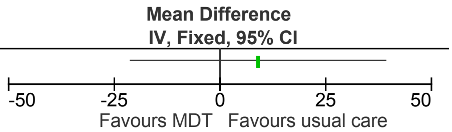


Figure 249: Proportion prescribed ACE-inhibitor

Study or Subgroup	MDT Events	MDT Total	Usual care Events	Usual care Total	Risk Ratio M-H, Fixed, 95% CI
Mejhert 2004 OPTIMAL	68	103	77	105	0.90 [0.75, 1.08]

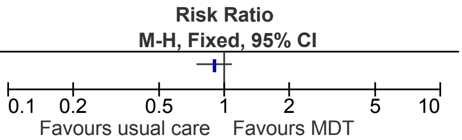
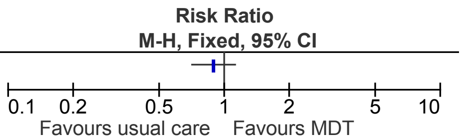


Figure 250: Proportion prescribed beta-blocker

Study or Subgroup	MDT Events	MDT Total	Usual care Events	Usual care Total	Risk Ratio M-H, Fixed, 95% CI
Mejhert 2004 OPTIMAL	57	103	65	105	0.89 [0.71, 1.12]



E.12.9 Long case management vs usual care for high risk

Figure 251: Proportion admitted to hospital during study

Study or Subgroup	MDT Events	MDT Total	Usual care Events	Usual care Total	Risk Ratio M-H, Fixed, 95% CI
Berger 2010	64	85	39	47	0.91 [0.76, 1.08]

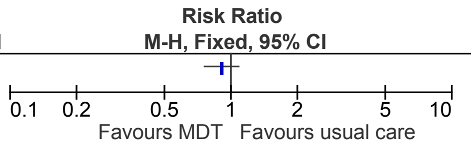


Figure 252: Deaths during study

Study or Subgroup	MDT Events	MDT Total	Usual care Events	Usual care Total	Risk Ratio M-H, Fixed, 95% CI
Berger 2010	21	96	35	90	0.56 [0.36, 0.89]

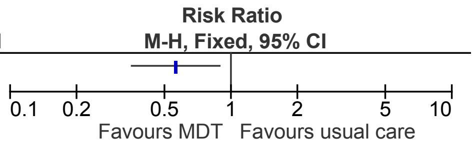


Figure 253: Proportion prescribed ACE-inhibitor or ARB

Study or Subgroup	MDT Events	MDT Total	Usual care Events	Usual care Total	Risk Ratio M-H, Fixed, 95% CI
Berger 2010	88	90	87	90	1.01 [0.96, 1.06]

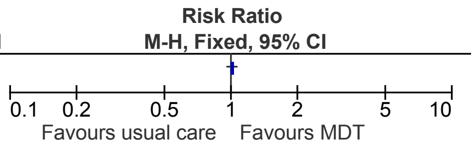
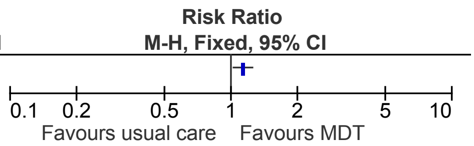


Figure 254: Proportion prescribed beta-blockers

Study or Subgroup	MDT Events	MDT Total	Usual care Events	Usual care Total	Risk Ratio M-H, Fixed, 95% CI
Berger 2010	92	96	76	90	1.13 [1.03, 1.25]



E.12.10 Extended follow-up in MDT clinic vs usual care for low risk

Figure 255: Admissions during study

Study or Subgroup	log[Rate Ratio]	SE	MDT Total	Usual care Total	Rate Ratio IV, Fixed, 95% CI
Schou 2013 (NorthStar study)	-0.05928	0.054457	460	460	0.94 [0.85, 1.05]

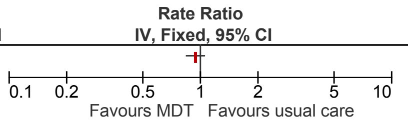


Figure 256: Deaths: time to event

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Fixed, 95% CI
Schou 2013 (NorthStar study)	0.0522	0.1803	1.05 [0.74, 1.50]

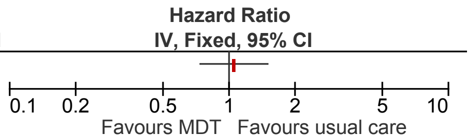


Figure 257: Prescribed ACE-Inhibitor at end of follow-up

Study or Subgroup	MDT Events	MDT Total	Usual care Events	Usual care Total	Risk Ratio M-H, Fixed, 95% CI
Schou 2013 (NorthStar study)	405	460	407	460	1.00 [0.95, 1.04]

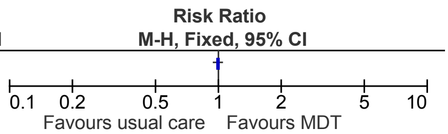


Figure 258: Prescribed beta-blockers at end of follow-up

Study or Subgroup	MDT Events	MDT Total	Usual care Events	Usual care Total	Risk Ratio M-H, Fixed, 95% CI
Schou 2013 (NorthStar study)	403	460	403	460	1.00 [0.95, 1.05]

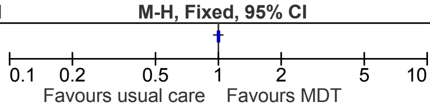


Figure 259: Adverse events: serum creatinine increased >50% at follow-up

Study or Subgroup	MDT Events	MDT Total	Usual care Events	Usual care Total	Risk Ratio M-H, Fixed, 95% CI
Schou 2013 (NorthStar study)	13	372	13	351	0.94 [0.44, 2.01]

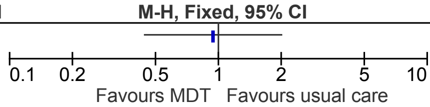


Figure 260: Adverse events: hyperkalaemia (K+>5mmol/l) at follow-up

Study or Subgroup	MDT Events	MDT Total	Usual care Events	Usual care Total	Risk Ratio M-H, Fixed, 95% CI
Schou 2013 (NorthStar study)	13	372	22	351	0.56 [0.29, 1.09]

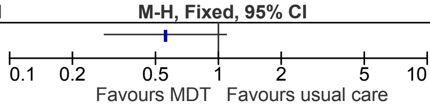
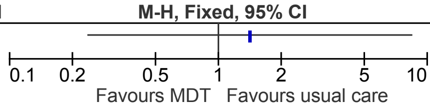


Figure 261: Adverse events: hypotensive (SBP<90mmHg) at follow-up

Study or Subgroup	MDT Events	MDT Total	Usual care Events	Usual care Total	Risk Ratio M-H, Fixed, 95% CI
Schou 2013 (NorthStar study)	3	372	2	351	1.42 [0.24, 8.42]



E.12.11 Long nurse-led clinic vs usual care for low risk

Figure 262: Admissions during study

Study or Subgroup	log[Rate Ratio]	SE	MDT Total	Usual care Total	Rate Ratio IV, Fixed, 95% CI
Agvall 2013	-0.32331	0.217682	79	81	0.72 [0.47, 1.11]

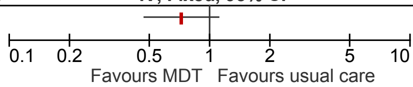


Figure 263: Deaths during study

Study or Subgroup	MDT Events	MDT Total	Usual care Events	Usual care Total	Risk Ratio M-H, Fixed, 95% CI
Agvall 2013	4	79	5	81	0.82 [0.23, 2.94]

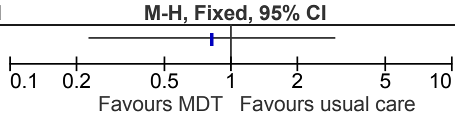


Figure 264: Prescribed ACE-inhibitors or ARB at follow-up

Study or Subgroup	MDT Events	MDT Total	Usual care Events	Usual care Total	Risk Ratio M-H, Fixed, 95% CI
Agvall 2013	79	79	68	81	1.19 [1.08, 1.31]

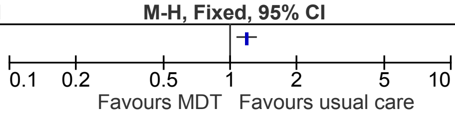


Figure 265: Prescribed beta-blocker at follow-up

Study or Subgroup	MDT Events	MDT Total	Usual care Events	Usual care Total	Risk Ratio M-H, Fixed, 95% CI
Agvall 2013	58	79	63	81	0.94 [0.79, 1.13]

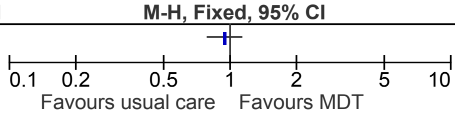
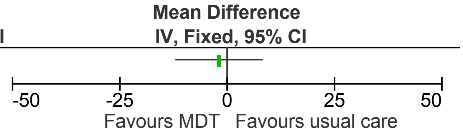


Figure 266: Adverse events: creatinine level (umol/l) at follow-up (lower = better)

	MDT			Usual care			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Agvall 2013	109.5	32.6	79	111.4	31.8	81	-1.90 [-11.88, 8.08]



E.12.12 Long pharmacist-led clinic vs usual care for low risk

Figure 267: Admissions during study

Study or Subgroup	log[Rate Ratio]	SE	MDT Total	Usual care Total	Rate Ratio IV, Fixed, 95% CI
Varma 1999	-0.68088	0.329341	42	41	0.51 [0.27, 0.97]

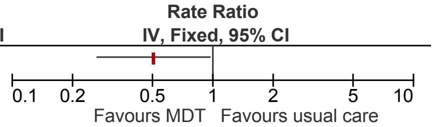


Figure 268: Deaths during study

	MDT		Usual care		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI
Varma 1999	7	42	7	41	0.98 [0.38, 2.54]

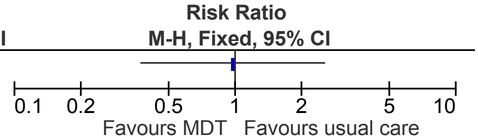


Figure 269: QoL: MLWHFQ final score (lower = better)

	MDT			Usual care			Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI
Varma 1999	12.7	9.9	26	19.1	10.2	23	-6.40 [-12.04, -0.76]

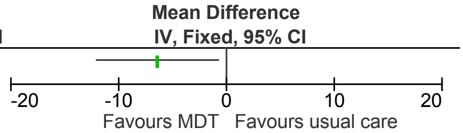


Figure 270: Proportion taking medicine as prescribed (self-report)

	MDT		Usual care		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI
Varma 1999	26	26	22	23	1.05 [0.93, 1.18]

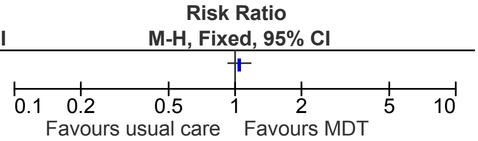
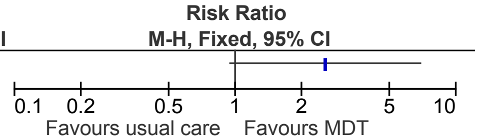


Figure 271: Proportion taking medicine as prescribed (objective measure)

	MDT		Usual care		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI
Varma 1999	10	13	3	10	2.56 [0.95, 6.92]



E.12.13 Long case management vs usual care for low risk

Figure 272: Admissions during study

Study or Subgroup	log[Rate Ratio]	SE	Rate Ratio IV, Fixed, 95% CI
Peters-Klimm 2010 (HICMan study)	0.20747	0.233263	1.23 [0.78, 1.94]

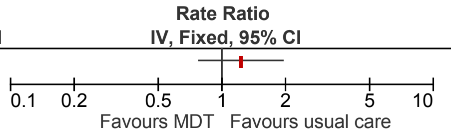


Figure 273: Deaths during study

Study or Subgroup	MDT Events	MDT Total	Usual care Events	Usual care Total	Risk Ratio M-H, Fixed, 95% CI
Martensson 2005	10	76	3	73	3.20 [0.92, 11.17]
Peters-Klimm 2010 (HICMan study)	5	92	5	98	1.07 [0.32, 3.56]

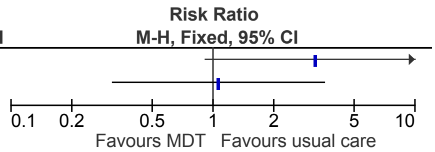


Figure 274: QoL: KCCQ final score (higher = better)

Study or Subgroup	MDT Mean	MDT SD	MDT Total	Usual care Mean	Usual care SD	Usual care Total	Mean Difference IV, Fixed, 95% CI
Peters-Klimm 2010 (HICMan study)	68	16.9	87	66.3	17.2	93	1.70 [-3.28, 6.68]

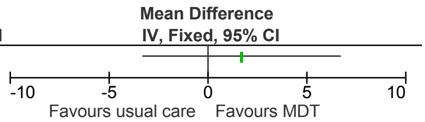


Figure 275: QoL: SF36 physical health composite final score 0-100 (higher = better)

Study or Subgroup	MDT Mean	MDT SD	MDT Total	Usual care Mean	Usual care SD	Usual care Total	Mean Difference IV, Fixed, 95% CI
Peters-Klimm 2010 (HICMan study)	38	8.6	61	38.3	8.6	70	-0.30 [-3.25, 2.65]

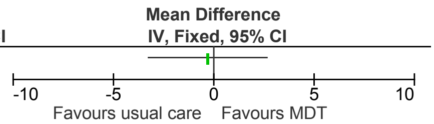


Figure 276: QoL: SF36 mental health composite final score 0-100 (higher = better)

Study or Subgroup	MDT Mean	MDT SD	MDT Total	Usual care Mean	Usual care SD	Usual care Total	Mean Difference IV, Fixed, 95% CI
Peters-Klimm 2010 (HICMan study)	46.5	9.9	61	46.6	9.9	70	-0.10 [-3.50, 3.30]

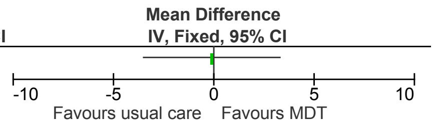


Figure 277: Prescribed ACE-inhibitor at target dose

Study or Subgroup	MDT Events	MDT Total	Usual care Events	Usual care Total	Risk Ratio M-H, Fixed, 95% CI
Martensson 2005	30	62	39	68	0.84 [0.61, 1.17]

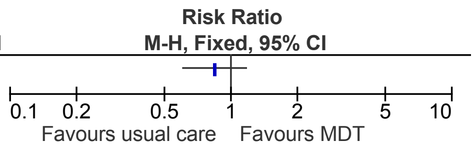


Figure 278: Prescribed beta-blockers at target dose

Study or Subgroup	MDT Events	MDT Total	Usual care Events	Usual care Total	Risk Ratio M-H, Fixed, 95% CI
Martensson 2005	14	62	16	68	0.96 [0.51, 1.80]

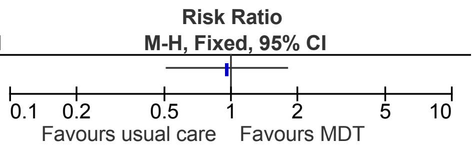
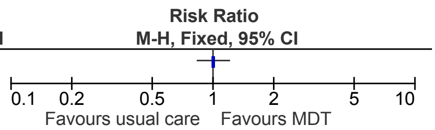


Figure 279: Prescribed double therapy of ACE/ARB and beta-blocker

Study or Subgroup	MDT Events	MDT Total	Usual care Events	Usual care Total	Risk Ratio M-H, Fixed, 95% CI
Peters-Klimm 2010 (HICMan study)	63	87	67	93	1.01 [0.84, 1.20]



E.13 Transition between heart failure care settings

None.

E.14 Communication needs regarding diagnosis and prognosis

None.

E.15 Diuretics in advanced heart failure

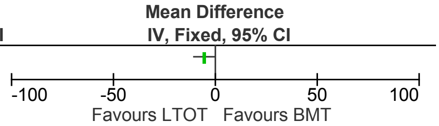
None.

E.16 Domiciliary oxygen therapy in people with advanced heart failure

E.16.1 Quality of life (MLWHF) at 3 months

Figure 280: Long term oxygen therapy versus best medical therapy

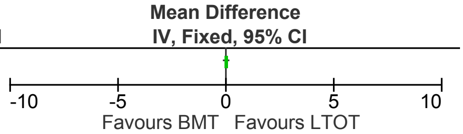
Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
Clark 2015	46.5	13.1042	53	52	13.1042	53	-5.50 [-10.49, -0.51]



E.16.2 Quality of life (EQ-5D-3L) at 6 months

Figure 281: Long term oxygen therapy versus best medical therapy

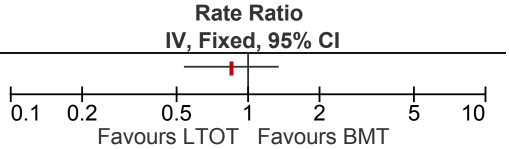
Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
Clark 2015	0.55	0.23	45	0.54	0.3	43	0.01 [-0.10, 0.12]



E.16.3 Hospitalisation at 24 months

Figure 282: Long term oxygen therapy versus best medical therapy

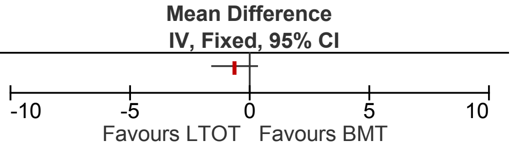
Study or Subgroup	log[Rate Ratio]	SE	Rate Ratio IV, Fixed, 95% CI
Clark 2015	-0.1625	0.2301	0.85 [0.54, 1.33]



E.16.4 NRS for breathlessness at 6 months

Figure 283: Long term oxygen therapy versus best medical therapy

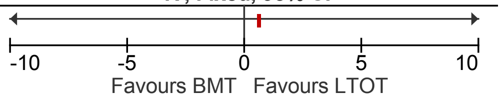
Study or Subgroup	Mean Difference	SE	Mean Difference IV, Fixed, 95% CI
Clark 2015	-0.63	0.4796	-0.63 [-1.57, 0.31]



E.16.5 6 minute walk test

Figure 284: Long term oxygen therapy versus best medical therapy

Study or Subgroup	Mean Difference	SE	Mean Difference IV, Fixed, 95% CI
Clark 2015	0.64	17.9493	0.64 [-34.54, 35.82]

Mean Difference IV, Fixed, 95% CI


E.17 Discussing Implantable Cardioverter Defibrillator (ICD) deactivation

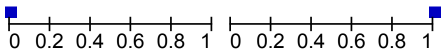
None.

E.18 Identifying patients with an increased risk of mortality

E.18.1 SHFM (at threshold 50% predicted mortality)

Figure 285: SHFM (at threshold 50% predicted mortality)

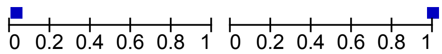
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Allen 2017	8	5	1653	7616	0.00 [0.00, 0.01]	1.00 [1.00, 1.00]

Sensitivity (95% CI) Specificity (95% CI)


E.18.2 MAGGIC project heart failure risk score (at threshold 50% predicted mortality)

Figure 286: MAGGIC project heart failure risk score (at threshold 50% predicted mortality)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Allen 2017	52	63	1609	7558	0.03 [0.02, 0.04]	0.99 [0.99, 0.99]

Sensitivity (95% CI) Specificity (95% CI)


Appendix F: Clinical evidence tables

F.1 BNP and NT-proBNP in diagnosing heart failure

F.1.1 General population

Reference	**Cowie 1997[330]**
Study type	Single gate diagnostic accuracy study (cross-sectional)
Study methodology	Data source: Part of the Hillingdon Heart Failure Study, which identified incident (new) cases of clinical heart failure developing in a population of 151 000 served by 81 general practitioners in 31 practices in Hillingdon District, west London. Recruitment: All consecutive patients referred to a rapid-access heart failure clinic with new suspected heart failure during 15 month study period (April 1995 to July 1996).
Number of patients	n = 122
Patient characteristics	Age, range: 24 – 87 Gender (male to female ratio): 59:63 Setting: Outpatient clinic Country: United Kingdom Inclusion criteria: Suspected heart failure Exclusion criteria: Previous history of heart failure. NYHA class: 86% of diagnosed patients had symptoms on mild/moderate exertion, 14% had symptoms at rest. Background medication: Long term diuretics – 31%, newly commenced diuretic – 21%.
Target condition(s)	Heart failure

Reference	Cowie 1997[330]
Index test(s) and reference standard	Index test(s) Plasma BNP at the following thresholds: 77 pg/mL. Measured with a 'standard commercial kit' (Peninsula Laboratories Europe Ltd). Between-assay and within-assay coefficients of variation: 14.8% and 9.9%. Laboratory reference range 8.0 – 15.2 pg/mL. The threshold for which results were reported was the one at which the NPV was 98%. Reference standard Criteria recommended by the Working Group on Heart Failure of the European Society of Cardiology as assessed by a panel of three cardiologists blinded to the peptide results. A diagnosis of heart failure required appropriate symptoms (shortness of breath, fatigue, fluid retention) with clinical signs of fluid retention (pulmonary or peripheral) in the presence of an underlying abnormality of cardiac structure and function. One cardiologist took a standardised medical history and clinically examined all patients. ECG, chest radiography and transthoracic echocardiography were performed (echo by same cardiologist or one of two experienced cardiac technicians in accordance with a standard protocol and accepted guidelines. Time between measurement of index test and reference standard: Cardiologist examination, imaging and collection of blood samples occurred on the same day.

2x2 table BNP 77 pg/mL		Reference standard +	Reference standard -	Total
	Index test +	30	12	42
	Index test -	1	63	64
	Total	31	75	106

Statistical measures	Index test: BNP 77 pg/mL Sensitivity: 97% Specificity: 84% PPV: 70% NPV: 98% AUC (95% CI): 0.96
Source of funding	British Heart Foundation and Wellcome Trust.
Limitations	Risk of bias: Low Indirectness: No serious indirectness
Comments	Prevalence of heart failure: 29%

Reference	**Kelder 2011[749]**
Study type	Single gate diagnostic accuracy study (cross-sectional)
Study methodology	Data source: Utrecht Heart Failure Organisation – Initial Assessment (UHFO-IA) study. Recruitment: First 200 patients included in UHFO-IA study had their blood drawn for assessment in this study. Patients suspected of heart failure by their general practitioner were referred to rapid access heart failure outpatient diagnostic facilities available in eight hospitals.
Number of patients	n = 200
Patient characteristics	Age, Mean (SD): 70.2 (11.3) Gender (male to female ratio): 59:113 Setting: Outpatient Country: The Netherlands Inclusion criteria: Patients suspected of heart failure by their general practitioner. Exclusion criteria: Previous diagnosis of heart failure or acute signs and symptoms demanding immediate treatment. Diabetes: 16.9%; Atrial fibrillation: 4.7%, eGFR, mL/min/m^2, mean (SD): 62.9 (15.0), Ejection fraction > 45-50% on echocardiogram: 75.6%, BMI, mean (SD): 29.5 (5.4) Background medication: ACEI – 30.2%, BB – 28.5%, loop diuretic – 35.5%.
Target condition(s)	Heart failure
Index test(s) and reference standard	<u>Index test(s)</u> • Plasma NT-proBNP at the following thresholds: 400 pg/mL, 2000 pg/mL. Measured with an automated noncompetitive immunoradiometric assay (Roche) on an Elecsys 1010 analyzer. Coefficient of variation: 4.4%. • Plasma BNP at the following thresholds: 100 pg/mL, 400 pg/mL. Measured with automated Abbott Axsym BNP immunoassay (Abbott). Coefficient of variation: 5.5%. • Plasma BNP at the following thresholds: 100 pg/mL, 400 pg/mL. Measured with Advia Centaur BNP immunoassay (Siemens Healthcare Diagnostics). Coefficient of variation: 0.8%. <u>Reference standard</u>

Reference	Kelder 2011[749]			
	Decision of an expert panel consisting of a cardiologist, a pulmonologist, and a GP, based on the results of all diagnostic tests: medical history, anamnesis, physical examination, laboratory values, ECG, spirometry, chest x-ray, echocardiography, and 6 months of clinical follow up data. The panel did not receive the BNP results. The final decision was made following the criteria for heart failure of the 2008 ESC guideline and the Heart Failure Society of America 2010 heart failure guideline. Time between measurement of index test and reference standard: NR.			
2x2 table		Reference standard +	Reference standard -	Total
	Index test +	1	0	1
NT proBNP	Index test -	50	121	171
2000 pg/mL	Total	51	121	172
2x2 table		Reference standard +	Reference standard -	Total
	Index test +	5	46	51
BNP	Index test -	0	121	121
400 pg/mL (Axsym assay)	Total	5	167	172
2x2 table		Reference standard +	Reference standard -	Total
	Index test +	3	0	3
BNP	Index test -	48	121	169
400 pg/mL (Centaur assay)	Total	51	121	172
2x2 table **NT pro-BNP 400pg/ml and BNP 100pg/ml**	Not calculable.			
Statistical measures **NT-proBNP**	 Index test: NT-proBNP 400 pg/mL NPV (95% CI): 76% (69% - 82%) Index test: NT-proBNP 2000 pg/mL			

Reference	Kelder 2011[749]
	Sensitivity: 2% Specificity: 100% PPV: 100% NPV: 71% <u>Index test: NT-proBNP</u> AUC (95% CI): 0.86 (0.80 – 0.92)
BNP – Axsym	<u>Index test: BNP 100 pg/mL</u> NPV (95% CI): 81% (73% - 87%) <u>Index test: BNP 400 pg/mL</u> Sensitivity: 10% Specificity: 100% PPV: 100% NPV: 72% <u>Index test: BNP</u> AUC (95% CI): 0.82 (0.73 – 0.90)
BNP - Centaur	<u>Index test: BNP 100 pg/mL</u> NPV (95% CI): 80% (73% - 86%) <u>Index test: BNP 400 pg/mL</u> Sensitivity: 6% Specificity: 100% PPV: 100% NPV: 72% <u>Index test: BNP</u> AUC (95% CI): 0.83 (0.76 - 0.91)
Source of funding	Government funded (Dutch Ministry of Health). Assays provided by industry.

Reference	**Kelder 2011[749]**
Limitations	Risk of bias: Low Indirectness: No serious indirectness
Comments	Prevalence of heart failure: 29.7%

1

Reference	**Nielsen 2003[1057]**
Study type	Single gate diagnostic accuracy study (cross-sectional)
Study methodology	Data source: 74 general practitioners Recruitment: Consecutive patients presenting to a general practitioner in the investigators' hospital region complaining of dyspnoea of at least 2 weeks duration. On referral the general practitioner indicated whether the cause of the dyspnoea was considered likely to be heart failure, lung disease or a combination. Inclusion period from October 1998 to October 2000.
Number of patients	n = 363
Patient characteristics	Age, Median (range): 65 (18-89) (however results in the 58 patients < 50 years of age were not reported) Gender (male to female ratio): 178:169 Setting: Hospital-based clinic Country: Denmark Inclusion criteria: Dyspnoea of at least 2 weeks duration Exclusion criteria: None reported Fletcher dyspnoea scale: Grade 1 – 19%, Grade 2 – 17%, Grade 3 – 16%, Grade – 24%, Grade 5 – 23% Suspected diagnosis on referral: heart failure – 39%, pulmonary disease – 36%, combination – 15%, other/no suspected diagnosis reported – 10%. Background medication: NR.
Target condition(s)	Heart failure
Index test(s)	Index test(s)

Reference	**Nielsen 2003[1057]**			
and reference standard	Plasma NT-proBNP at the following thresholds: Men ≥ 50 years: 76 pg/mL, 93 pg/mL, 152 pg/mL. Women ≥ 50 years: 67 pg/mL, 144 pg/mL, 26 pg/mL. Analysed using a sandwich immunoassay (EIMA) with two antibodies (Roche Diagnostics). The results were stratified for both age and sex and the reported thresholds selected from the ROC curves, with the middle threshold in each group representing NPV of 97%. The results for < 50 years (58 patients) were not reported due to the low prevalence (3%) in this group. <u>Reference standard</u> Criteria for heart failure published by the European Society of Cardiology, demanding symptoms of heart failure and objective evidence of cardiac dysfunction at rest. Cardiac dysfunction was diagnosed and categorised by echocardiography (included both systolic and diastolic dysfunction). Time between measurement of index test and reference standard: NR			
2x2 table		Reference standard +	Reference standard -	Total
	Index test +	47	40	87
Men ≥ 50 years	Index test -	0	59	60
NT-proBNP 76 pg/mL	Total	47	99	146
2x2 table		Reference standard +	Reference standard -	Total
	Index test +	45	33	77
Men ≥ 50 years	Index test -	2	66	68
NT-proBNP 93 pg/mL	Total	47	99	146
2x2 table		Reference standard +	Reference standard -	Total
	Index test +	42	21	63
Men ≥ 50 years	Index test -	5	78	83
NT-proBNP 152 pg/mL	Total	47	99	146
2x2 table		Reference standard +	Reference standard -	Total
	Index test +	34	78	112
Women ≥ 50 years	Index test -	0	29	29
NT-proBNP 67 pg/mL	Total	34	107	141
2x2 table		Reference standard +	Reference standard -	Total
	Index test +	32	33	65

Reference	Nielsen 2003[1057]			
Women ≥ 50 years NT-proBNP 144 pg/mL	Index test -	2	74	76
	Total	34	107	141
2x2 table **Women ≥ 50 years NT-proBNP 220 pg/mL**		Reference standard +	Reference standard -	Total
	Index test +	31	17	48
	Index test -	3	90	93
	Total	34	107	141
Statistical measures	**Men ≥ 50 years** <u>Index test: NT-proBNP </u> 76 pg/mL Sensitivity: 100% Specificity: 60% PPV: 53% NPV: 100% <u>Index test: NT-proBNP </u> 93 pg/mL Sensitivity: 96% Specificity: 67% PPV: 57% NPV: 97% <u>Index test: NT-proBNP </u> 152 pg/mL Sensitivity: 89% Specificity: 79% PPV: 66% NPV: 94% <u>Index test: NT-proBNP</u> AUC (95% CI): 0.93 (0.89 – 0.97) **Women ≥ 50 years**			

Reference	Nielsen 2003[1057]
	<u>Index test: NT-proBNP</u> 67 pg/mL Sensitivity: 100% Specificity: 27% PPV: 29% NPV: 100% <u>Index test: NT-proBNP</u> 144 pg/mL Sensitivity: 94% Specificity: 69% PPV: 48% NPV: 97% <u>Index test: NT-proBNP</u> 220 pg/mL Sensitivity: 91% Specificity: 84% PPV: 64% NPV: 97% <u>Index test: NT-proBNP</u> AUC (95% CI): 0.90 (0.84 – 0.97)
Source of funding	Danish Heart Foundation. Roche Diagnostics supplied the assays for analysis.
Limitations	Risk of bias: High (patient selection – uncertain whether all consecutive patients were referred; flow and timing – the results of patients under 50 years of age were not reported “due to the low prevalence of heart failure in this group”) Indirectness: Serious indirectness (population – see above)
Comments	Prevalence of heart failure: 24%

1

Reference	O’Shea 2012[1068]
Study type	Single gate prospective diagnostic accuracy study (cross-sectional)
Study methodology	Data source: Cardiology Department (single centre) Recruitment: Patients presenting with dyspnoea, or oedema and a working diagnosis of HF referred to the Cardiology Department at Beaumont

Reference	O'Shea 2012[1068]
	Hospital in Dublin by their GP were invited to participate.
Number of patients	n = 105 (74 patients completed study)
Patient characteristics	*NB: Below details are of completing patients, not all patients recruited* Age, Median (range): 69 (47-85) Gender (male to female ratio): 41:33 Setting: Outpatient Country: Ireland Inclusion criteria: Dyspnoea, or oedema and a working diagnosis of HF Exclusion criteria: People aged under 18 years and pregnant women were excluded NYHA class: class I – 4%, class II – 81%, class III – 15% Myocardial infarction: 18%; Diabetes: 24%; Hypertension: 55%; eGFR, mL/min/m^2, median (range): 75 (27-105); BNP, pg/mL, median (range): 111 (4-1175); BMI, mean (SD): 29 (20-51). Background medication: ACEi – 61%, BB – 45%, calcium channel blockers – 23%, statins – 57%, diuretics – 53%, no medication – 10%.
Target condition(s)	Heart failure
Index test(s) and reference standard	<u>Index test(s)</u> Plasma BNP at the following thresholds: 178 pg/mL. Biosite assay using the Beckman DxI Immunoassay analyser. Based on immobilised 2-site immunoenzymatic assay, measuring range 5-5000 pg/mL, coefficient of variation at BNP concentrations of 87.4 pg/mL, 416.1 pg/mL and 22555.9 pg/mL were 3.6%, 1.7% and 2.1% respectively. The inter-assay precision (n=20) at BNP concentrations of 85.6 pg/mL, 419.1 pg/mL, and 2204.2 pg/mL were CVs of 5.7%, 6.2%, and 4.4% respectively. Threshold was selected to "rule in" HF to prioritise patients for ECHO. <u>Reference standard</u> HF was diagnosed on clinical assessment and objective evidence based on ECHO. ECHO was performed by a cardiac technician and confirmed by a

Reference	O'Shea 2012[1068]			
	cardiology specialist, who observed all ECHOs performed. Both technicians and clinicians were blind to the BNP results. A consultant cardiologist reviewed the report and patients were graded according to one of four groups: normal, systolic heart failure, diastolic heart failure and HF as a result of valvular disease. Time between measurement of index test and reference standard: Average time between bloods being taken for BNP and ECHO was 75 days (range 38-142 days) for men and 80 days (range 21-163 days) for women.			
2x2 table BNP 178 pg/mL		Reference standard +	Reference standard -	Total
	Index test +	23	2	25
	Index test -	26	23	49
	Total	49	25	74
Statistical measures	<u>Index test: BNP 178 pg/mL</u> Sensitivity: 47% Specificity: 92% PPV: 92% NPV: 47% <u>Index test: BNP</u> AUC (95% CI): 0.69 (0.57 – 0.79)			
Source of funding	NR			
Limitations	Risk of bias: Very high (patient selection – not clear that a consecutive or random sample of patients enrolled; flow and timing – high proportion of recruited patients lost to follow up without explanation, long time period between BNP test and ECHO). Indirectness: Serious indirectness (population with prevalence of HF over two times higher than other populations included in review suggesting it is not representative of target population in review protocol).			
Comments	Prevalence of heart failure: 66.2%			

1

Reference	Taylor 2017[1365]
Study type	Single gate diagnostic accuracy study (cross-sectional)
Study methodology	Data source: Random sample of 28 general practices, stratified by practice list size and deprivation quartile. Recruitment: Participating practices were asked to invite all presenting patients who met the inclusion criteria to join the study consecutively.

Reference	Taylor 2017[1365]
	Assessment was then undertaken at the research clinic within 7 days of initial presentation to GP.
Number of patients	n = 304
Patient characteristics	Age, Mean (SD): 73.9 (8.8) Gender (male to female ratio): 124:180 Setting: GP/outpatient Country: United Kingdom Inclusion criteria: Primary care patients > 55 years presenting with recent new-onset shortness of breath, lethargy or peripheral ankle oedema of > 48 hours duration for which there was no other obvious cause. Exclusion criteria: Unable to consent, previous confirmed diagnosis of heart failure (with objective evidence), obvious alternative diagnosis, severe symptoms requiring immediate management, or recent (within 60 days) acute coronary syndrome. NYHA class: NR (Presenting symptoms as follows: ankle oedema – 82%, breathlessness – 81%, lethargy – 74%. Over half of participants had all three symptoms.) Myocardial infarction: 11%; Diabetes: 28%; Hypertension: 73%, COPD: 6%. Background medication: ACEi – 32.3%, ARB – 19.1%, BB – 27%, diuretics – 44.7%.
Target condition(s)	Heart failure
Index test(s) and reference standard	<u>Index test(s)</u> • Plasma NT-proBNP at the following thresholds: 125 pg/mL, 280 pg/mL*, 400 pg/mL. Measured with point-of-care device (Roche Diagnostics, UK). *Data at this threshold were obtained directly from the authors. <u>Reference standard</u> Expert consensus panel of three cardiology specialists, who reviewed each case blinded to the assessments by other panel members. The ESC 2012

Reference	Taylor 2017[1365]			
	guideline was used to define heart failure. To assess incorporation bias, the panel was presented with clinical information and investigation results in three separate stages. At Step 1, clinical assessment (excluding the clinical decision rule (CDR) variables), ECG, and echo findings were presented. At Step 2, the CDR components (male, history of myocardial infarction, crepitations, and oedema) were added and finally, at Step 3, the NT-proBNP result was included. The cardiology specialists were asked to record if the patient did or did not have heart failure at each of the three steps. The diagnostic accuracy results extracted and analysed in this review are after Step 2 (that is, panel members were blinded to the NT-proBNP test results). Time between measurement of index test and reference standard: None (same day)			
2x2 table		Reference standard +	Reference standard -	Total
	Index test +	75	125	200
NT-proBNP 125 pg/mL	Index test -	14	90	104
	Total	89	215	304
2x2 table		Reference standard +	Reference standard -	Total
	Index test +	59	66	125
NT-proBNP 280 pg/mL	Index test -	30	149	179
	Total	89	215	304
2x2 table		Reference standard +	Reference standard -	Total
	Index test +	52	45	96
NT-proBNP 400 pg/mL	Index test -	37	170	208
	Total	89	215	304
Statistical measures	<u>Index test: NT-proBNP 125 pg/mL</u> Sensitivity: 84% Specificity: 42% PPV: 38% NPV: 87% <u>Index test: NT-proBNP 280 pg/mL</u> Sensitivity: 66% Specificity: 69%% PPV: 47%			

Reference	Taylor 2017[1365]
	NPV: 83% <u>Index test: NT-proBNP 400 pg/mL</u> Sensitivity: 58% Specificity: 79% PPV: 54% NPV: 82% <u>Index test: NT-proBNP</u> AUC (95% CI): 0.74 (0.68 – 0.80)
Source of funding	Roche Diagnostics provided the NT-proBNP testing equipment but did not have any influence on study design, conduct, or reporting. Two authors report support/fees from industry unrelated to the present study.
Limitations	Risk of bias: Low Indirectness: No serious indirectness
Comments	Prevalence of heart failure: 29.3% (calculated by review authors from accuracy statistics, based on Step 2 application of reference standard)

Reference	Verdu 2012[1442]
Study type	Single gate diagnostic accuracy study (cross-sectional)
Study methodology	Data source: Two primary care centres in Barcelona staffed by 28 GPs with catchment population of 40,000 inhabitants Recruitment: All consecutive patients in whom echocardiography was requested by a primary care physician to investigate suspected HF were invited to participate, regardless of their comorbidities or current medical treatment. Enrolment period was January 2007 to June 2009. 221 patients were conducted by telephone and only 1 declined to participate.
Number of patients	n = 220
Patient characteristics	Age, Mean (SD): 73.2 (19.2) Gender (male to female ratio): 76:144 Setting: Primary care Country: Spain

Reference	Verdu 2012[1442]			
	Inclusion criteria: GP-suspected heart failure Exclusion criteria: Previous diagnosis of heart failure or severe valve disease in the digitized clinical history, and those included in a home care programme. NYHA class: class I – 10.9%, class II – 86.4%, class II – 2.7% Diabetes: 18.2%; Complete arrhythmia caused by atrial fibrillation: 19.3%; hypertension: 85.6%; eGFR <60 mL/min: 23.6%; BMI, mean (SD): 30.4 (4.9). Background medication: ACEi or ARB – 61.5%, BB – 24.5%, loop diuretics – 27.3%, thiazide – 27.3%, spironolactone – 2.7%, digoxin – 5.4%.			
Target condition(s)	Heart failure			
Index test(s) and reference standard	<u>Index test(s)</u> Plasma NT-proBNP at the following thresholds: 125 pg/mL, 280 pg/mL, 400 pg/mL, Hildebrant age-specific thresholds as follows: <50 years 50 pg/mL, 50-75 years 75 pg/mL, > 75 years 250 pg/mL. Measured with a Cobas h 232 system from Roche Diagnostics, which uses an immunochromatographic reagent strip to obtain quantitative results in whole blood (150 uL) at point of care. Test results were obtained in 12 mins. The instrument was calibrated using a 1 code chip every 10 measurements. Analytical range 60 – 3000 pg/mL. The threshold of 280 pg/mL was reported as it was “the optimal cut-off point to rule out HF”. <u>Reference standard</u> The diagnosis was based on the presence of signs and symptoms of HF and objective evidence of a structural or functional cardiac abnormality at reset. Diagnosis was made by a single cardiologist in the HF unit of the reference hospital (where the echocardiography was carried out). Diagnosis was based on individual data obtained for each patient in the enrolment visit (clinical history, physical examination, ECG, chest X-ray) and echocardiography, strictly following the criteria of the ESC. Time between measurement of index test and reference standard: NR			
2x2 table		Reference standard +	Reference standard -	Total
	Index test +	52	57	109
NT-proBNP 125 pg/mL	Index test -	0	111	111
	Total	52	168	220
2x2 table		Reference standard +	Reference standard -	Total

Reference	Verdu 2012[1442]			
NT-proBNP 280 pg/mL	Index test +	52	20	72
	Index test -	0	148	148
	Total	52	168	220
2x2 table NT-proBNP 400 pg/mL		Reference standard +	Reference standard -	Total
	Index test +	46	17	62
	Index test -	6	151	158
	Total	52	168	220
2x2 table Hildebrandt age specific thresholds: < 50 years NT-proBNP 50 pg/mL 50-75 years NT-proBNP 75 pg/mL > 75 years NT-proBNP 250 pg/mL		Reference standard +	Reference standard -	Total
	Index test +	52	50	102
	Index test -	0	118	118
	Total	52	168	220
Statistical measures	<u>Index test: NT-proBNP 125 pg/mL</u> Sensitivity: 100% Specificity: 66% PPV: 48% NPV: 100% <u>Index test: NT-proBNP 280 pg/mL</u> Sensitivity: 100% Specificity: 88%			

Reference	Verdu 2012[1442]
	PPV: 72% NPV: 100% Index test: NT-proBNP 400 pg/mL Sensitivity: 88% Specificity: 90% PPV: 73% NPV: 96% Index test: NT-proBNP age specific threshold (<50 years 50 pg/mL, 50-75 years 75 pg/mL, > 75 years 250 pg/mL) Sensitivity: 100% Specificity: 70% PPV: 50% NPV: 100% Index test: NT-proBNP AUC (95% CI): 0.94 (0.91 – 0.97)
Source of funding	Catalan Society of Family and Community Medicine.
Limitations	Risk of bias: Low Indirectness: No serious indirectness
Comments	Prevalence of heart failure: 23.6%

Reference	Zaphiriou 2005[1524]
Study type	Single gate diagnostic accuracy study (cross-sectional)
Study methodology	Data source: General practitioner referrals to rapid access heart failure clinics in five participating centres. Recruitment: Consecutive patients referred by their GPs to the rapid access heart failure clinics in five participating centres.
Number of patients	n = 306
Patient	Age, Median (90% range): 74 (52 – 87)

Reference	Zaphiriou 2005[1524]
characteristics	Gender (male to female ratio): 130:176 Setting: Outpatient Country: United Kingdom Inclusion criteria: Patients presenting to their GP with new symptoms suggestive of heart failure. Exclusion criteria: Previous documented history of heart failure. NYHA class: class 1 – 6%, class 2 – 63.1%, class 3 – 25.5%, class 4 – 4.6%. Myocardial infarction: 14%; Diabetes: 19%. Background medication: NR
Target condition(s)	Heart failure
Index test(s) and reference standard	Index test(s) • Plasma NT-proBNP at the following thresholds: 125 pg/mL, 166 pg/mL, 280 pg/mL*, 400 pg/mL*. Measured with automated ELISA assay on the Elecsys system (Roche) at core laboratory in Glasgow. • Plasma BNP at the following thresholds: 100 pg/mL, 65 pg/mL, 30 pg/mL. Measured using point-of-care fluorescence immunoassay (Biosite Diagnostics) at each centre. *Data at these thresholds were obtained directly from the authors. Reference standard Heart failure was diagnosed by the cardiologist only if there was at least one symptom of heart failure (shortness of breath, fatigue, leg oedema) at rest or on exertion and objective evidence of cardiac dysfunction at rest on assessment including echocardiography, as recommended by the ESC. The diagnosing physicians were blind to the BNP and NT-proNBP results. Time between measurement of index test and reference standard: NR

2x2 table		Reference standard +	Reference standard -	Total

Reference	Zaphiriou 2005[1524]			
NT-proBNP 125 pg/mL	Index test +	101	128	229
	Index test -	2	71	73
	Total	103	199	302
2x2 table		Reference standard +	Reference standard -	Total
NT-proBNP 166 pg/mL	Index test +	99	113	212
	Index test -	4	86	90
	Total	103	199	302
2x2 table		Reference standard +	Reference standard -	Total
NT-proBNP 280 pg/mL	Index test +	92	75	167
	Index test -	11	124	135
	Total	103	199	302
2x2 table		Reference standard +	Reference standard -	Total
NT-proBNP 400 pg/mL	Index test +	87	62	149
	Index test -	16	137	153
	Total	103	199	302
2x2 table		Reference standard +	Reference standard -	Total
BNP 30 pg/mL	Index test +	97	129	226
	Index test -	5	70	75
	Total	102	199	301
2x2 table		Reference standard +	Reference standard -	Total
BNP 65 pg/mL	Index test +	89	85	174
	Index test -	13	113	127
	Total	102	199	301
2x2 table		Reference standard +	Reference standard -	Total
BNP 100 pg/mL	Index test +	80	56	136
	Index test -	21	143	165
	Total	102	199	301

Reference	Zaphiriou 2005[1524]
Statistical measures	Index test: NT-proBNP 125 pg/mL Sensitivity: 98% Specificity: 36% PPV: 44% NPV: 97% Index test: NT-proBNP 166 pg/mL Sensitivity: 96% Specificity: 43% PPV: 47% NPV: 96% Index test: NT-proBNP 280 pg/mL Sensitivity: 89% Specificity: 62% PPV: 55% NPV: 92% Index test: NT-proBNP 400 pg/mL Sensitivity: 84% Specificity: 69% PPV: 58% NPV: 90% Index test: NT-proBNP AUC (95% CI): 0.85 (0.81 – 0.90) Index test: BNP 30 pg/mL Sensitivity: 95% Specificity: 35% PPV: 43% NPV: 93% Index test: BNP 65 pg/mL

Reference	Zaphiriou 2005[1524]
	Sensitivity: 87% Specificity: 57% PPV: 51% NPV: 90% <u>Index test: BNP 100 pg/mL</u> Sensitivity: 79% Specificity: 72% PPV: 59% NPV: 87% <u>Index test: BNP</u> AUC (95% CI): 0.84 (0.79 – 0.89)
Source of funding	Costs of assays met by industry.
Limitations	Risk of bias: Low Indirectness: No serious indirectness
Comments	Prevalence of heart failure: 34%

Reference	Zuber 2009[1536]
Study type	Single gate prospective diagnostic accuracy study (cross-sectional)
Study methodology	Data source: Multi-centre study in three hospital-based ambulatory cardiology centres and five cardiology private practices Recruitment: Consecutive patients referred by the GP with a suspected clinical diagnosis of congestive heart failure
Number of patients	n = 384
Patient characteristics	Age, Mean (SD): 65 (13) Gender (male to female ratio): 245:139 Setting: Outpatient Country: Switzerland

Reference	Zuber 2009[1536]
	Inclusion criteria: GP suspected congestive heart failure based on symptoms and clinical examination Exclusion criteria: None reported NYHA class: class II - 85%, class III – 11%, class IV – 4% CAD: 26%; Diabetes: 27%; Atrial fibrillation: 3%; creatinine clearance MDRF (ml/min), mean (SD): 62 (36); BMI, mean (SD): 27 (4.3). Background medication: ACEi/ARB – 50%, BB – 50%, diuretics – 39%, digoxin – 4%.
Target condition(s)	Congestive heart failure
Index test(s) and reference standard	<u>Index test(s)</u> • Plasma BNP at the following thresholds: to rule out CHF: < 100 pg/mL or < 200 pg/mL in patients with eGFR < 60 ml/min or < 60 pg/mL in patients with BMI > 30; to confirm CHF: > 400 pg/mL or > 200 pg/mL in patients with BMI > 30. Measured with the Biosite Triage test. • Plasma NT-proBNP at the following thresholds: to rule out CHF: < 125 pg/mL; to confirm CHF: > 450 pg/mL in patients < 50 years, > 900 pg/mL for patients 50-75 years, and > 1800 pg/mL in patients older than 75 years. Carried out in central laboratory with fully automated immune-assay Elecsys pro BNP test within 2 days. <u>Reference standard</u> Examining cardiologist (one of seven) confirmed or excluded heart failure according to the results of the echocardiography as the gold standard for the documentation of a systolic and/or diastolic dysfunction. Systolic heart failure was defined as presence of CHF symptoms and an EF < 50%, according to the ESC criteria. Isolated diastolic heart failure was defined as presence of clinical signs and/or symptoms of CHF accompanied by Doppler parameters indicating elevated LV filling pressure. Inter-observer variability was tested and was 0.9 for the ejection fraction, 0.99 for the E-wave, 0.92 for deceleration time, 0.97 for A-wave and 0.98 for Ea. Time between measurement of index test and reference standard: NR
2x2 table	Not calculable – data on total number of heart failure diagnoses, number of true positives, false negatives and false positives does not add up.
Statistical measures	<u>Index test: BNP</u> AUC (95% CI): 0.691 <u>Index test: NT-proBNP</u>

Reference	Zuber 2009[1536]
	AUC (95% CI): 0.742
Source of funding	Roche Diagnostics provided an “unrestricted grant to measure NTproBNP levels”. Unclear if this related to the conduct of the whole study or just the assays.
Limitations	Risk of bias: Very high (patient selection – appears that patients may have been selectively referred; flow and timing – missing data rates not reported; reporting – accuracy data reported throughout paper does not add up) Indirectness: Serious indirectness (population with prevalence of HF two times higher than other populations included in review suggesting it is not representative of target population in review protocol).
Comments	Prevalence of heart failure: 58%

F.1.2 Chronic kidney disease

Reference	Yang 2008[1508]
Study type	Single gate diagnostic accuracy study (cross-sectional)
Study methodology	Data source: Nephrology Department Recruitment: Patients with CKD who visited the Department of Internal Medicine (Division of Nephrology) between May 2001 and May 2006 with respiratory distress.
Number of patients	n = 182
Patient characteristics	Age, Mean (SD): 60 (13) Gender (male to female ratio): 99:83 Setting: Outpatient Country: South Korea Inclusion criteria: Patients with ≥ 6 month history of impaired renal function (eGFR < 60 mL/min/1.73m2) who had been diagnosed with CKD, whose chief complaint was respiratory distress greater than/at least (?inconsistent reporting in paper) NYHA class II. Exclusion criteria: Patients with past histories of COPD, liver cirrhosis, malignant tumour, or multiple trauma.

Reference	Yang 2008[1508]
	CKD class: class III – 32%, class IV – 29%, class V – 39% (of whom 53% on haemodialysis and 32% on peritoneal dialysis) Ejection fraction, % mean (SD): 56% (15.6); BMI, mean (SD): 22.9 (3.3). Background medication: Nitrates – 39%, ACEi – 79%, ARB – 47%, BB – 66%, diuretics – 63%.
Target condition(s)	Heart failure
Index test(s) and reference standard	Index test(s) Plasma BNP at the following thresholds: 859 pg/mL (whole study population), 410 pg/mL (CKD stages 3 & 4), 1650 pg/mL (CKD stage 5). Measurements were performed prior to dialysis in dialysis patients. Measurements were obtained by immunofluorescence labelling using a BNP kit (Triage; Biosite), with upper and lower limits of detection of 5,000 pg/mL and 5 pg/mL respectively. Reference standard Diagnostic criteria for HF were based on history, radiological findings, and echocardiographic findings, which included clinical symptoms fulfilling Framingham's criteria, LVEF < 50% on echocardiography, and (sic) LV diameter at end-diastole greater than 5.5 cm. [NB: assume that this was meant to read EF< 50% "OR" dilated LV, not "AND". No mention of whether or not a cardiologist carried out this assessment.] Time between measurement of index test and reference standard: NR
2x2 table **CKD 3 & 4 BNP 410 pg/mL**	

		Reference standard +	Reference standard -	Total
2x2 table		Reference standard +	Reference standard -	Total
CKD 3 & 4 BNP 410 pg/mL	Index test +	39	6	46
	Index test -	9	57	65
	Total	48	63	111

Statistical measures	Index test: CKD 3 & 4 BNP 410 pg/mL Sensitivity: 82% Specificity: 90% PPV: 86% NPV: 87% AUC: 0.94

Reference	Yang 2008[1508]
Source of funding	Not reported.
Limitations	Risk of bias: Very high (patient selection – manner of patient enrolment not specified; reference standard – not clear whether adjudicators were blinded to BNP results; flow and timing – whether any patients were missing not reported). Indirectness: Serious indirectness (reference standard – reference standard unclear and may not match protocol).
Comments	Prevalence of heart failure: overall – 44%, CKD 3 & 4 – 43%, CKD 5 – 45%

F.2 Cardiac Magnetic Resonance Imaging in heart failure

No clinical evidence was identified.

F.3 Salt and fluid restriction

Study	Colin-ramirez 2015[300]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=38)
Countries and setting	Conducted in Canada; Setting: Specialty HF clinic. Used electronic capture tools.
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Normal sodium

Subgroup analysis within study	Not applicable:
Inclusion criteria	Adults with confirmed diagnosis (HFREF or HFPEF) on optimally tolerated therapy according to guidelines, NYHA II-III
Exclusion criteria	Serum sodium<130, GFR <20, cardiac event in last month (including fitting device), comorbidities included uncontrolled thyroid disease, atrial fibrillation >90bpm, end-stage hepatic failure, anything likely to interfere with protocol or expected life expectancy <2y due to non-cardiac cause.
Recruitment/selection of patients	Patients were recruited from a specialty heart failure clinic, the Heart Function Clinic of the Mazankowski Alberta Heart Institute in Edmonton, Canada.
Age, gender and ethnicity	Age - Median (IQR): 65.5 (56.3 - 72.1). Gender (M:F): 20:18. Ethnicity: White - 95%; Afro-American - 3%; and, South Asian - 3%.
Further population details	
Extra comments	Baseline Characteristics, median(IQR): Ejection fraction (%): Low - 46.5 (30.0-59.5), moderate - 34.5 (24.0-45.0) NYHA class II, (%): low - 84.2, moderate - 94.7 Creatinine (umol/L): low - 104 (75-138), moderate - 93 (75-118) On beta-blockers (%): low - 90, mod 90 On loop diuretics (%): low - 15.8, mod 21.1
Indirectness of population	No indirectness
Interventions	(n=19) Intervention 1: Programme - Salt restriction programme. Salt restriction <1500 mg/day. Provided with dietary recommendations and a set of six daily sample menus according to their energy requirements and targeted sodium intake. Patients were told to avoid sodium-rich foods (processed, packaged, preprepared, cured, and fast foods) and condiments such as mustard, ketchup, soy sauce, teriyaki sauce, and salad dressings. They were also asked to use low or free-sodium cereals. Patients in this group were not allowed to use salt for cooking or at the table; they were encouraged to flavor foods with lemon juice, vinegar, herbs, spices, garlic, onions, and no added salt seasonings instead of salt. Duration 6 months Concurrent medication/care: Patients were prescribed a normocaloric diet consistent with the guidelines for a

	cardiovascular healthy diet. Patients received conventional pharmacological and nonpharmacological treatment of heart failure, according to current CCS guidelines, and were asked to follow the recommendations for fluid restriction provided by the clinician as per clinical practice. Comments: Actual sodium intake after six months median 1398mg/day (IQR 1090-2060) (n=19) Intervention 2: Programme - Salt restriction programme. Salt restriction <2300 mg/day. Provided with dietary recommendations and a set of six daily sample menus according to their energy requirements and targeted sodium intake. Patients were encouraged to avoid sodium rich foods (processed, packaged, pre-prepared, cured, and fast foods) and to limit condiments such as mustard, ketchup, soy sauce, teriyaki sauce, and salad dressings. Patients in this group were allowed to use only 1/4 of teaspoon of salt (575 mg sodium) a day for preparing their meals (to cook meat, potato, pasta, bean, or to prepare homemade salad dressings). Duration 6 months. Concurrent medication/care: Patients were prescribed a normocaloric diet consistent with the guidelines for a cardiovascular healthy diet. Patients received conventional pharmacological and nonpharmacological treatment of heart failure, according to current CCS guidelines, and were asked to follow the recommendations for fluid restriction provided by the clinician as per clinical practice. Comments: Actual sodium intake after six months median 1461 mg/day (IQR 1086-1765)
Funding	Academic or government funding (Study was funded by a University Hospital Foundation (Edmonton, Canada) grant.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOW SALT PROGRAMME versus MODERATE SALT PROGRAMME

Protocol outcome 1: Quality of life at 12 months
- Actual outcome for Normal sodium: Quality of life at 6 months; Other: Median and quartile scores:
Low salt programme - baseline 59.6 (39.1-73.2), 6mo 64.6 (50.3 - 86.1)
Mod salt programme - baseline 65.5 (55.2-82.3), 6mo 72.4 (63.8-86.3).
Kansas City Cardiomyopathy Questionnaire (KCCQ) 0-100 Top=High is good outcome;
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Differed in outcome at baseline (>5pt difference), pt not blind.; Indirectness of outcome: No indirectness; Baseline details: Low salt - 59.6 (39.1-73.2); moderate salt - 65.5 (47.7 - 82.3).; Blinding details: Only the patient and the dietician were aware of treatment allocation. Patients were asked not to disclose their treatment allocation with the rest of the clinical or research team. ; Group 1 Number missing: 2, Reason: 1x Withdrew consent, 1 x died.; Group 2 Number missing: 1, Reason: 1x Withdrew consent.

Protocol outcome 2: Adverse events - Renal function at 12 months - Actual outcome for Normal sodium: Creatinine umol/L at 6 months ; Other: Median (IQR): Low sodium group - baseline 104 (75-138), 6 months 110.5 (92.5-133); Moderate sodium group - 93 (75-118), 6 months 106.5 (78-114); Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Differed in outcome at baseline (>10pt difference).; Indirectness of outcome: No indirectness, Comments: Continuous creatinine rather than dichotomous renal function; Baseline details: Low salt: 104 (75-138), Mod salt: 93 (75-118); Blinding details: Only the patient and the dietician were aware of treatment allocation. Patients were asked not to disclose their treatment allocation with the rest of the clinical or research team. ; Group 1 Number missing: 2, Reason: 1x Withdrew consent, 1 x died.; Group 2 Number missing: 1, Reason: 1x Withdrew consent.	
Protocol outcomes not reported by the study	Unplanned Hospitalisation at as reported ; Adverse events - Hyperkalaemia at 12 months; Change in weight at 12 months; Change in oedema at 12 months ; Change in sodium level at 12 months; Change in appetite at 12 months

Study	**Reilly 2015**[1195]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=25)
Countries and setting	Conducted in USA; Setting: Large centre for heart failure in south-east USA
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable

Inclusion criteria	NYHA class II-IV with a prescribed fluid regimen of 1.5-2L/day. All were enrolled in a trial of intrathoracic impendence monitoring device, had been hospitalised during the last six months and were on appropriate medical treatment with daily diuretics, ACEi/ARB and beta-blocker (or documented contraindication).
Exclusion criteria	More than 100 miles from centre, physical or mental impairment that would prevent engagement, inability to read English, presence of a medical disorder that could exacerbate heart failure, eg renal failure, anaemia, uncontrolled hypothyroidism.
Age, gender and ethnicity	Age - Mean (SD): 62.96 (9.76). Gender (M:F): 14:11. Ethnicity: African American 20%, Caucasian 80%
Further population details	
Extra comments	60% had heart failure >4y, 52% grade III or higher HF. All had fluid restriction, 92% attempting to follow this prior to the intervention.. 76% married, 40% college or higher educated, 80% attempting to follow a sodium restriction at baseline
Indirectness of population	Serious indirectness: Required to have been hospitalised in the last six months and have intrathoracic impendence monitoring device The paper reports that this study is "… part of a larger trial evaluating FR adherence and outcomes in patients with an intrathoracic impedance measurement (IIM) device… Although inclusion criteria required the presence of an IIM device, the impedance values were not collected by the researcher until study conclusion… the values were being evaluated for their clinical utility, and care was primarily influenced by traditional provider physical assessment. Thus, patients with an IIM device in this study received care comparable with patients who did not have an IIM device."
Interventions	(n=13) Intervention 1: Programme - Fluid restriction programme. Educational-based intervention: Used self-care framework, aiming to increase adherence with fluid prescription. Included education and motivation sessions, daily logging of fluid intake, phonecalls providing support, giving feedback and encouraging adherence with fluid restriction. Duration 6 months. Concurrent medication/care: Medical therapy, 2000mg/day sodium restriction. Given an hour-long education session about HF, prescribed medication, and the need for salt and fluid restriction and daily weights. Comments: Actual fluid intake at three months in ml was mean 1703 (sd 433) (n=12) Intervention 2: Advice - Attention control received same fluid prescription and contacts, but interaction more general. Received phonecalls to review weight log. Duration 6 months. Concurrent medication/care: Medical treatment, 2000mg/day sodium restriction. Given an hour-long education session about HF, prescribed medication, and the need for salt and fluid restriction and daily weights.

	Comments: Actual fluid intake at three months was 2021ml (sd 881)
Funding	Academic or government funding (Supported by NIH grant (through National Centre for Advancing Translational Science); and Biosite, inc. grant in aid of equipment and supplies)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FLUID RESTRICTION PROGRAMME versus FLUID RESTRICTION ADVICE Protocol outcome 1: Quality of life at 12 months - Actual outcome: EQ5D-VAS at 6 months; Group 1: mean 61.82 (SD 19.27); n=11, Group 2: mean 70.5 (SD 18.77); n=10; EQ5D-VAS 0-100 Top=High is good outcome; Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Disequilibrium for many plausible confounding factors at baseline. Unclear whether pts would have been aware whether they were int or control groups.; Indirectness of outcome: No indirectness ; Baseline details: EQ5D Vas scores: programme 56.8, advice 58.6; Blinding details: Advice group were given attention equal to education group - unlikely to be aware control group; Group 1 Number missing: 2, Reason: 2 "did not complete"; Group 2 Number missing: 2, Reason: 2 "did not complete" Protocol outcome 2: Change in oedema at 12 months - Actual outcome: Congestion score at 3 months; Group 1: mean 1.25 (SD 1.6); n=12, Group 2: mean 1.18 (SD 1.25); n=11; Congestion score 0-5 Top=Unclear; Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Disequilibrium of some confounding variables at baseline. Unclear if established scale. Unclear level of blinding; Indirectness of outcome: Serious indirectness, Comments: Measures "congestion", which is compound of orthopnea, JV distension, peripheral oedema, increase in weight, need to adjust diuretic dose.; Baseline details: Congestion scores: Control 1.50 (1.51), programme 1.46 (1.33); Blinding details: Advice group were given attention equal to education group - unlikely to be aware control group; Group 1 Number missing: 2, Reason: 2 "did not complete"; Group 2 Number missing: 2, Reason: 2 "did not complete"	
Protocol outcomes not reported by the study	Unplanned Hospitalisation at as reported ; Adverse events - Renal function at 12 months; Adverse events - Hyperkalaemia at 12 months; Change in weight at 12 months; Change in sodium level at 12 months; Change in appetite at 12 months

F.4 Beta-blockers in people with heart failure and atrial fibrillation

Study (subsidiary papers)	Kotecha 2014[791] (Dargie 1999[345], Dargie 2001[346], Domanski 1994[392] Packer 2001[1095], Tepper 1999[1370], Flather 2005[467], Waagstein 1993[1454], Bollano 1997[182], Packer 1996[1093], Beta-blocker evaluation of survival trial 2001[159])
Study type	Systematic review (IPD meta-analysis)
Number of studies (number of participants)	10 (n=3066)
Countries and setting	Conducted in Multiple countries; Setting: Primary and secondary care.
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): Due to the difference in follow-up times reported in the individual studies, data was censored at 1200 days (3.3 years).
Method of assessment of guideline condition	Systematic review: method of assessment mixed: Methods include: discharge diagnosis, NYHA classification, left ventricular ejection fraction of 40% or less by two-dimensional echocardiography or by radionuclide or contrast ventriculography etc.
Stratum	18 - 75
Subgroup analysis within study	Post-hoc subgroup analysis: Using individual patient data from the original trials, study investigators analysed people diagnosed with both CHF and AF, and split them into those randomized (in the original trials) to receive placebo or beta-blocker therapy, and analysed them. Baseline data for both groups is provided.
Inclusion criteria	Randomised controlled trials in which mortality was a primary or composite outcome of the comparison of β blockers versus placebo in people with heart failure were included in the meta-analysis. Only uncounfounded head-to-head trials with recruitment of more than 300 people and a planned follow-up of more than 6 months.
Exclusion criteria	Atrial fibrillation as an exclusion criteria in the original trial.
Recruitment/selection of people	SENIORS: Screened from hospital outpatient lists and admissions for heart failure within the previous year; MDC: Not reported; CIBIS: Not reported; CAPRICORN: Not reported; BEST: Not reported; US-HF: Not reported; COPERNICUS: No access to paper; MERIT-HF: No access to paper; CIBIS II:
Age, gender and ethnicity	Age - Median (IQR): Beta-blocker - 69 (60-75); placebo - 69 (61-74).. Gender (M:F): Beta-blocker - women 18.9%; placebo - women 19.8%. Ethnicity: Not reported.
Further population details	1. Anti-coagulant use vs no anti-coagulant use: Systematic review: mixed (Beta-blocker - 58.3%; placebo - 57.3% of people used oral anti-coagulants.). 2. Heart rate on entry: Heart rate on entry ≤90 bpm (median bpm (IQR): beta-blocker - 81 (72-92); placebo - 81 (73-92).).
Extra comments	Baseline characteristics: NYHA class III/IVl: beta-blocker - 72.2%; placebo - 72.1%. LVEF, median (IQR): beta-blocker - 0.27 (0.21-0.33); placebo - 0.21 (0.22-0.33). Estimated GFR, median mL/min (IQR):beta-blocker - 61 (49-74); placebo - 61

	(48 - 73). ACEi or ARB use: beta-blocker - 95.3%; placebo - 93.8%. Digoxin: beta-blocker - 83.7%; placebo - 83.3%.
Indirectness of population	No indirectness: Meets protocol.
Interventions	(n=1523) Intervention 1: Class of drug - Beta-blockers. ANZ: Participants had a 2-3 week run-in period where they were titrated up to 6.25mg carvedilol twice daily. Those who tolerated the dose were randomized in a double blind setting, to continue treatment with carvedilol or receive matching placebo. There was a 2-5 week dose titration period with weekly assessment , the aim being to increase the dose of carvedilol to a maximum of 25mg twice daily (or equivalent dose of matching placebo) or to the highest tolerated dose. Participants were followed up for an average of 19 months. BEST: On the day of randomization, participants were given an initial oral dose of 3 mg of bucindolol, twice daily for one week. Subsequently doses were increased (by doubling) on a weekly basis to a maximum target dose of 50 mg twice daily. For people who weighed 75 kg or more, they had a target dose of 100 mg twice daily. These dose increases were slowed or stopped and the doses of diurectics and concomitant medications adjusted at the discretion of the investigator. The mean duration of follow-up reported to the time the study was terminated was 2.0 years. CAPRICORN: Study medication was uptitrated to the higher tolerated dose for each patient, to a maximum of 25 mg twice daily. The initial dose of 6.25 mg of carvedilol, if tolerated was continued on a daily basis. If it was not tolerated, the same dose was readministered or reduced by half. If that dose was not tolerated, the patient received no study medication but was followed up anyway. Participants were followed up for a mean of 1.3 years. At follow up appointments, adjusting background treatments to optimal doses was encouraged. CIBIS I: Study treatment was titrated and administered blindly using divisible 2.5 mg pills. The initial dose was 1.25 mg /day, increased 48 hours later to 2.5 mg daily and 1 month after to 5 mg/daily. Study treatment initiation and dose increments were performed during hospitalization for periods between 2 and 6 days. The mean duration of follow up was 1.9 (0.1) years. CIBIS II: Participants were started on bisoprolol 1.25 mg or placebo daily, the drug being increased successively to 2.5 mg, 3.75 mg, 5.0 mg, 7.5 mg, and 10.0 mg, according to tolerance. Participants received the first three concentration of each dose for 1 week, and higher concentrations for 4 weeks. Investigators were asked to ensure that the highest tolerated dose was reached and maintained, if possible, for the duration of the trial. In people with worsening heart failure, the study investigators recommended that the baseline heart-failure treatments be increased before the study drug was decreased. There was no run-in period. Participants were followed up for an average of 1.3 years COPERNICUS: N/A

	MERIT-HF: N/A MDC: Metoprolol was available in 5 mg and 50mg tablets. The target dose was 100-150 mg daily, depending on body weight, age, heart rate, and blood pressure. A test dose of metoprolol (5 mg twice daily) was given for 2-7 days; those tolerating this dose entered randomization. Treatment started with a titration period; the daily dose was increased over 6 weeks with a starting dose of 10 mg. Placebo was given the same way. If the patient could not tolerate an increase in dose after a week, the previous dose could be kept for another week before dose increase. The highest dose tolerated during the titration period was used for the trial. The mean dose of metoprolol at 3 months after randomisation was 108 (51) mg. Participants were followed up for 18 months. SENIORS: Nebivolol tablets were provided in identical packaging and tablet appearance. The initial dose was 1.25 mg once daily, and, if tolerated, this was increased to 2.5 mg, every 1- 2 weeks, reaching a target of 10 mg once daily over a maximum of 16 weeks. Dose titration was performed during a visit to the hospital or clinic, and participants were observed for up to 2 hours after taking the new dose to assess tolerability. Up-titration could be stopped or delayed depending on symptoms, possible side-effects, or at the judgment of the local investigator. The mean duration of follow up was 21(9) months.. Duration 3.3 years. Concurrent medication/care: Background treatment was consistent among all the studies included: ACEI if tolerated and diuretics (not specified). Digoxin was featured a background treatment for some people but often prescribed at the discretion of the investigator. Comments: N/A US HF: After baseline evaluation, all participants received 6.25 mg of Carvedilol twice daily for two weeks (during the open-label portion of the trial). If this was tolerated, participants were up titrated to a maximum dose of 50mg over a period of 2 to 10 weeks. People receiving treatment according to the moderate-heart failure protocol, were treated for a total of 12 months, people on the other 3 protocols were treated for 6 months.. Duration 3.3 years. Concurrent medication/care: Background treatment was consistent among all the studies included: ACEI if tolerated and diuretics (not specified). Digoxin was featured a background treatment for some people but often prescribed at the discretion of the investigator. Comments: N/A (n=1543) Intervention 2: Placebo . ANZ: matching placebo (double-blind) BEST: matching placebo

	CAPRICORN: No additional information reported. CIBIS I: matched placebo (double-blind) CIBIS II: placebo (double-blind) COPERNICUS: N/A MERIT-HF:N/A MDC: The mean dose of placebo at 3 months after randomisation was 115 (51) mg. SENIORS: placebo (double-blind); placebo tablets were provided in identical packaging and tablet appearance. The initial dose was 1.25 mg once daily, and, if tolerated, this was increased to 5 mg, every 1- 2 weeks, reaching a target of 10 mg once daily over a maximum of 16 weeks US HF: placebo (double-blind).. Duration 3.3 years. Concurrent medication/care: Background treatment was consistent among all the studies included: ACEI if tolerated and diuretics (not specified). Digoxin was featured a background treatment for some people but often prescribed at the discretion of the investigator. Comments: N/A
Funding	Study funded by industry (The study received an administrative support grant by Menarini Farmaceutica Internazionale.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BETA-BLOCKERS versus PLACEBO

Protocol outcome 1: All-cause mortality at 12 months
- Actual outcome for 18 - 75: All-cause mortality (ANZ) at 3.3 years; HR 0.28 (95%CI 0.05 to 1.63) Reported; Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Comments - Actual result extracted from the IPD, not the original trial.; Indirectness of outcome: No indirectness; Baseline details: Previous NYHA II, n(%): carvedilol - 56(27 %), placebo - 54 (26%); NYHA III, n (%): carvedilol - 59 (29%), placebo - 65 (31%); NYHA IV, n (%): carvedilol - 92 (44%), placebo - 87 (42%). ; Blinding details: Reported as double-blind, use of matching placebo.; Group 1 Number missing: N/A, Reason: N/A; Group 2 Number missing: N/A, Reason: N/A
- Actual outcome for 18 - 75: All-cause mortality (CAPRICORN) at 3.3 years; HR 0.9 (95%CI 0.46 to 1.75) Reported; Risk of bias: All domain - Very high, Selection - Very high, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness, Comments: Meets the protocol; Baseline details: % LVEF, mean(SD): carvedilol - 32.9 (6.4); placebo - 32.7 (6.4); Heart rate (beats/min), mean(SD): carvedilol - 77.3 (11.4); placebo - 77.2 (11.3).; Blinding details: Blinding not reported.; Group 1 Number missing: N/A, Reason: N/A; Group 2 Number missing: N/A, Reason: N/A

- Actual outcome for 18 - 75: All-cause mortality (CIBIS I) at 3.3 years; HR 1.14 (95%CI 0.46 to 2.83) Reported; Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: NYHA class III, n(%): bisoprolol - 305 (95%), placebo - 304 (95%); NYHA class IV, n (%): bisoprolol - 15 (5%), placebo - 17 (5%); mean (CIs) LVEF (%): bisoprolol - 25.0 (0.9%), placebo - 25.8 (0.9%); mean (CIs) heart rate (beats/min): bisoprolol - 82.8 (1.5); placebo - 82.5 (1.6). ; Blinding details: Reported as double-blind, use of matching placebo.; Group 1 Number missing: N/A, Reason: N/A; Group 2 Number missing: N/A, Reason: N/A
- Actual outcome for 18 - 75: All-cause mortality (CIBIS II) at 3.3 years; HR 0.98 (95%CI 0.64 to 1.51) Reported; Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: NYHA class III, n(%): bisoprolol - 1106 (83%), placebo - 1096 (83%); NYHA class IV, n (%): bisoprolol - 221 (17%), placebo - 224 (17%); mean (SD) LVEF (%): bisoprolol - 27.5 (6%), placebo - 27.6 (5.5%); mean (SD) heart rate (beats/min): bisoprolol - 79.9 (14.5); placebo - 81.0 (15.5). ; Blinding details: Reported as double-blind, use of matching placebo.; Group 1 Number missing: N/A, Reason: N/A; Group 2 Number missing: N/A, Reason: N/A
- Actual outcome for 18 - 75: All-cause mortality (COPERNICUS) at 3.3 years; HR 0.91 (95%CI 0.54 to 1.54) Reported; Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: LVEF, median(IQR): 0.27 (0.22 - 0.33); NYHA III or IV, n(%): 1901(72 %); Heart rate (bpm), median(IQR): 81 (72-92).; Blinding details: Although there's no report on the blinding of the outcome assessors, the data was adjusted for age, sex, baseline left ventricular ejection fraction, baseline heart rate, and use of angiotensin-converting-enzyme inhibitor or angiotensin-receptor blocker. ; Group 1 Number missing: N/A, Reason: Not clearly reported.; Group 2 Number missing: N/A, Reason: Not clearly reported
- Actual outcome for 18 - 75: All-cause mortality (MDC) at 3.3 years; HR 1 (95%CI 0.34 to 2.95) Reported; Risk of bias: All domain - Very high, Selection - Very high, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: NYHA class III, n(%): metoprolol - 98(51%), placebo - 88 (47%); NYHA class IV, n (%): metoprolol - 8(4%), placebo - 7(4%); mean (SD) EF (%): metoprolol - 0.22 (0.08), placebo - 0.22 (0.09); mean (SD) heart rate (beats/min): metoprolol - 90 (17); placebo - 91 (18). ; Blinding details: No report of blinding, though placebo was used.; Group 1 Number missing: N/A, Reason: N/A; Group 2 Number missing: N/A, Reason: N/A
- Actual outcome for 18 - 75: All-cause mortality (MERIT-HF) at 3.3 years; HR 1.03 (95%CI 0.65 to 1.64) Reported; Risk of bias: All domain - Unclear, Selection - Unclear, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: N/A; Blinding details: Original paper not available.; Group 1 Number missing: N/A, Reason: N/A; Group 2 Number missing: N/A, Reason: N/A
- Actual outcome for 18 - 75: All-cause mortality (SENIORS) at 3.3 years; HR 1.14 (95%CI 0.81 to 1.62) Reported; Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: NYHA class III, n(%): nebivolol - 413 (38.7%), placebo - 411 (38.7%); NYHA class IV, n (%): nebivolol - 19 (1.8%), placebo - 24 (2.3%); mean (SD) EF (%): nebivolol - 36 (13), placebo - 36 (12); mean (SD) heart rate (beats/min): nebivolol - 79.2 (13.6); placebo - 78.9 (13.7). ; Blinding details: Reported as double-blind, use of matching placebo.; Group 1 Number missing: N/A, Reason: N/A; Group 2 Number missing: N/A, Reason: N/A
- Actual outcome for 18 - 75: All-cause mortality (US-HF) at 3.3 years; HR 1.14 (95%CI 0.56 to 2.32) Reported; Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: NYHA class II, n: carvedilol - 374, placebo - 208; NYHA class III, n: carvedilol - 303, placebo - 177; NYHA class IV, n: carvedilol - 19, placebo - 13; mean (SD) LVEF : carvedilol - 0.23 (0.07), placebo - 0.22 (0.07); mean (SD) heart rate (beats/min): carvedilol - 84 (12); placebo - 83 (12). ; Blinding details: Said to be double blinded, no additional information.; Group 1 Number missing: N/A, Reason: N/A; Group 2 Number missing: N/A, Reason: N/A

Protocol outcome 2: Unplanned hospitalisation (including HF-related unplanned hospitalisation) at 12 months

- Actual outcome for 18 - 75: First heart failure related hospitalization at 3.3 years; HR 0.93 (95%CI 0.77 to 1.12) Cox model, adjusted for co-variates:age, sex, and baseline left-ventricular ejection fraction (LVEF), heart rate, and use of ACEi or angiotensin-receptor blockers, p-value: 0.44; Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Comments - Actual result extracted from the IPD sensitivity analysis excluding BEST trial.; Indirectness of outcome: Serious indirectness, Comments: Study reports 'first heart-failure related hospitalization' which does not capture all types of hospitalizations of equal clinical significance. ; Baseline details: Previous NYHA II, n(%): carvedilol - 56(27 %), placebo - 54 (26%);NYHA III, n (%): carvedilol - 59 (29%), placebo - 65 (31%); NYHA IV, n (%): carvedilol - 92 (44%), placebo - 87 (42%). ; Blinding details: Reported as double-blind, use of matching placebo.; Group 1 Number missing: N/A, Reason: N/A; Group 2 Number missing: N/A, Reason: N/A Protocol outcome 3: Adverse events - Stroke at 12 months - Actual outcome for 18 - 75: Fatal and non-fatal stroke at 3.3 years; HR 1.11 (95%CI 0.71 to 1.74) Cox model, adjusted for co-variates:age, sex, and baseline left-ventricular ejection fraction (LVEF), heart rate, and use of ACEi or angiotensin-receptor blockers; Risk of bias: All domain - Low, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Comments - Actual result extracted from the IPD sensitivity analysis excluding BEST trial.; Indirectness of outcome: No indirectness, Comments: Meets the protocol; Baseline details: Previous NYHA II, n(%): carvedilol - 56(27 %), placebo - 54 (26%);NYHA III, n (%): carvedilol - 59 (29%), placebo - 65 (31%); NYHA IV, n (%): carvedilol - 92 (44%), placebo - 87 (42%). ; Blinding details: Reported as double-blind, use of matching placebo.; Group 1 Number missing: N/A, Reason: N/A; Group 2 Number missing: N/A, Reason: N/A	
Protocol outcomes not reported by the study	Quality of life (Kansas city, Kansas city short version, Minnesota, EQ-5D and SF-36) at 12 months; Unplanned hospitalisation(including HF-related unplanned hospitalisation) at 12 months; Improvement of NYHA class at 12 months; Adverse events - Hypotension at 12 months; Adverse events - Bradycardia at 12 months

F.5 Mineralocorticoid Receptor Antagonists

F.5.1 Mineralocorticoid receptor antagonists in heart failure with preserved ejection fraction

Study (subsidiary papers)	Aldo-DHF trial: Edelmann 2013[426] (Edelmann 2010[425])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=422)
Countries and setting	Conducted in Austria, Germany; Setting: Multicentre (10 trial centres) - both inpatients and outpatients
Line of therapy	Adjunctive to current care

Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Current heart failure symptoms consistent with NYHA classes II or III
Stratum	Overall
Subgroup analysis within study	Not stratified but pre-specified
Inclusion criteria	- Current heart failure symptoms consistent with NYHA classes II or III - Left ventricular ejection fraction (LVEF) ≥ 50% at rest - Echocardiographic evidence of diastolic dysfunction (Grade ≥ I) or atrial fibrillation - Peak VO2 ≤ 25mL/kg/min - Males and females aged ≥ 50 years - Written informed consent
Exclusion criteria	-Prior documented systolic heart failure (LVEF ≤ 40%) - Significant coronary artery disease (current angina pectoris or ischaemia on stress tests; untreated coronary stenosis .50%) - Myocardial infarction or CABG within the last 3 months - Definite or probable pulmonary disease (VC,80% or FEV1,80% of reference values on spirometry) -Severe obesity (BMI ≥ 36 kg/m2) -Significant renal dysfunction (creatinine. 1.8 mg/dL) -Significant hypotension (blood pressure , 90 mmHg systolic and/or ,50 mmHg diastolic) -Mental disorders suspected to interact with study outcome -Significant laboratory abnormalities (potassium ≥ 5.1 mmol/L; haemoglobin ≤ 11g/dL, haematocrit ≤ 33%) -Changes in concomitant medication within the last 2 weeks prior to screening visit -Known contraindications for spironolactone or prior documented intolerance to an aldosterone receptor antagonist -Insulin-dependent diabetes mellitus with a history of ketoacidosis -Suspected metabolic acidosis -Pregnant or nursing women -Any patient characteristic that may interfere with adherence to the study protocol, such as dementia, substance abuse, history of non-compliance with prescribed medications, or medical appointments -Concomitant therapy with a potassium-sparing diuretic (e.g. triamterene, amiloride), potassium substitution, high-dose acetylsalicylic acid (.500 mg/d) or permanent intake of non-steroidal anti-inflammatory agents, digitalis -Women with child bearing potency without effective contraception (except for implants, hormonal depot injections, combined oral contraceptives, IUDs or vasectomized partner) -Concomitant participation in other clinical trials -Therapy with an aldosterone receptor antagonist within the last 3 months -Participation in another clinical trial within the last 30 days
Recruitment/selection of patients	Participating trial centres screened all consecutive outpatients and inpatients that fulfill the pre-screening criteria i.e. signs and symptoms of heart failure and an LVEF ≥50% ('initial screen'). Patients who fulfilled all criteria for entry into the study were randomized to receive either spironolactone or placebo for 12 months (randomization ratio 1:1) stratified by echo-cardiographic grade of diastolic dysfunction, rhythm and study centre.
Age, gender and ethnicity	Age - Mean (SD): 67 (8). Gender (M:F): 201:221. Ethnicity: Not reported
Further population details	1. Age: Not applicable / Not stated / Unclear 2. Diabetes status: Not applicable / Not stated / Unclear 3. Renal function: Not applicable / Not stated / Unclear
Extra comments	Diabetic: MRA - 17%; Placebo - 16%. eGRF, mean (SD), mL/min/1.73m2: MRA - 79 (19), 78 (18). ACEI/ARB: MRA - 78%; Placebo: 76%. BB: MRA - 69%: Placebo - 75%. NYHA functional class II or III: MRA - 85% class II: Placebo - 88% class II.

	LVEF: MRA - 67%; Placebo - 68%.
Indirectness of population	No indirectness
Interventions	(n=213) Intervention 1: Mineralocorticoid receptor antagonist - Spironolactone (up to 50mg/day). 25mg/day, Verospiron T. . Duration 12 months. Concurrent medication/care: Standard therapies at discretion of treating physicians. 69% on BB, 78% on ACEI or ARB. Comments: No up-titration. Reduction to 25mg every other day if required due to adverse effects. (n=209) Intervention 2: Placebo . Placebo. Duration 12 months. Concurrent medication/care: Standard therapies at discretion of treating physicians. 75% on BB, 76% on ACEI or ARB.
Funding	Academic or government funding (German-Austrian Heart Failure Study Network, German Competence Network of Heart Failure, Federal Ministry of Education and Research, University of Gottingen.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SPIRONOLACTONE (UP TO 50MG/DAY) versus PLACEBO

Protocol outcome 1: All-cause mortality
- Actual outcome: All-cause mortality at 12 months; Group 1: 1/205, Group 2: 0/196; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: See population; Blinding details: Production of identical matching packaging and quality control, packaging, labeling, storage and dispensing of both spironolactone and placebo performed by Allphamed PHARBIL.; Group 1 Number missing: 8, Reason: 6 withdrew consent, 2 lost to follow up; Group 2 Number missing: 13, Reason: 9 withdrew consent, 3 lost to follow up, 1 physician decision

Protocol outcome 2: Quality of life at 12 months
- Actual outcome: Quality of life - Minnesota at 12 months; Group 1: mean 21 (SD 18.22); n=204, Group 2: mean 21 (SD 17.86); n=196; Minnesota Living With Heart Failure Questionnaire total score 0 to 105 Top=High is poor outcome; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Comments - Outcome reported as mean (95% CI) but CI not symmetrical about the mean and may have been calculated on transformed values.; Indirectness of outcome: No indirectness ; Baseline details: Baseline scores (mean (SD)): MRA - 22 (16), Placebo 21 (15); Blinding details: Production of identical matching packaging and quality control, packaging, labeling, storage and dispensing of both spironolactone and placebo performed by Allphamed PHARBIL.; Group 1 Number missing: 9, Reason: 6 withdrew consent, 2 lost to follow up, 1 died; Group 2 Number missing: 13, Reason: 9 withdrew consent, 3 lost to follow up, 1 physician decision
- Actual outcome: Quality of life - SF-36 Physical Functioning at 12 months; Group 1: mean 64 (SD 25.51); n=204, Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Comments - Outcome reported as mean (95% CI) but CI not symmetrical about the mean and may have been calculated on transformed values.; Indirectness of outcome: No indirectness ; Baseline details: Baseline scores (mean (SD)): MRA - 62 (22), Placebo 63 (23); Blinding details: Production of identical matching packaging and quality control, packaging, labeling, storage and dispensing of both

spironolactone and placebo performed by Allphamed PHARBIL.; Group 1 Number missing: 9, Reason: 6 withdrew consent, 2 lost to follow up, 1 died; Group 2 Number missing: 13, Reason: 9 withdrew consent, 3 lost to follow up, 1 physician decision

Protocol outcome 3: Unplanned hospitalisation
- Actual outcome: Hospitalisation at 12 months; Group 1: 60/204, Group 2: 50/196; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: See population; Blinding details: Production of identical matching packaging and quality control, packaging, labeling, storage and dispensing of both spironolactone and placebo performed by Allphamed PHARBIL.; Group 1 Number missing: 8, Reason: 6 withdrew consent, 2 lost to follow up; Group 2 Number missing: 13, Reason: 9 withdrew consent, 3 lost to follow up, 1 physician decision

Protocol outcome 4: Improvement of NYHA class at 12 months
- Actual outcome: Participants with NYHA class I status at 12 months; Group 1: 8/204, Group 2: 11/196; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Only reports numbers in each NYHA class at baseline and end of study. ; Baseline details: See population. NYHA class at baseline: Class I: MRA - 0, Placebo - 0. Class II: MRA - 180 (85%), Placebo - 183 (88%). Class III: MRA - 33 (15%), Placebo - 26 (12%).; Blinding details: Production of identical matching packaging and quality control, packaging, labeling, storage and dispensing of both spironolactone and placebo performed by Allphamed PHARBIL.; Group 1 Number missing: 8, Reason: 6 withdrew consent, 2 lost to follow up; Group 2 Number missing: 13, Reason: 9 withdrew consent, 3 lost to follow up, 1 physician decision

Protocol outcome 5: Adverse events - Renal function at 12 months
- Actual outcome: Worsening renal function (as reported by physician, eGFR < 30mL/min/1.73m2, or eGFR decrease > 15mL/min/1.73m2 versus baseline) at 12 months; Group 1: 77/204, Group 2: 43/196; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: See population. Baseline eGFR (Mean (SD)): MRA - 79 (19), Placebo 78 (18); Blinding details: Production of identical matching packaging and quality control, packaging, labeling, storage and dispensing of both spironolactone and placebo performed by Allphamed PHARBIL.; Group 1 Number missing: 8, Reason: 6 withdrew consent, 2 lost to follow up; Group 2 Number missing: 13, Reason: 9 withdrew consent, 3 lost to follow up, 1 physician decision

Protocol outcome 6: Adverse events - Gynaecomastia at 12 months
- Actual outcome: Gynaecomastia at 12 months; Group 1: 9/204, Group 2: 1/196; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: See population. ; Blinding details: Production of identical matching packaging and quality control, packaging, labeling, storage and dispensing of both spironolactone and placebo performed by Allphamed PHARBIL.; Group 1 Number missing: 8, Reason: 6 withdrew consent, 2 lost to follow up; Group 2 Number missing: 13, Reason: 9 withdrew consent, 3 lost to follow up, 1 physician decision

Protocol outcome 7: Adverse events - Hyperkalaemia at 12 months
- Actual outcome: Serum potassium ever increased > 5.5 mmol/L at 12 months; Group 1: 4/204, Group 2: 3/196; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: See

population. Baseline serum potassium (Mean (SD)): MRA - 4.2 (0.4), Placebo - 4.2 (0.4); Blinding details: Production of identical matching packaging and quality control, packaging, labeling, storage and dispensing of both spironolactone and placebo performed by Allphamed PHARBIL.; Group 1 Number missing: 8, Reason: 6 withdrew consent, 2 lost to follow up; Group 2 Number missing: 13, Reason: 9 withdrew consent, 3 lost to follow up, 1 physician decision	
Protocol outcomes not reported by the study	Adverse events - Hypotension at 12 months

Study (subsidiary papers)	TOPCAT trial: Pitt 2014[1156] (Lewis 2016[874], Shah 2015[1275], Shah 2015[1273], Pfeffer 2015[1137], Shah 2014[1276], Shah 2014[1274], Shah 2013[1279], Desai 2011[374])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=3445)
Countries and setting	Conducted in Argentina, Brazil, Canada, Georgia, Russia, USA; Setting: Multicentre, 233 sites (setting not reported)
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 3.3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: At least one sign and one symptom of heart failure on a prespecified list of clinically defined signs and symptoms, plus HF related hospitalisation in last 12 months or elevated BNP in last 60 days (see inclusion criteria).
Stratum	Overall
Subgroup analysis within study	Not stratified but pre-specified
Inclusion criteria	Patients 50 years of age or older were eligible if they provided written informed consent and had at least one sign and at least one symptom of heart failure on a prespecified list of clinically defined signs and symptoms, a left ventricular ejection fraction of 45% or more as measured at the local site by means of echocardiography or radionuclide ventriculography, controlled systolic blood pressure (defined as a target systolic blood pressure of <140 mm Hg or ≤160 mm Hg if the patient was taking three or more medications to control blood pressure), and a serum potassium level of less than 5.0 mmol per liter. In addition, eligible patients had a history of hospitalization within the previous 12 months, with management of heart failure a major component of the care provided (not adjudicated by the clinical-events adjudication committee), or an elevated natriuretic peptide level within 60 days before randomization (a brain natriuretic peptide [BNP] level ≥100 pg per milli liter or an N-terminal pro-BNP [NT-proBNP] level ≥360 pg per milliliter).
Exclusion criteria	Exclusion criteria were severe systemic illness with a life expectancy of less than 3 years, severe renal dysfunction (an estimated glomerular filtration rate [GFR] of <30 ml per minute per 1.73 m2 of body-surface area or a serum creatinine level that was ≥2.5 mg per deciliter [221 µmol per liter]), and specific coexisting conditions, medications, or acute events.
Recruitment/selection of patients	Recruitment not reported. Randomisation was 1:1 with use of permuted blocks, stratified according to whether the patient met the criterion for previous hospitalisation or BNP elevation.
Age, gender and ethnicity	Age - Median (IQR): MRA: 68.7 (61.0 - 76.4), Placebo: 68.7 (60.7 - 75.5). Gender (M:F): 1670:1775. Ethnicity: "White race": MRA - 88.6%, Placebo 89.2%
Further population details	1. Age: Not applicable / Not stated / Unclear 2. Diabetes status: Not applicable / Not stated / Unclear 3. Renal function:

	Not applicable / Not stated / Unclear
Extra comments	Diabetic: MRA - 32.8%; Placebo - 32.2%. eGRF, median (IQR), mL/min/1.73m2: MRA - 65.3 (53.9 - 79.2), Placebo - 65.5 (53.5 - 79.1). ACEI/ARB: MRA - 84.3%; Placebo: 84.2%. BB: MRA - 78.2%; Placebo - 77.3%. NYHA functional class: MRA - 63.3% class II; Placebo - 64.1% class II. LVEF, median (IQR): MRA - 56% (51-56); Placebo - 56% (51-62).
Indirectness of population	No indirectness
Interventions	(n=1722) Intervention 1: Mineralocorticoid receptor antagonist - Spironolactone (up to 50mg/day). Starting dose 15mg/day, increased up to 45mg/day. Novel formulation as commercial brands not available in low dose. . Duration 3.3 years (mean). Concurrent medication/care: See population details for background treatments. Not an inclusion criterion. Existing treatment with MRAs/potassium-sparing diuretics permitted after 14 day washout period. (n=1723) Intervention 2: Placebo . Placebo. Duration 3.3 years. Concurrent medication/care: See population details for background treatments. Not an inclusion criterion. Existing treatment with MRAs/potassium-sparing diuretics permitted after 14 day washout period.
Funding	Academic or government funding (National Heart, Lung and Blood Institute, National Institutes of Health)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SPIRONOLACTONE (UP TO 50MG/DAY) versus PLACEBO

Protocol outcome 1: All-cause mortality
- Actual outcome: All-cause mortality at During study (3.3 year follow up); HR 0.91 (95%CI 0.77 to 1.08) Reported; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Authors conducted ITT analysis, imputation method unclear; Indirectness of outcome: No indirectness; Baseline details: See population panel.; Blinding details: Placebo and spironolactone are reported to be identical in packaging and appearance; Group 1 Number missing: 67, Reason: withdrew or lost to follow up (unknown vitals as of last expected visit); Group 2 Number missing: 65, Reason: withdrew or lost to follow up (unknown vitals as of last expected visit)

Protocol outcome 2: Quality of life at 12 months
- Actual outcome: Quality of life - Kansas City at 12 months; MD 1.35 (SE = 0.58 P = 0.02) Kansas City Cardiomyopathy Questionnaire (KCCQ) 0 to 100 Top=High is good outcome; Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Very high, Measurement - Low, Crossover - Low, Comments - Analysis conducted by authors unclear (ie whether ACA or ITT). Only mean difference reported rather than difference in each group - outcome reported incompletely. Total missing data 15.8% at 12 months but not reported for each group. The standard error was not reported and was calculated based on the p value, assuming the same number of participants in each group (also not reported).; Indirectness of outcome: No indirectness; Baseline details: Baseline scores not reported separately for each group; Blinding details: Placebo and spironolactone are reported to be identical in packaging and appearance; Group 1 Number missing: , Reason: Data unavailable; Group 2 Number missing: , Reason: Data unavailable
- Actual outcome: Quality of life - EQ5D-VAS at Unclear; MD: 0.47 (SE = 0.38; P = 0.223) EQ-VAS 0 to 100 Top=High is good outcome. Comments: The summary statistic is

the additional increase in score compared with the increase for subjects randomised to placebo, adjusted for a multitude of other variables. This is the only information reported in an extractable form. The change scores for the placebo and intervention groups are only represented separately in figures so cannot be extracted. The time point is unclear - it is some sort of combined measure from all of the time points. ;
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Very high, Measurement - Low, Crossover - Low, Comments - Analysis conducted by authors unclear (ie whether ACA or ITT). Only mean difference reported rather than difference in each group - outcome reported incompletely. Total missing data 16.2% at 12 months but not reported for each group. The study states that 'impacts of therapy on changes in [the scores] over time were examined using a repeated -measure analysis of covariance (using all follow-up time points (4, 12 24, 36, 48 and 60 months)'.; Indirectness of outcome: No indirectness ; Baseline details: Baseline scores not reported separately for each group; Blinding details: Placebo and spironolactone are reported to be identical in packaging and appearance; Group 1 Number missing: , Reason: Data unavailable; Group 2 Number missing: , Reason: Data unavailable

Protocol outcome 3: Unplanned hospitalisation
- Actual outcome: All-cause hospitalisation at During study (3.3 years); Other: Incidence rate, no. per 100 person-year: MRA - 18.8, Placebo - 20.0; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Authors conducted ITT analysis, imputation method unclear; Indirectness of outcome: No indirectness ; Baseline details: See population panel.; Blinding details: Placebo and spironolactone are reported to be identical in packaging and appearance; Group 1 Number missing: 160, Reason: Ended study participation early, not necessarily missing data on this outcome; Group 2 Number missing: 151, Reason: Ended study participation early, not necessarily missing data on this outcome

Protocol outcome 4: Adverse events - Renal function at 12 months
- Actual outcome: Elevated serum creatinine level (≥2 times the baseline value and above the upper limit of the normal range) at 3.3 years; Group 1: 176/1722, Group 2: 121/1723; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Analysis conducted by authors unclear (ie whether ACA or ITT). ; Indirectness of outcome: No indirectness ; Baseline details: Serum Creatinine mg/dl, median (IQR): MRA - 1.0 (0.9 - 1.2), Placebo - 1.1 (0.9 - 1.2); Blinding details: Placebo and spironolactone are reported to be identical in packaging and appearance; Group 1 Number missing: 160, Reason: Ended study participation early, not necessarily missing data on this outcome; Group 2 Number missing: 151, Reason: Ended study participation early, not necessarily missing data on this outcome

Protocol outcome 5: Adverse events - Gynaecomastia at 12 months
- Actual outcome: Breast tenderness or enlargement leading to study drug discontinuation at 3.3 years; Group 1: 41/1722, Group 2: 4/1723; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Analysis conducted by authors unclear (ie whether ACA or ITT). ; Indirectness of outcome: Serious indirectness, Comments: Total rates of gynaecomastia could be higher than this figure; Baseline details: See population panel.; Blinding details: Placebo and spironolactone are reported to be identical in packaging and appearance; Group 1 Number missing: 160, Reason: Ended study participation early, not necessarily missing data on this outcome; Group 2 Number missing: 151, Reason: Ended study participation early, not necessarily missing data on this outcome

Protocol outcome 6: Adverse events - Hyperkalaemia at 12 months
- Actual outcome: Hyperkalaemia (serum potassium ≥ 5.5mm/L) at 3.3 years; Group 1: 322/1722, Group 2: 157/1723; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Analysis conducted by authors unclear (ie

whether ACA or ITT). ; Indirectness of outcome: No indirectness ; Baseline details: Serum potassium mmol/L, median (IQR): MRA - 4.3 (4.0 - 4.6), Placebo - 4.3 (4.0 - 4.6); Blinding details: Placebo and spironolactone are reported to be identical in packaging and appearance; Group 1 Number missing: 160, Reason: Ended study participation early, not necessarily missing data on this outcome. Also 102 (5.9%) were ineligible but retained and 79 were on open-label MRA (4.6%). ; Group 2 Number missing: 151, Reason: Ended study participation early, not necessarily missing data on this outcome. Also 136 (7.9%) were ineligible but retained and 91 were on open-label MRA (5.3%)	
Protocol outcomes not reported by the study	Improvement of NYHA class at 12 months; Adverse events - Hypotension at 12 months

F.5.2 Mineralocorticoid receptor antagonists in heart failure with reduced ejection fraction

Study (subsidiary papers)	EMPHASIS-HF trial: Zannad 2011[1522] (Eschalier 2013[441], Krum 2013[803], Girerd 2015[522], Rossignol 2014[1228], Collier 2013[303], Rogers 2012[1221], Zannad 2010[1521])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=2737)
Countries and setting	Conducted in Multiple countries; Setting: Primary and secondary care.
Line of therapy	Adjunctive to current care
Duration of study	Follow up (post intervention): 3 years
Method of assessment of guideline condition	Method of assessment /diagnosis not stated: Not reported.
Stratum	Overall:
Subgroup analysis within study	Not stratified but pre-specified:
Inclusion criteria	Aged ≥ 55 years; NYHA functional class II symptoms, an ejection fraction of no more than 30% (or, if >30 to 35%, a QRS duration of >130 msec on electrocardiography), and treatment with an ACEI, ARB, or both and a beta-blocker (unless contraindicated) at the recommended dose or maximal tolerated dose. Radomization was to occur within 6 months after hospitalization for a cardiovascular reason. Patients who had not been hospitalized for a cardiovascular reason within 6 months before the screening visit could be enrolled if the plasma level of B-type natriuretic peptide (BNP) was at least 250 pg per milliliter or if the plasma level of N-terminal pro-BNP was at least 500 pg per mililiter in men and 750 pg per mililiter in women.
Exclusion criteria	Acute mycardial infarction, NYHA class III or IV heart failure, a serum potassium level exceeding 5.0 mmol per liter, an estimated glomerular filteration rate (GFR) of less than 30 ml per minute per 1.73m^2 of body surface area, a need for a potassium-sparing diuretic, and any other clinically significant, coexisting condition,
Recruitment/selection of patients	Not reported.
Age, gender and ethnicity	Age - Mean (SD): Eplerenone - 68.7(7.7); placebo - 68.6 (7.6). Gender (M:F): Eplerenone - 1055/309; placebo - 1072/301. Ethnicity: White - 2268; Black - 67; Asian - 316; other - 86.
Further population details	1. Age: Not applicable / Not stated / Unclear (Subgroup data available for: age < 75 years and age ≥ 75 years. Overall data has been extracted.). 2. Diabetes status: Not applicable / Not stated / Unclear (Subgroup data available for: history of diabetes and no history of diabetes. Overall data has been extracted.). 3. Renal function: Not applicable / Not stated / Unclear (Subgroup data available for: eGFR < 60mL/min and eGFR ≥ 60mL/min. Overall data has been extracted.).

Extra comments	Baseline characteristics: mean LVEF %, (SD): Eplerenone - 26.2(4.6); placebo - 26.1 (4.7).
Indirectness of population	No indirectness: Meets protocol.
Interventions	(n=1364) Intervention 1: Mineralocorticoid receptor antagonist - Eplerenone (up to 50mg/day). Eplerenone was started at a dose of 25 mg once daily and was increased after 4 weeks to 50mg once daily and was increased after 4 weeks to 50 mg once daily (or started at 25 mg on alternate days, and increased to 25 mg daily, if the estimated GFR was 30 to 49 ml per minute per 1.73 m^2), provided the serum potassium level was no more than 5.0 mmol per litre). Thereafter, investigators evaluated patients every 4 months and were instructed to decrease the dose of the study drug if the serum potassium level was 5.5 to 5.9 mmol per litre and to withhold the study drug if the serum potassium level was 6.0 mmol per litre or more. Potassium was to be remeasured within 72 hours after the dose reduction or study-drug withdrawal, and the study drug was to be restarted only if the level was below 5.0 mmol per litre.. Duration 21 months. Concurrent medication/care: No. of patients on background therapy at point of randomization: Diuretic - 1150; ACEI - 1068; ARB - 261; beta-blocker - 1181; digitalis glycosides - 363; anti-arrhythmic drug - 196; anti-thrombotic (antiplatelet/anticoagulant) drug - 1205; lipid-lowering agents - 857. Comments: Duration - median time from randomization to the last dose. After the trial cuttoff date, the study drug had been discontinued in 222 patients receiving eplerenone and 228 patients for placebo. (n=1373) Intervention 2: Placebo . Patients were randomized to receive matching placebo. No other detail was reported. . Duration 21 months (median). Concurrent medication/care: No. of patients on background therapy at point of randomization: Diuretic - 1176; ACEI - 1055; ARB - 266; beta-blocker - 1193; digitalis glycosides - 377; anti-arrhythmic drug - 192; anti-thrombotic (antiplatelet/anticoagulant) drug - 1214; lipid-lowering agents - 856. Comments: Duration - median time from randomization to the last dose. After the trial cuttoff date, the study drug had been discontinued in 222 patients receiving eplerenone and 228 patients for placebo.
Funding	Study funded by industry (The study was supported by Pfizer.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: EPLERENONE (UP TO 50MG/DAY) versus PLACEBO

Protocol outcome 1: All-cause mortality
- Actual outcome: All-cause mortality at During study (21 months mean follow up); HR 0.76 (95%CI 0.62 to 0.93) Reported; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - Authors used ITT analysis, but imputation method not clear.; Indirectness of outcome: No indirectness, Comments: Meets protocol; Baseline details: Heart rate, beats/min: eplerenone - 72 (12); placebo - 72 (13); diabetes mellitus , n(%): eplerenone - 459 (33.7); placebo - 400 (29.1); serum creatine, mg/dl: eplerenone - 1.14 (0.3); placebo - 1.16 (0.31); eGFR, mL/min/1.73m^2: eplerenone - 71.2(21.9); placebo - 70.4 (21.7). ; Group 1 Number missing: 243, Reason: 4 did not start the study medication. At trial cut-off, 222 patients had discontinued study drug and 17 patients were lost to follow up.; Group 2 Number missing: 247, Reason: 4 did not start the study medication. At trial cut-off,

228 patients had discontinued study drug and 15 patients were lost to follow up.

Protocol outcome 2: Unplanned hospitalisation
- Actual outcome: All-cause hospitalisation at During study (25 months mean follow up); Other: All-cause hospitalisation, total admissions - Group 1: 862, Group 2: 1123; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - ITT analysis conducted but method of imputation not specified by authors. Rate of missing data determined to be low based on dichotomous event rate, for reference purposes. ; Indirectness of outcome: No indirectness, Comments: Meets protocol; Baseline details: Heart rate, beats/min: eplerenone - 72 (12); placebo - 72 (13); diabetes mellitus , n(%): eplerenone - 459 (33.7); placebo - 400 (29.1); serum creatine, mg/dl: eplerenone - 1.14 (0.3); placebo - 1.16 (0.31); eGFR, mL/min/1.73m^2: eplerenone - 71.2(21.9); placebo - 70.4 (21.7). ; Group 1 Number missing: 243, Reason: 4 did not start the study medication. At trial cut-off, 222 patients had discontinued study drug and 17 patients were lost to follow up.; Group 2 Number missing: 247, Reason: 4 did not start the study medication. At trial cut-off, 228 patients had discontinued study drug and 15 patients were lost to follow up.

Protocol outcome 3: Adverse events - Renal function at 12 months
- Actual outcome: Change in creatinine at 21 months; Group 1: mean 8 µmol/L (SD 32.7); n=1360, Group 2: mean 3.5 µmol/L (SD 35.4); n=1369; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Other 1 - Low, Comments - Authors used ITT analysis (except for patients not starting study medication), but imputation method not clear.; Indirectness of outcome: No indirectness, Comments: Meets protocol; Baseline details: mean (SD) Serum creatinine, mg/dL: eplerenone - 1.14 (0.3); placebo - 1.16 (0.31).; Group 1 Number missing: 243, Reason: 4 did not start the study medication and were not included in the safety analysis. At trial cut-off, 222 patients had discontinued study drug and 17 patients were lost to follow up.; Group 2 Number missing: 247, Reason: 4 did not start the study medication and were not included in the safety analysis. At trial cut-off, 228 patients had discontinued study drug and 15 patients were lost to follow up.
- Actual outcome: Change in eGFR at 21 months; Group 1: mean -3.18 ml/min/1.73 m^2 (SD 18.4); n=1364, Group 2: mean -1.29 ml/min/1.73 m^2 (SD 18.2); n=1373; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Comments - Authors used ITT analysis, but imputation method not clear.; Indirectness of outcome: No indirectness, Comments: Meets protocol; Baseline details: mean (SD) eGFR, mL/min/1.73m^2: Eplerenone - 71.2 (21.9), placebo - 70.4 (21.7); Group 1 Number missing: 243, Reason: 4 did not start the study medication. At trial cut-off, 222 patients had discontinued study drug and 17 patients were lost to follow up.; Group 2 Number missing: 247, Reason: 4 did not start the study medication. At trial cut-off, 228 patients had discontinued study drug and 15 patients were lost to follow up.
- Actual outcome: Renal failure at 21 months; Group 1: 38/1360, Group 2: 41/1369; Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Other 1 - Low, Comments - Authors used ITT analysis (except for those not starting study drug), but imputation method not clear.; Indirectness of outcome: No indirectness, Comments: Meets protocol; Baseline details: serum creatine, mg/dl: eplerenone - 1.14 (0.3); placebo - 1.16 (0.31); eGFR, mL/min/1.73m^2: eplerenone - 71.2(21.9); placebo - 70.4 (21.7); heart rate, beats/min: eplerenone - 72 (12); placebo - 72 (13); diabetes mellitus , n(%): eplerenone - 459 (33.7); placebo - 400 (29.1).; Group 1 Number missing: 243, Reason: 4 did not start the study medication. At trial cut-off, 222 patients had discontinued study drug and 17 patients were lost to follow up.; Group 2 Number missing: 247, Reason: 4 did not start the study medication. At trial cut-off, 228 patients had discontinued study drug and 15 patients were lost to follow up.

Protocol outcome 4: Adverse events - Gynaecomastia at 12 months
- Actual outcome: Gynaecomastia or other breast disorders at 21 months; Group 1: 10/1360, Group 2: 14/1369; Risk of bias: Risk of bias: All domain - High, Selection -

Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Other 1 - Low, Comments - Authors used ITT analysis (except for patients not starting the study medication), but imputation method not clear.; Indirectness of outcome: No indirectness, Comments: Meets protocol; Baseline details: Female (no. (%)): Eplerenone - 309 (22.7%), Placebo - 301 (21.9%); Group 1 Number missing: 243, Reason: 4 did not start the study medication and were not included in the safety analysis. At trial cut-off, 222 patients had discontinued study drug and 17 patients were lost to follow up.; Group 2 Number missing: 247, Reason: 4 did not start the study medication and were not included in the safety analysis. At trial cut-off, 228 patients had discontinued study drug and 15 patients were lost to follow up. Protocol outcome 5: Adverse events - Hypotension at 12 months - Actual outcome: Hypotension at 21 months; Group 1: 46/1360, Group 2: 37/1369; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Other 1 - Low; Indirectness of outcome: No indirectness, Comments: Meets protocol; Baseline details: Blood pressure at baseline, mm Hg (SD): Eplerenone - Systolic 124 (17), Diastolic 75 (1); Placebo - Systolic 124 (17), Diastolic 75 (10).; Group 1 Number missing: 243, Reason: 4 did not start the study medication and were not included in the safety analysis. At trial cut-off, 222 patients had discontinued study drug and 17 patients were lost to follow up.; Group 2 Number missing: 247, Reason: 4 did not start the study medication and were not included in the safety analysis. At trial cut-off, 228 patients had discontinued study drug and 15 patients were lost to follow up. Protocol outcome 6: Adverse events - Hyperkalaemia at 12 months - Actual outcome: Hyperkalemia (serum potassium > 5.5 mmol / L) at 21 months; Group 1: 158/1336, Group 2: 96/1340; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness, Comments: Meets protocol.; Baseline details: Serum potassium at baseline, mmol/liter (SD): Eplerenone - 4.3 (0.4), Placebo - 4.3 (0.4); Group 1 Number missing: 243, Reason: 4 did not start the study medication and were not included in the safety analysis. At trial cut-off, 222 patients had discontinued study drug and 17 patients were lost to follow up.; Group 2 Number missing: 247, Reason: 4 did not start the study medication and were not included in the safety analysis. At trial cut-off, 228 patients had discontinued study drug and 15 patients were lost to follow up.	
Protocol outcomes not reported by the study	Quality of life at 12 months; Improvement of NYHA class at 12 months

Study	J-EMPHASIS-HF: Eplerenone in Japanese patients with HFrEF trial: Tsutsui 2017[1410]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=221)
Countries and setting	Conducted in Japan; Setting: Multicenter, randomised, double-blind, placebo-controlled, parallel-group study (J-EMPHASIS-HF). The study was conducted at 52 sites in Japan from 30th July 2010 to 7th September 2015.
Line of therapy	1st line
Duration of study	Intervention + follow up: maximum of 4 years intervention plus 1 year follow-up

Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Japanese patients ≥55 years of age who had chronic HF of either ischemic or non-ischemic aetilogy (duration ≥4 weeks); symptoms of NYHA functional class II or higher; left ventricular ejection fraction (LVEF) ≤30% (or ≤35% in addition to QRS duration >130 ms on ECG); and treatment with ACE inhibitor, ARB, β-blocker, or diuretic. Randomisation was performed within 6 months after hospitalisation for cardiovascular causes. Patients who had not been hospitalised for cardiovascular causes within 6 months before randomisation could be enrolled if their plasma level of B-type natriuretic peptide (BNP) was ≥250pg/mL or their plasma level of N-terminal proBNP (NT-proBNP) was ≥500 pg/mL for men and ≥750 pg/mL for women within 15 days of randomisation.
Exclusion criteria	acute myocardial infarction or stroke within 30 days prior to randomisation, serum potassium level >5.0 mEq/L, estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 within 24h prior to randomisation, need for potassium-sparing diuretic such as spironolactone, and any other clinically significant co-existing conditions
Recruitment/selection of patients	Randomisation was performed within 6 months after hospitalisation for cardiovascular causes. Patients who had not been hospitalised for cardiovascular causes within 6 months before randomisation could be enrolled if they met certain criteria detailed in the inclusion section.
Age, gender and ethnicity	Age - Mean (SD): Eplerenone group: 69.0 (8.7) years, placebo group: 68.4 (7.7) years . Gender (M:F): 4/1. Ethnicity: na
Further population details	1. Age: Not applicable / Not stated / Unclear (aged 55 years or over). 2. Diabetes status: Not applicable / Not stated / Unclear (mixed population; approx 40% of patients had diabetes in each group). 3. Renal function: Not applicable / Not stated / Unclear (patients in each group had on average 1.0 mg/dL serum creatinine).
Indirectness of population	No indirectness
Interventions	(n=111) Intervention 1: Mineralocorticoid receptor antagonist - Eplerenone (up to 50mg/day). Eplerenone group Eplerenone was initiated at a dose of 25mg once daily provided that the serum potassium level was <5.0mEq/L when dosage was initiated, and increased after 4 weeks to 50 mg once daily (or initiated at 25mg on alternate days and increased to 25mg daily, if eGFR was 30 to <50mL/min/1.73m²). Thereafter, serum potassium level was measured at each visit except for months 2, 3, and 4. Investigators were instructed to decrease the dose of study drug if the serum potassium level was 5.5-5.9 mEq/L and to withhold the study drug if the serum potassium level was ≥6.0 mEq/L. Potassium was to be re-measured within 72 h after withholding from the study drug, and the study drug was to be restarted only if the level was <5.0 mEq/L. Duration Patients were treated with the study drug for a maximum of 48 months. The study was completed when the last randomised patient had been followed for a year. Concurrent medication/care: not mentioned. Indirectness: No indirectness

	(n=110) Intervention 2: Placebo . matching placebo (no details given). Duration Patients were treated with the study drug for a maximum of 48 months. the study was completed when the last randomised patient had been followed for a year. Concurrent medication/care: not mentioned. Indirectness: No indirectness
Funding	Study funded by industry (funded by Pfizer)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: EPLERENONE (UP TO 50MG/DAY) versus PLACEBO

Protocol outcome 1: All-cause mortality at During study
- Actual outcome: death from any cause at during study period (max 4 years plus follow-up of 1 year); Group 1: Observed events 17 n=111 ; Group 2: Observed events 10 n=110; HR 1.77; Lower CI 0.81 to Upper CI 3.87
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: More people with diabetes, angina pectoris and coronary artery bypass grafting in the placebo group.; Group 1 Number missing: 0 ; Group 2 Number missing: 0

Protocol outcome 2: All-cause mortality at 12 months
- Actual outcome: death from any cause at during study period (max 4 years plus follow-up of 1 year); Group 1: 17/111, Group 2: 10/110
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Baseline details: More people with diabetes, angina pectoris and coronary artery bypass grafting in the placebo group.; Group 1 Number missing: 0 ; Group 2 Number missing: 0

Protocol outcome 3: Unplanned hospitalisation at During study
- Actual outcome: hospitalisation for any cause at during study period (max 4 years plus follow-up of 1 year); Group 1: 45/111, Group 2: 58/110
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Comments - Authors state ITT analysis was used but do not specify how missing data was dealt with or how much data was missing.; Indirectness of outcome: No indirectness ; Baseline details: More people with diabetes, angina pectoris and coronary artery bypass grafting in the placebo group.; Group 1 Number missing: unknown; Group 2 Number missing: unknown

Protocol outcome 4: Adverse events - Renal function at 12 months
- Actual outcome: Renal impairment at during study period (max 4 years plus follow-up of 1 year); Group 1: 5/111, Group 2: 10/110
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Comments - Authors state that ITT analysis was used but do not specify how missing data was dealt with and what the rate of missing data was.; Indirectness of outcome: No indirectness ; Baseline details: More people with diabetes, angina pectoris and coronary artery bypass grafting in the placebo group.; Group 1 Number missing: unknown; Group 2 Number missing: unknown

Protocol outcome 5: Adverse events - Gynaecomastia at 12 months - Actual outcome: Gynaecomastia at during study period (max 4 years plus follow-up of 1 year); Group 1: 0/111, Group 2: 0/110 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Comments - Authors state that ITT analysis was used but do not specify how missing data was dealt with and what the rate of missing data was.; Indirectness of outcome: No indirectness ; Baseline details: More people with diabetes, angina pectoris and coronary artery bypass grafting in the placebo group.; Group 1 Number missing: unknown; Group 2 Number missing: unknown Protocol outcome 6: Adverse events - Hypotension at 12 months - Actual outcome: Hypotension at during study period (max 4 years plus follow-up of 1 year); Group 1: 4/111, Group 2: 7/110 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Comments - Authors state that ITT analysis was used but do not specify how missing data was dealt with and what the rate of missing data was.; Indirectness of outcome: No indirectness ; Baseline details: More people with diabetes, angina pectoris and coronary artery bypass grafting in the placebo group.; Group 1 Number missing: unknown; Group 2 Number missing: unknown Protocol outcome 7: Adverse events - Hyperkalaemia at 12 months - Actual outcome: Hyperkalaemia at during study period (max 4 years plus follow-up of 1 year); Group 1: 8/111, Group 2: 6/110 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Comments - Authors state that ITT analysis was used but do not specify how missing data was dealt with and what the rate of missing data was.; Indirectness of outcome: No indirectness ; Baseline details: More people with diabetes, angina pectoris and coronary artery bypass grafting in the placebo group.; Group 1 Number missing: unknown; Group 2 Number missing: unknown	
Protocol outcomes not reported by the study	Quality of life at 12 months; Improvement of NYHA class at 12 months

Study (subsidiary papers)	Randomizd Aldactone Evaluation Study (RALES) trial: Pitt 1999[1159] (Vardeny 2012[1433], Vardeny 2014[1432])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1663)
Countries and setting	Conducted in Multiple countries; Setting: 195 centres in 15 countries
Line of therapy	Adjunctive to current care
Duration of study	Follow up (post intervention): Randomisation begun March 1995; follow-up planned to December 1999 but trial stopped early in August 1998. Mean follow-up was 24 months.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not stratified but pre-specified:
Inclusion criteria	Patients were eligible for enrollment if they had had New York Heart Association (NYHA) class IV heart failure within the six months before enrollment and were in NYHA class III or IV at the time of enrollment, had been given a diagnosis of heart failure at least six weeks before enrollment, were being treated with an ACE inhibitor (if tolerated) and a loop diuretic, and had a left ventricular ejection fraction of no more than 35 percent within the six months before enrollment (with no clinically significant intercurrent event). Treatment with digitalis and vasodilators was allowed, but potassium-sparing diuretics were not permitted. Oral potassium supplements were not recommended unless hypokalemia (defined as a serum potassium concentration of less than 3.5 mmol per liter) developed.
Exclusion criteria	Patients were excluded from the study if they had primary operable valvular heart disease (other than mitral or tricuspid regurgitation with clinical symptoms due to left ventricular systolic heart failure), congenital heart disease, unstable angina, primary hepatic failure, active cancer, or any life-threatening disease (other than heart failure). Patients who had undergone heart transplantation or were awaiting the procedure were also ineligible. Other criteria for exclusion were a serum creatinine concentration of more than 2.5 mg per deciliter (221 µmol per liter) and a serum potassium concentration of more than 5.0 mmol per liter. The institutional review boards or ethics committees of all participating institutions approved the protocol, and all patients gave written informed consent.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): For spironolactone and placebo respectively: 65 (12); 65 (12). Gender (M:F): For spironlactone and placebo respectively: 603:219; 614: 227. Ethnicity: White race (%), placebo versus spironlactone: 86% versus 87%
Further population details	1. Age: Not applicable / Not stated / Unclear (Results are available separately for particpants < 67 years and those ≥ 67 years - these have not been extracted but can be considered if there is heterogeneity. Overall results have been extracted.). 2. Diabetes status: Not applicable / Not stated / Unclear 3. Renal function: Abnormal (creatinine

	>130 µmol/l or EGFR < 60mL/min) (Results are available separately for particpants with normal versus abnormal renal function - these have not been extracted but can be considered if there is heterogeneity. Overall results have been extracted.).
Extra comments	For placebo versus spironolactone respectively: Heart rate (beats/min, mean (SD)): 81 (15) versus 81 (14); NYHA class (no (%)): II: 3(0.4) versus 4 (0.5); III: 581(69) versus 592 (72); IV: 257(31) versus 226 (27); LVEF (%, mean (SD): 25.2 (6.8) versus 25.6 (6.7).
Indirectness of population	Serious indirectness: The vast majority of patients (~90%) were not on beta-blockers, which are now part of standard first line therapy.
Interventions	(n=822) Intervention 1: Mineralocorticoid receptor antagonist - Spironolactone (up to 50mg/day). 25mg spironlactone (Aldactone, Searle) once daily, increased to 50mg once daily if patient showed symptoms of progression of heart failure without evidence of hyperkalaemia. If hyperkalemia developed at any time, the dose could be decreased to 25mg every other day; however, the investigator was encouraged first to adjust the doses of concomitant medications.. Duration Mean 24 months. Concurrent medication/care: Loop diuretics 100%; ACE inhibitors 95%; Digitalis 75%; Aspirin 36%; Potassium supplements: 29%; Beta-blockers 11% (n=841) Intervention 2: Placebo . Matching placebo. Duration Mean 24 months. Concurrent medication/care: Loop diuretics 100%; ACE inhibitors 95%; Digitalis 72%; Aspirin 37%; Potassium supplements: 27%; Beta-blockers 10%
Funding	Study funded by industry ('supported by a grant from Searle, Skokie, Illinois')

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SPIRONOLACTONE (UP TO 50MG/DAY) versus PLACEBO

Protocol outcome 1: All-cause mortality
- Actual outcome: All-cause mortality at During study (24 months mean follow up); HR 0.7 (95%CI 0.6 to 0.82) Reported; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: See population panel.; Group 1 Number missing: 222, Reason: No missing data, but 222 participants had discontinued the study drug for various reasons by the study cutoff date. Vital status was followed up over the phone. ; Group 2 Number missing: 211, Reason: No missing data, but 211 participants had discontinued the study drug for various reasons by the study cutoff date. Vital status was followed up over the phone.

Protocol outcome 2: Unplanned hospitalisation
- Actual outcome: All-cause hospitalisation at During study (24 months mean follow up); Other: Number of events - Group 1: 1060, Group 2: 1317; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Rate of missing data based on the dichotomous event rate for assessment purposes; Indirectness of outcome: No indirectness ; Baseline details: See population details.; Group 1 Number missing: 222, Reason: 222 patients discontinued treatment for various reasons ; Group 2 Number missing: 211, Reason: 211 patients discontinued treatment for

various reasons

Protocol outcome 3: Improvement of NYHA class at 12 months
- Actual outcome: Change in NYHA class - Improved at 24 months (mean); Group 1: 246/600, Group 2: 208/630; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Comments - ITT analysis conducted by authors, imputation method not clear. ; Indirectness of outcome: No indirectness ; Baseline details: NYHA class at baseline, %: Class II: Spironolactone - 0.5%, Placebo - 0.4%; Class III: Spironolactone - 72%, Placebo - 69%, Class IV: Spironolactone - 27%, Placebo - 31%.; Group 1 Number missing: 222, Reason: 222 discontinued study drug for various reasons and presumably not included in final analysis for outcome; Group 2 Number missing: 211, Reason: 211 discontinued study drug for various reasons and presumably not included in final analysis for outcome

Protocol outcome 4: Adverse events - Renal function at 12 months
- Actual outcome: Worsening renal function (30% reduction in eGFR from baseline) at 3 months; Group 1: 140/822, Group 2: 59/841; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - ITT analysis conducted by authors, imputation method not clear. Very short time point reported, borderline high ROB for outcome reporting bias. Measurement cutoff not clinically justifiable, borderline high ROB for measurement bias. ; Indirectness of outcome: No indirectness ; Baseline details: eGFR at baseline (SD): Spironolactone - 65.3 (23.1), Placebo - 64.5 (22.8); Group 1 Number missing: , Reason: No data missing, but number discontinuing study drug during first three months not reported. ; Group 2 Number missing: , Reason: No data missing, but number discontinuing study drug during first three months not reported.

Protocol outcome 5: Adverse events - Gynaecomastia at 12 months
- Actual outcome: Gynaecomastia in men at 24 months (mean); Group 1: 55/603, Group 2: 8/614; Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: See population panel. ; Group 1 Number missing: 222, Reason: 222 patients discontinued treatment for various reasons. Not reported how many men discontinued. No clear how many of those who discontinued had data on this outcome. ; Group 2 Number missing: 211, Reason: 211 patients discontinued treatment for various reasons. Not reported how many men discontinued. No clear how many of those who discontinued had data on this outcome

Protocol outcome 6: Adverse events - Hyperkalaemia at 12 months
- Actual outcome: Hyperkalaemia (serum potassium ≥ 5.5 mmol/L) at 24 months (mean); Group 1: 156/822, Group 2: 47/841; Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Comments - ITT analysis conducted by authors, imputation method not clear. HR reported by study in text different from HR in table. ; Indirectness of outcome: No indirectness ; Baseline details: Baseline serum potassium, mmol/L (SD): Spironolactone - 4.29 (0.5), Placebo - 4.26 (0.44); Blinding details: Outcome assessment said to be 'not blinded' though not clear whether this applied to intervention or to confounders (some suggestion that it is the latter and that this could have influenced comparability of care in terms of concomittant medication); Group 1 Number missing: 222, Reason: 222 discontinued study drug for various reasons. No clear how many of those who discontinued had data on this outcome. ; Group 2 Number missing: 211, Reason: 211 discontinued study drug for various reasons. No clear how many of those who discontinued had data on this outcome.

Protocol outcomes not reported by the study	Quality of life at 12 months; Adverse events - Hypotension at 12 months

Study	Udelson 2010[1413]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=226)
Countries and setting	Conducted in USA; Setting: Primary and secondary care.
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 36 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Measurement of LVEF of 35% by equilibrium-gated RVG at screening.
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Male or nonpregnant female subjects aged 21 years and older with current symptoms consistent with mild-to-moderate HF (NYHA functional class II and III) who had LVEF of 35% by equilibrium-gated RVG at screening and were on therapy with an ACEI and/or angiotensin receptor blocker and BB (unless docu-mented intolerance) for at least 3 months duration and at a dose that has not been adjusted within the previous 4 weeks.
Exclusion criteria	Patients with current decompensated HF or HF hospitalization or severe HF (NYHA functional class IV) within 6 months of screen-ing, serum potassium 5.5 mEq/L, history of hyperkalemia (K 6.0 mEq/L) with eplerenone or spironolactone, creatinine clearance of 30 mL/min based on the Cockcroft-Gault formula, biventricular pacemaker placed within 6 months of screening, or subjects on or requiring potassium-sparing diuretics or spironolactone.
Recruitment/selection of patients	Not reported.
Age, gender and ethnicity	Age - Mean (SD): Eplerenone - 63.3 (12.2); placebo - 62.0 (12.9). Gender (M:F): Eplerenone - 98/19; placebo - 91/18.. Ethnicity: % Caucasian - Eplerenone - 81.2; placebo - 85.3
Further population details	1. Age: Not applicable / Not stated / Unclear 2. Diabetes status: Not applicable / Not stated / Unclear 3. Renal function: Not applicable / Not stated / Unclear
Extra comments	Baseline characteristics: n (%), NYHA class II/III: Eplerenone - 116(99); placebo - 109 (100). mean (SE) LVEF: Eplerenone - 26.2 (0.6); placebo - 27.0 (0.6).
Indirectness of population	No indirectness: Meets protocol.
Interventions	(n=117) Intervention 1: Mineralocorticoid receptor antagonist - Eplerenone (up to 50mg/day). Initially after randomization, patients were given 25 mg of eplerenone daily. After 4 weeks of treatment, the dose of eplerenone was increased to the target dose of 50 mg (two 25 mg tablets daily). Serum potassium was monitored throughout the study, and if necessary, doses of eplerenone were titrated down. . Duration 36 weeks. Concurrent medication/care:

	Background medications:n (%), ACEI and/or ARB: 86 + 25 (94.9); BB: 113 (96.6); Diurectic: 83 (70.9). (n=109) Intervention 2: Placebo . Initially after randomization, patients were given 25 mg of matching placebo. After 4 weeks of treatment, the dose of placebo was increased to the target dose of 50 mg (two 25 mg tablets daily). Serum potassium was monitored throughout the study, and if necessary, doses of placebo were titrated down.. Duration 36 weeks. Concurrent medication/care: Background therapies: n (%), ACE and/or ARB: 86 + 21(98.2); BB: 102 (93.6); Diuretic: 76 (69.7).
Funding	Study funded by industry (Trial was funded by Pfizer Inc, and thus, all investigators and/or their institutions received research funding from Pfizer Inc.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: EPLERENONE (UP TO 50MG/DAY) versus PLACEBO

Protocol outcome 1: Quality of life at 12 months
- Actual outcome: Quality of life (Kansas City) at 36 weeks ; Other: Statement that "there was no evidence of a difference between the groups in changes on the [...] overall summary score". (p-value = 0.78); Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Very high, Measurement - Low, Crossover - Low, Comments - ITT analysis by authors, but imputation method unclear; Indirectness of outcome: No indirectness; Baseline details: Not reported.; Group 1 Number missing: 13, Reason: not reported - but said not to differ in baseline characteristics from those remaining in study; Group 2 Number missing: 20, Reason: not reported - but said not to differ in baseline characteristics from those remaining in study

Protocol outcome 2: Improvement of NYHA class at 12 months
- Actual outcome: Changes in NYHA class - Improved at 36 weeks ; Group 1: 32/117, Group 2: 19/109; Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Authors used ITT analysis, but imputation method not clear.; Indirectness of outcome: No indirectness, Comments: Meets protocol.; Baseline details: (n) NYHA class I: Eplerenone - 1, placebo - 0; NYHA class II: Eplerenone - 79, placebo - 87; NHYA class III: Eplerenone - 37, placebo - 22.; Blinding details: No information was given on blinding.; Group 1 Number missing: 13, Reason: Not reported, baseline characteristics said to not differ from participants remaining ; Group 2 Number missing: 20, Reason: Not reported, baseline characteristics said to not differ from participants remaining

Protocol outcome 3: Adverse events - Renal function at 12 months
- Actual outcome: Creatinine increased at 36 weeks ; Group 1: 11/117, Group 2: 6/109; Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - High, Crossover - Low, Comments - Authors used ITT analysis, but imputation method not clear. Number of patients with increased creatinine reported, rather than the continuous results.; Indirectness of outcome: Serious indirectness; Baseline details: Serum creatinine (median), mg/dL: Eplerenone - 1.2, Placebo - 1.20; Group 1 Number missing: 13, Reason: Not reported, though baseline characteristics said to not differ from participants remaining; Group 2 Number missing: 20, Reason: Not reported, though baseline characteristics said to not differ from participants remaining

Protocol outcome 4: Adverse events - Hypotension at 12 months - Actual outcome: Hypotension at 36 weeks ; Group 1: 9/117, Group 2: 4/109; Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - Authors used ITT analysis, but imputation method not clear.; Indirectness of outcome: No indirectness, Comments: Meets protocol.; Baseline details: Not reported.; Group 1 Number missing: 13, Reason: Not reported, though baseline characteristics said to not differ from participants remaining; Group 2 Number missing: 20, Reason: Not reported, though baseline characteristics said to not differ from participants remaining Protocol outcome 5: Adverse events - Hyperkalaemia at 12 months - Actual outcome: Hyperkalaemia (no definition) at 36 weeks ; Group 1: 14/117, Group 2: 6/109; Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Authors used ITT analysis, but imputation method not clear.; Indirectness of outcome: No indirectness, Comments: Meets protocol.; Baseline details: Serum potassium (median), mEq/L: eplerenone - 4.3; placebo - 4.3.; Group 1 Number missing: 13, Reason: Not reported, though baseline characteristics said to not differ from participants remaining; Group 2 Number missing: 20, Reason: Not reported, though baseline characteristics said to not differ from participants remaining	
Protocol outcomes not reported by the study	All-cause mortality; Unplanned hospitalisation; Adverse events - Gynaecomastia at 12 months

F.6 Iron supplementation for iron deficiency in heart failure

Study	CONFIRM-HF trial: Ponikowski 2015[1163]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=304)
Countries and setting	Conducted in Multiple countries; Setting: 41 sites
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: NYHA class II or III
Stratum	Overall
Subgroup analysis within study	Stratified then randomised: Stratified by site and by Hb levels (< 12g/dL versus >=12g/dL)
Inclusion criteria	Eligible patients included stable ambulatory HF patients in New York Heart Association (NYHA) class II or III, with left ventricular ejection fraction (LVEF) ≤45%, elevated natriuretic peptides (brain natriuretic peptide > 100 pg/mL and/or N-terminal-pro-brain natriuretic peptide > 400 pg/mL), presence of ID [defined as serum ferritin level <100 ng/ mL, or between 100 and300 ng/mL if transferrin saturation (TSAT) < 20%] and haemoglobin (Hb) <15 g/dL (all at the screening visit). All subjects must have been capable of completing the 6 min walk test (6MWT). There was no upper age limit.
Exclusion criteria	Patients with uncontrolled hypertension, infection, clinical evidence of current malignancy, or significantly impaired liver or renal function were excluded. There was no lower limit for Hb, but subjects with an immediate need for transfusion were excluded.
Recruitment/selection of patients	589 patients were screened, of whom 304 were randomised.
Age, gender and ethnicity	Age - Mean (SD): Iron - 69 (9.5), Placebo - 70 (9.3). Gender (M:F): 160:141. Ethnicity: White - 99%
Further population details	1. Anaemia: Not applicable (Mixed population).
Extra comments	NYHA class II: Iron - 53%, Placebo - 60% LVEF % (SD): Iron 37.1 (7.5), Placebo - 36.5 (7.3) 6MWT: Iron - 288 (98), Placebo 302 (97) Ischemic cause of HF, %: Iron - 83%, Placebo - 83%.
Indirectness of population	No indirectness

Interventions	(n=152) Intervention 1: Iron supplementation - Intravenous iron. Ferric carboxymaltose (FCM) solution was given as undiluted bolus i.v. injections of 10 or 20 mL (equivalent to 500 or 1000mg of iron) administered over at least 1 minute. Administered as doses based on subject weight and Hb value at screening, according to a scheduled dosing scheme. This included both therapy dosing (correction phase) and maintenance dosing (maintenance phase). In summary, total FCM doses were between 500 and 2000 mg iron FCM in the therapy phase (dosed at baseline and week 6) and thereafter maintenance FCM dosing of 500 mg iron at each of weeks 12, 24 and 36, if ID was still present. . Duration Up to 36 weeks. Concurrent medication/care: ACEi treatment: 77%, BB treatment: 89% (n=152) Intervention 2: Placebo. Normal saline solution administered in equivalent volumes on same dosing schedule. Duration Up to 36 weeks. Concurrent medication/care: ACEi treatment: 78%, BB treatment: 92%
Funding	Study funded by industry (Vifor Pharma Ltd)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRAVENOUS IRON versus PLACEBO

Protocol outcome 1: Mortality
- Actual outcome: Mortality at 12 months; Group 1: 12/150, Group 2: 14/151; Comments: One additional patient in the iron group died in the 30 day safety follow up period after completing the study.
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: See population tab; Blinding details: FCM is a dark brown and cannot easily be masked from placebo. Unblinded study personnel not involved in any study assessments were responsible for preparing and administering the study treatment injections in black syringes and using a curtain (or similar) to maintain subject blinding; Group 1 Number missing: 19, Reason: 2 excluded from analysis as no post-baseline efficacy assessment, 17 discontinued (3 adverse event, 1 physician decision, 2 protocol violation, 8 withdrawal, 3 other); Group 2 Number missing: 11, Reason: 1 excluded from analysis as no post-baseline efficacy assessment, 10 discontinued (3 adverse event, 2 lost to follow up, 1 physician decision, 3 withdrawal, 1 other)

Protocol outcome 2: Quality of life at 12 months
- Actual outcome: EQ-5D VAS at 12 months; Group 1: mean 7 mm (SD 12.8); n=114, Group 2: mean 4.4 mm (SD 12.9); n=106; EQ-5D VAS 0-100 Top=High is good outcome
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: comparable at baseline (54.7 v 54.1); Blinding details: FCM is dark brown and cannot easily be masked from placebo. Unblinded study personnel not involved in any study assessments were responsible for preparing and administering the study treatment injections in black syringes and using a curtain (or similar) to maintain subject blinding; Group 1 Number missing: 38, Reason: 38 patients missing from analysis. 2 excluded from analysis as no post-baseline efficacy assessment. 29 discontinued patients discontinued but not clear whether included in analysis (3 adverse event, 1 physician decision, 2 protocol violation, 8 withdrawal, 3 other). ; Group 2 Number missing: 46, Reason: 46 patients missing from analysis. 1 excluded from analysis as no post-baseline efficacy assessment. 24 discontinued (3 adverse event, 14 deaths, 2 lost to follow up, 1 physician decision, 3 withdrawal, 1 other).

- Actual outcome: KCCQ at 12 months; Group 1: mean 6.8 (SD 13.07); n=114, Group 2: mean 2.3 (SD 13.13); n=106; Kansas City Cardiomyopathy Questionnaire 0-100 Top=High is good outcome
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable at baseline (59.0 v 58.8); Blinding details: FCM is dark brown and cannot easily be masked from placebo. Unblinded study personnel not involved in any study assessments were responsible for preparing and administering the study treatment injections in black syringes and using a curtain (or similar) to maintain subject blinding; Group 1 Number missing: 38, Reason: 38 patients missing from analysis. 2 excluded from analysis as no post-baseline efficacy assessment, 29 discontinued (3 adverse event, 1 physician decision, 2 protocol violation, 8 withdrawal, 3 other), 7 unknown reasons; Group 2 Number missing: 46, Reason: 46 patients missing from analysis. 1 excluded from analysis as no post-baseline efficacy assessment, 24 discontinued (3 adverse event, 14 deaths, 2 lost to follow up, 1 physician decision, 3 withdrawal, 1 other), 21 reasons not reported

Protocol outcome 3: Unplanned hospitalisation (all-cause)
- Actual outcome: Hospitalisation (all-cause) at 12 months; Other: Number of hospitalisations: Iron - 46; Placebo - 69
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: See population tab; Blinding details: FCM is dark brown and cannot easily be masked from placebo. Unblinded study personnel not involved in any study assessments were responsible for preparing and administering the study treatment injections in black syringes and using a curtain (or similar) to maintain subject blinding; Group 1 Number missing: 31, Reason: 2 excluded from analysis as no post-baseline efficacy assessment, 29 discontinued (3 adverse event, 1 physician decision, 2 protocol violation, 8 withdrawal, 3 other); Group 2 Number missing: 25, Reason: 1 excluded from analysis as no post-baseline efficacy assessment, 24 discontinued (3 adverse event, 14 deaths, 2 lost to follow up, 1 physician decision, 3 withdrawal, 1 other)
Protocol outcome 4: Improvement in exercise tolerance at 12 months
- Actual outcome: Six minute walk test (6MWT) distance at 12 months; Group 1: mean 14 metres (SD 85.56); n=125, Group 2: mean -22 metres (SD 84.18); n=121
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Similar at baseline (iron - 288, placebo - 302); Blinding details: FCM is dark brown and cannot easily be masked from placebo. Unblinded study personnel not involved in any study assessments were responsible for preparing and administering the study treatment injections in black syringes and using a curtain (or similar) to maintain subject blinding; Group 1 Number missing: 27, Reason: 27 missing from analysis, including 2 excluded from analysis as no post-baseline efficacy assessment. 29 discontinued (3 adverse event, 1 physician decision, 2 protocol violation, 8 withdrawal, 3 other); Group 2 Number missing: 31, Reason: 31 missing from analysis, including 1 excluded from analysis as no post-baseline efficacy assessment. 24 discontinued (3 adverse event, 14 deaths, 2 lost to follow up, 1 physician decision, 3 withdrawal, 1 other)
Protocol outcome 5: Withdrawal due to adverse events/tolerability
- Actual outcome: Discontinuation due to adverse events at 12 months; Group 1: 14/152, Group 2: 19/152
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Comments - Inconsistent reporting of outcome data (reported as 3 in flow chart and 14 in table); Indirectness of outcome: No indirectness ; Baseline details: See population tab; Blinding details: FCM is dark brown and cannot easily be masked from placebo. Unblinded study personnel not involved in any study assessments were responsible for preparing and administering the study treatment injections in black syringes and using a curtain (or similar) to maintain subject blinding; Group 1 Number missing: 31, Reason: 2 excluded from analysis as no post-baseline efficacy assessment, 29 discontinued (3 adverse event, 1 physician decision, 2 protocol violation, 8 withdrawal, 3 other); Group 2 Number missing: 25, Reason: 1 excluded from analysis as no post-baseline efficacy assessment, 24 discontinued (3 adverse event, 14 deaths, 2 lost to follow up, 1 physician decision, 3 withdrawal, 1 other)

Protocol outcome 6: Adverse events - stroke - Actual outcome: Drug related vascular disorders at 12 months; Group 1: 1/152, Group 2: 1/152 Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - Unclear what constituted 'drug related' or what is encompassed by 'vascular disorders'; Indirectness of outcome: Serious indirectness ; Baseline details: See population tab; Blinding details: FCM is dark brown and cannot easily be masked from placebo. Unblinded study personnel not involved in any study assessments were responsible for preparing and administering the study treatment injections in black syringes and using a curtain (or similar) to maintain subject blinding; Group 1 Number missing: 31, Reason: 2 excluded from analysis as no post-baseline efficacy assessment, 29 discontinued (3 adverse event, 1 physician decision, 2 protocol violation, 8 withdrawal, 3 other); Group 2 Number missing: 25, Reason: 1 excluded from analysis as no post-baseline efficacy assessment, 24 discontinued (3 adverse event, 14 deaths, 2 lost to follow up, 1 physician decision, 3 withdrawal, 1 other) Protocol outcome 7: Adverse events - gastrointestinal - Actual outcome: Drug related GI disorders at 12 months; Group 1: 2/152, Group 2: 0/152 Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - Unclear what constituted 'drug related' or what is encompassed by 'GI disorders'; Indirectness of outcome: No indirectness ; Baseline details: See population tab; Blinding details: FCM is dark brown and cannot easily be masked from placebo. Unblinded study personnel not involved in any study assessments were responsible for preparing and administering the study treatment injections in black syringes and using a curtain (or similar) to maintain subject blinding; Group 1 Number missing: 31, Reason: 2 excluded from analysis as no post-baseline efficacy assessment, 29 discontinued (3 adverse event, 1 physician decision, 2 protocol violation, 8 withdrawal, 3 other); Group 2 Number missing: 25, Reason: 1 excluded from analysis as no post-baseline efficacy assessment, 24 discontinued (3 adverse event, 14 deaths, 2 lost to follow up, 1 physician decision, 3 withdrawal, 1 other)	
Protocol outcomes not reported by the study	Change in haemoglobin in anaemic patients at 12 months; Adverse events - anaphylaxis/hypersensitivity; Adverse events - hypertension

Study (subsidiary papers)	**FAIR-HF trial: Anker 2009[79] (Anker 2009[78], Comin-colet 2013[308], Filippatos 2013[464], Gutzwiller 2013[566], Ponikowski 2015[1162])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=461)
Countries and setting	Conducted in Multiple countries; Setting: 75 sites in 11 countries
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 24 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: NYHA class II or III with reduced ejection fraction
Stratum	Overall:

1

Subgroup analysis within study	Stratified then randomised: Stratified by region. Subgroup analysis of patients with and without anaemia, unclear if pre-specified
Inclusion criteria	Ambulatory patients with CHF of NYHA class II or III, LVEF ≤ 40% (class II) or ≤ 45% (class III), Hb at screening between 95 - 135 g/L, and iron deficiency (as per this review protocol's definition).
Exclusion criteria	Uncontrolled hypertension, other clinically significant heart disease, inflammation, or clinically significantly impaired liver or renal function.
Recruitment/selection of patients	957 patients signed informed consent, 461 were randomised. Reasons for non-randomisation not reported.
Age, gender and ethnicity	Age - Mean (SD): Iron - 68 (10.3), Placebo - 67 (11.1). Gender (M:F): 215:244. Ethnicity: 1 non-white patient
Further population details	1. Anaemia: Not applicable (Mixed population).
Extra comments	NYHA class III: Iron - 82.6%, Placebo - 81.3% LVEF, % (SD): Iron - 31.9 (5.5), Placebo - 33.0 (6.1) 6MWT distance: Iron - 274 (105), Placebo - 269 (109) Ischaemic cause of HF: Iron - 81%, Placebo - 79.4% Hb, g/L: Iron - 119 (13), Placebo - 119 (14).
Indirectness of population	No indirectness
Interventions	(n=304) Intervention 1: Iron supplementation - Intravenous iron. Ferric carboxymaltose solution (Ferinject, Vifor International) for parenteral application, 50mg iron/mL iron. Medication is given as an i.v. bolus of 200 mg iron in 4 mL (can by 100 mg iron i.v. for last injection in correction phase). Dosing frequency was weekly until iron repletion was achieved (the correction phase), and then every 4 weeks during the maintenance phase, which started at week 8 or week 12, depending on the required iron-repletion dose. The total dose required for iron repletion was calculated at baseline according to Ganzoni's formula and the mean of the two Hb values obtained during the screening period. Duration 24 weeks. Concurrent medication/care: ACEi or ARB - 92%, BB - 86.2% (n=155) Intervention 2: Placebo. Saline placebo. Duration 24 weeks. Concurrent medication/care: ACEi or ARB - 91% BB - 83%
Funding	Study funded by industry (Vifor Pharma Ltd)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRAVENOUS IRON versus PLACEBO

Protocol outcome 1: Mortality
- Actual outcome: Mortality at 26 weeks; Group 1: 5/305, Group 2: 4/154

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - 2 patients randomised but not started medication, not included in any analysis (not clear which group they were in). Protocol re discontinuation: if ferritin or Hb at certain level, iron was stopped and placebo given instead until levels dropped, when iron was restarted. if severe anaemia developed, study drug was permanently discontinued. Follow up of such patients continued and further management of anaemia was performed at the investigators discretion. The number of patients in each of these groups was not reported. 1 patient in the placebo group received ferric carboxymaltose (switched); Indirectness of outcome: No indirectness ; Baseline details: See pop panel; Blinding details: Study personnel preparing and administering drug were aware of assignments and were not involved in any study assessments. Black syringes were used to administer the study treatment and a curtain shielded the injection site from patient. ; Group 1 Number missing: 21, Reason: Withdrawn (did not complete 24 weeks of follow up). Unknown number of patients discontinued study drug but were continued to be followed up. ; Group 2 Number missing: 17, Reason: 16 withdrawn (did not complete 24 weeks of follow up). Unknown number of patients discontinued study drug but were continued to be followed up. 1 patient switched.

Protocol outcome 2: Quality of life at 12 months
- Actual outcome: EQ-5D index score at 24 weeks; Group 1: mean 0.066 (SD 0.209); n=304, Group 2: mean -0.01 (SD 0.224); n=155; EQ-5D 0-1 Top=High is good outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - 2 patients randomised but not started medication, not included in any analysis (not clear which group they were in). Protocol re discontinuation: if ferritin or Hb at certain level, iron was stopped and placebo given instead until levels dropped, when iron was restarted. if severe anaemia developed, study drug was permanently discontinued. Follow up of such patients continued and further management of anaemia was performed at the investigators discretion. The number of patients in each of these groups was not reported. 1 patient in the placebo group received ferric carboxymaltose (switched) Imputation method depended on status of individual (why data missing); Indirectness of outcome: No indirectness ; Baseline details: comparable at baseline (0.01 points difference); Blinding details: Study personnel preparing and administering drug were aware of assignments and were not involved in any study assessments. Black syringes were used to administer the study treatment and a curtain shielded the injection site from patient. ; Group 1 Number missing: 16, Reason: 20 withdrawn (did not complete 24 weeks of follow up). 16 said to be missing for this outcome, unknown number of those had data imputed. Unknown number of patients discontinued study drug but were continued to be followed up. ; Group 2 Number missing: 7, Reason: 16 withdrawn (did not complete 24 weeks of follow up). 7 said to be missing for this outcome. Unknown number of patients discontinued study drug but were continued to be followed up. 1 patient switched.
- Actual outcome: EQ-5D VAS score at 24 weeks; Group 1: mean 9.1 (SD 17.44); n=304, Group 2: mean 3.4 (SD 19.92); n=155; EQ-5D VAS 0-100 Top=High is good outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - 2 patients randomised but not started medication, not included in any analysis (not clear which group they were in). Protocol re discontinuation: if ferritin or Hb at certain level, iron was stopped and placebo given instead until levels dropped, when iron was restarted. if severe anaemia developed, study drug was permanently discontinued. Follow up of such patients continued and further management of anaemia was performed at the investigators discretion. The number of patients in each of these groups was not reported. 1 patient in the placebo group received ferric carboxymaltose (switched) Imputation method depended on status of individual (why data missing); Indirectness of outcome: No indirectness ; Baseline details: comparable at baseline (0 points difference); Blinding details: Study personnel preparing and administering drug were aware of assignments and were not involved in any study assessments. Black syringes were used to administer the study treatment and a curtain shielded the injection site from patient. ; Group 1 Number missing: 19, Reason: 20 withdrawn (did not complete 24 weeks of follow up). 19 said to be missing for this outcome, unknown number of those had data imputed. Unknown number of patients discontinued study drug but were continued to be followed up. ; Group 2

Number missing: 9, Reason: 16 withdrawn (did not complete 24 weeks of follow up). 9 said to be missing for this outcome. Unknown number of patients discontinued study drug but were continued to be followed up. 1 patient switched.
- Actual outcome: KCCQ at 24 weeks; Group 1: mean 12.8 (SD 22.67); n=304, Group 2: mean 6.2 (SD 18.67); n=155; Kansas City Cardiomyopathy Questionnaire, overall summary score 0-100 Top=High is good outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - 2 patients randomised but not started medication, not included in any analysis (not clear which group they were in). Protocol re discontinuation: if ferritin or Hb at certain level, iron was stopped and placebo given instead until levels dropped, when iron was restarted. if severe anaemia developed, study drug was permanently discontinued. Follow up of such patients continued and further management of anaemia was performed at the investigators discretion. The number of patients in each of these groups was not reported. 1 patient in the placebo group received ferric carboxymaltose (switched) Imputation method depended on status of individual (why data missing); Indirectness of outcome: No indirectness ; Baseline details: comparable at baseline (1 points difference); Blinding details: Study personnel preparing and administering drug were aware of assignments and were not involved in any study assessments. Black syringes were used to administer the study treatment and a curtain shielded the injection site from patient. ; Group 1 Number missing: 18, Reason: 20 withdrawn (did not complete 24 weeks of follow up). 18 said to be missing for this outcome, unknown number of those had data imputed. Unknown number of patients discontinued study drug but were continued to be followed up. ; Group 2 Number missing: 10, Reason: 16 withdrawn (did not complete 24 weeks of follow up). 10 said to be missing for this outcome. Unknown number of patients discontinued study drug but were continued to be followed up. 1 patient switched.

Protocol outcome 3: Unplanned hospitalisation (all-cause)
- Actual outcome: Hospitalisation (all cause) at 26 weeks; Other: Iron - 28 hospitalisations, Placebo - 22 hospitalisations
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - 2 patients randomised but not started medication, not included in any analysis (not clear which group they were in). Protocol re discontinuation: if ferritin or Hb at certain level, iron was stopped and placebo given instead until levels dropped, when iron was restarted. if severe anaemia developed, study drug was permanently discontinued. Follow up of such patients continued and further management of anaemia was performed at the investigators discretion. The number of patients in each of these groups was not reported. 1 patient in the placebo group received ferric carboxymaltose (switched); Indirectness of outcome: No indirectness ; Baseline details: See pop panel; Blinding details: Study personnel preparing and administering drug were aware of assignments and were not involved in any study assessments. Black syringes were used to administer the study treatment and a curtain shielded the injection site from patient. ; Group 1 Number missing: 26, Reason: 5 died, 21 withdrawn (did not complete 24 weeks of follow up). Unknown number of patients discontinued study drug but were continued to be followed up. ; Group 2 Number missing: 20, Reason: 4 died, 16 withdrawn (did not complete 24 weeks of follow up). Unknown number of patients discontinued study drug but were continued to be followed up. 1 patient switched.

Protocol outcome 4: Improvement in exercise tolerance at 12 months
- Actual outcome: 6-Minute-Walk Test distance at 24 weeks; Group 1: mean 313 metres (SD 114.6); n=268, Group 2: mean 277 metres (SD 115.8); n=134
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - 2 patients randomised but not started medication, not included in any analysis (not clear which group they were in). Protocol re discontinuation: if ferritin or Hb at certain level, iron was stopped and placebo given instead until levels dropped, when iron was restarted. if severe anaemia developed, study drug was permanently discontinued. Follow up of such patients continued and further management of anaemia was performed at the investigators discretion. The number of patients in each of these groups was not reported. 1 patient in the placebo group received ferric carboxymaltose (switched) No mention of imputation for this outcome; Indirectness of

<table>
<tr><td colspan="2">outcome: No indirectness ; Baseline details: comparable at baseline (5 metres difference); Blinding details: Study personnel preparing and administering drug were aware of assignments and were not involved in any study assessments. Black syringes were used to administer the study treatment and a curtain shielded the injection site from patient. ; Group 1 Number missing: 36, Reason: 20 withdrawn (did not complete 24 weeks of follow up). 36 said to be missing for this outcome, unknown number of those had data imputed. Unknown number of patients discontinued study drug but were continued to be followed up. ; Group 2 Number missing: 21, Reason: 16 withdrawn (did not complete 24 weeks of follow up). 21 said to be missing for this outcome. Unknown number of patients discontinued study drug but were continued to be followed up. 1 patient switched.

Protocol outcome 5: Adverse events - stroke
- Actual outcome: Ischaemic stroke at 26 weeks; Group 1: 2/305, Group 2: 0/154
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - 2 patients randomised but not started medication, not included in any analysis (not clear which group they were in). Protocol re discontinuation: if ferritin or Hb at certain level, iron was stopped and placebo given instead until levels dropped, when iron was restarted. if severe anaemia developed, study drug was permanently discontinued. Follow up of such patients continued and further management of anaemia was performed at the investigators discretion. The number of patients in each of these groups was not reported. 1 patient in the placebo group received ferric carboxymaltose (switched); Indirectness of outcome: No indirectness ; Baseline details: See pop panel; Blinding details: Study personnel preparing and administering drug were aware of assignments and were not involved in any study assessments. Black syringes were used to administer the study treatment and a curtain shielded the injection site from patient. ; Group 1 Number missing: 26, Reason: 5 died, 21 withdrawn (did not complete 24 weeks of follow up). Unknown number of patients discontinued study drug but were continued to be followed up. ; Group 2 Number missing: 20, Reason: 4 died, 16 withdrawn (did not complete 24 weeks of follow up). Unknown number of patients discontinued study drug but were continued to be followed up. 1 patient switched.

Protocol outcome 6: Adverse events - gastrointestinal
- Actual outcome: Gastrointestinal disorders at 26 weeks; Group 1: 24/305, Group 2: 5/154
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - 2 patients randomised but not started medication, not included in any analysis (not clear which group they were in). Protocol re discontinuation: if ferritin or Hb at certain level, iron was stopped and placebo given instead until levels dropped, when iron was restarted. if severe anaemia developed, study drug was permanently discontinued. Follow up of such patients continued and further management of anaemia was performed at the investigators discretion. The number of patients in each of these groups was not reported. 1 patient in the placebo group received ferric carboxymaltose (switched); Indirectness of outcome: No indirectness ; Baseline details: See pop panel; Blinding details: Study personnel preparing and administering drug were aware of assignments and were not involved in any study assessments. Black syringes were used to administer the study treatment and a curtain shielded the injection site from patient. ; Group 1 Number missing: 26, Reason: 5 died, 21 withdrawn (did not complete 24 weeks of follow up). Unknown number of patients discontinued study drug but were continued to be followed up. ; Group 2 Number missing: 20, Reason: 4 died, 16 withdrawn (did not complete 24 weeks of follow up). Unknown number of patients discontinued study drug but were continued to be followed up. 1 patient switched.</td></tr>
<tr><td>Protocol outcomes not reported by the study</td><td>Change in haemoglobin in anaemic patients at 12 months; Withdrawal due to adverse events/tolerability; Adverse events - anaphylaxis/hypersensitivity; Adverse events - hypertension</td></tr>
</table>

Study (subsidiary papers)	IRON-HF trial: Beck-da-silva 2013[142] (Beck-da-silva 2007[143])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=23)
Countries and setting	Conducted in Brazil; Setting: Outpatient clinic
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical diagnosis of HF, NYHA class II-IV, LVEF < 40%
Stratum	Overall
Subgroup analysis within study	Not applicable:
Inclusion criteria	18 years of age or older Outpatients followed at a HF clinic in a tertiary care hospital with clinical diagnosis of HF for at least 3 months before study entry NYHA functional Class II-IV, who are able to perform ergospirometry Documentation of LVEF <40% within the last 6 months Adequate baseline therapy for HF based on patient's functional class (β-blockers, ACE inhibitors irrespective of functional class except if contraindications, digoxin, spironolactone if NYHA Class III or IV) Stable baseline HF therapy with same doses of medications and no intent to increase doses for the following 3 months Hemoglobin ≤12 g/dL and ≥9 g/dL Transferrin saturation <20% and ferritin <500 mg/L Ability to provide written informed consent
Exclusion criteria	Any clinically overt bleeding: gastrointestinal bleeding, hypermenorrhea, history of peptic ulcer without evidence of healing or inflammatory intestinal diseases Uncorrected hypothyroidism Other inflammatory, neoplastic or infectious disease Serum creatinine >1.5 mg/dL Previous intolerance to oral elemental iron compounds HF from alcoholic cardiomyopathy, current regular drinker of alcoholic beverages, or HF from peripartum cardiomyopathy Recent admission for decompensated HF (last month) Recent myocardial revascularization procedures (last 3 months)

	Recent ACS, stroke, or TIA (last 3 months) Active or metastatic neoplastic disease with life expectancy of less than 1 year Patients on heart transplantation list Patients that had participated in any other clinical trial or study within the last month Pregnant or lactating women Premenopausal women who are not using any effective method of contraception Patients using prohibited medications or that have not yet accomplished the washout period Patients participating in cardiovascular rehabilitation programs
Recruitment/selection of patients	Outpatients followed at a HF clinic in a tertiary care hospital (8 sites)
Age, gender and ethnicity	Age - Mean (SD): 66 (11.7). Gender (M:F): 16:7. Ethnicity: NR
Further population details	1. Anaemia: All patients anaemic (All patients hemoglobin ≤12 g/dL and ≥9 g/dL).
Extra comments	LVEF, % (SD) - 28 (7.8) Hb, g/dL - 11.2 (0.6) Creatinine, mg/dL - 1.1 (0.3) Ischemic - 39.1%
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: Iron supplementation - Intravenous iron. Iron sucrose 200 mg intravenously, once a week, in 30 min infusions, for 5 weeks and placebo of oral presentation, 3 times a day, for 8 weeks. Duration 5 weeks. Concurrent medication/care: Adequate baseline therapy - see inclusion criteria. (n=7) Intervention 2: Iron supplementation - Oral iron. Ferrous sulfate 200 mg, orally, three times a day, for 8 weeks and placebo of IV presentation once a week, for 5 weeks. Duration 8 weeks. Concurrent medication/care: Adequate baseline therapy - see inclusion criteria (n=6) Intervention 3: Placebo. Placebo of oral presentation, three times a day, for 8 weeks and placebo of IV presentation once a week, for 5 weeks. Duration 5/8 weeks. Concurrent medication/care: Adequate baseline therapy - see inclusion criteria
Funding	Study funded by industry (Altana Pharma, Brazil)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRAVENOUS IRON versus ORAL IRON Protocol outcome 1: Mortality	

- Actual outcome: Mortality at 3 months; Group 1: 2/10, Group 2: 0/7
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Missing data: 2 patients unable to perform the second ergospirometric evaluation at 90 days but data on vital status assumed to be known. ; Indirectness of outcome: No indirectness ; Baseline details: Differences in age, LVEF, Peak VO2, aetiology, % male; Blinding details: each participating centre elected a third party blind individual who opened the allocated medication box, prepared the sucrose infusions or saline, and administer the preparations to patients using opaque devices. Both patient and attending physicians or nurses will be blind to allocated therapy. ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Quality of life at 12 months
- Actual outcome: Improvement in NYHA class at 3 months; Group 1: 2/10, Group 2: 6/7
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Missing data: 2 patients unable to perform the second ergospirometric evaluation at 90 days but treatment arm not known so cannot use ACA. ; Indirectness of outcome: Serious indirectness, Comments: Protocol outcome was quality of life; Baseline details: Differences in age, LVEF, Peak VO2, aetiology, % male. NYHA class at baseline not reported. ; Blinding details: each participating centre elected a third party blind individual who opened the allocated medication box, prepared the sucrose infusions or saline, and administer the preparations to patients using opaque devices. Both patient and attending physicians or nurses will be blind to allocated therapy. ; Group 1 Number missing: 0; Group 2 Number missing: 0

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRAVENOUS IRON versus PLACEBO

Protocol outcome 1: Mortality
- Actual outcome: Mortality at 3 months; Group 1: 3/10, Group 2: 1/6
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Missing data: 2 patients unable to perform the second ergospirometric evaluation at 90 days but data on vital status assumed to be known. ; Indirectness of outcome: No indirectness ; Baseline details: Differences in LVEF, aetiology; Blinding details: each participating centre elected a third party blind individual who opened the allocated medication box, prepared the sucrose infusions or saline, and administer the preparations to patients using opaque devices. Both patient and attending physicians or nurses will be blind to allocated therapy. ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Quality of life at 12 months
- Actual outcome: Improvement in NYHA class at 3 months; Group 1: 2/10, Group 2: 1/6
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Missing data: 2 patients unable to perform the second ergospirometric evaluation at 90 days but treatment arm not known so cannot use ACA. ; Indirectness of outcome: Serious indirectness, Comments: Protocol outcome was quality of life; Baseline details: Differences in LVEF, aetiology. NYHA class at baseline not reported. ; Blinding details: each participating centre elected a third party blind individual who opened the allocated medication box, prepared the sucrose infusions or saline, and administer the preparations to patients using opaque devices. Both patient and attending physicians or nurses will be blind to allocated therapy. ; Group 1 Number missing: 0; Group 2 Number missing: 0

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL IRON versus PLACEBO

Protocol outcome 1: Mortality - Actual outcome: Mortality at 3 months; Group 1: 0/7, Group 2: 1/6 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Missing data: 2 patients unable to perform the second ergospirometric evaluation at 90 days but data on vital status assumed to be known. ; Indirectness of outcome: No indirectness ; Baseline details: Differences in age, Peak VO2, aetiology, % male; Blinding details: each participating centre elected a third party blind individual who opened the allocated medication box, prepared the sucrose infusions or saline, and administer the preparations to patients using opaque devices. Both patient and attending physicians or nurses will be blind to allocated therapy. ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Quality of life at 12 months - Actual outcome: Improvement in NYHA class at 3 months; Group 1: 6/7, Group 2: 1/6 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Missing data: 2 patients unable to perform the second ergospirometric evaluation at 90 days but treatment arm not known so cannot use ACA. ; Indirectness of outcome: Serious indirectness, Comments: Protocol outcome was quality of life; Baseline details: Differences in age, Peak VO2, aetiology, % male. Baseline NYHA classes not reported. ; Blinding details: each participating centre elected a third party blind individual who opened the allocated medication box, prepared the sucrose infusions or saline, and administer the preparations to patients using opaque devices. Both patient and attending physicians or nurses will be blind to allocated therapy. ; Group 1 Number missing: ?; Group 2 Number missing: ?	
Protocol outcomes not reported by the study	Unplanned hospitalisation (all-cause); Improvement in exercise tolerance at 12 months; Change in haemoglobin in anaemic patients at 12 months; Withdrawal due to adverse events/tolerability; Adverse events - anaphylaxis/hypersensitivity; Adverse events - stroke; Adverse events - gastrointestinal; Adverse events - hypertension

Study (subsidiary papers)	**Toblli 2007[1394] (Toblli 2015[1393])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=60)
Countries and setting	Conducted in Argentina; Setting: Outpatient clinic
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of CHF, NYHA class II - IV, LVEF ≤ 35%
Stratum	Overall
Subgroup analysis within study	Not applicable

1

Inclusion criteria	Patients with: 1) LV ejection fraction (EF) ≤35%; 2) New York Heart Association (NYHA) functional class II to IV; 3) anemia with an iron deficit defined by Hb <12.5 g/dl for men and <11.5 g/dl for women, and some of the following: serum ferritin <100 ng/ml and/or with transferrin saturation (TSAT) ≤20%; and 4) creatinine clearance ≤90 ml/min were included in the study.
Exclusion criteria	Patients with: 1) hemodialysis therapy; 2) anemia not due to iron deficiency available for erythropoiesis; 3) NYHA functional class I; 4) history of allergy to the iron supplements; 5) acute bacterial infections, parasitism known in the 4 previous weeks, and neoplasm; 6) chronic digestive diseases; 7) hypothyroidism; 8) congenital cardiopathies; 9) receiving iron supplements in the 4 previous weeks; 10) receiving rhEPO in the 4 previous weeks; and 11) history of hospitalization during the 4 weeks before enrollment into the study were excluded from the study.
Recruitment/selection of patients	Consecutive patients from the general population that spontaneously consulted the outpatient's office who met the inclusion criteria. Initially 40 patients were recruited and the initial analysis published. Subsequently an additional 20 patients were recruited and additional analyses published.
Age, gender and ethnicity	Age - Mean (SD): Iron - 75 (6), Placebo - 75 (7). Gender (M:F): 27:33. Ethnicity: NR
Further population details	1. Anaemia: All patients anaemic (All patients Hb <12.5 g/dl for men and <11.5 g/dl for women).
Extra comments	Ischaemic aetiology - 68% NYHA class - Placebo: 3.1 (0.6), Iron: 3.0 (0.7) NT-proBNP (pg/mL) - Placebo: 378 (195), Iron: 366 (200) LVEF, % - Placebo: 29.9 (3.2), Iron: 30.2 (3.5).
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Iron supplementation - Intravenous iron. 200mg/200mL of IV iron sucrose in saline solution every week for 5 weeks. Duration 5 weeks. Concurrent medication/care: Optimum treatment for CHF according to the current recommendations. 97% on loop diuretics, 97% on ACEi, 100% on BBs, 93% on anti-aldosteronic agents (n=30) Intervention 2: Placebo. Saline solution . Duration 5 weeks. Concurrent medication/care: All patients received the optimum treatment for CHF according to the current recommendations. 93% on loop diuretics, 100% on ACEi, 100% on BBs, 93% on antialdosteronic agents
Funding	Principal author funded by industry (Prof Toblli received scientific grants by Vifor Pharma in the last 5 years.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRAVENOUS IRON versus PLACEBO

Protocol outcome 1: Mortality
- Actual outcome: Mortality at 6 months; Group 1: 0/30, Group 2: 0/30
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable for age, gender, aetiology, medication useage, BMI, NYHA class, NT-pro-BNP, LVEF; Blinding details: Bag and IV tubing were covered in black material so that neither patient nor physician was able to identify the content. nurses who prepared the solution were different to those who later administered the infusion. ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Quality of life at 12 months
- Actual outcome: Minnesota living with heart failure questionnaire at 6 months; Group 1: mean 41 (SD 7); n=20, Group 2: mean 59 (SD 8); n=20; Minnesota Living with Heart Failure Questionnaire 0-105 Top=High is poor outcome
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Note: analysis on first 40 patients recruited into the study only. ; Indirectness of outcome: No indirectness ; Baseline details: Comparable for age, gender, aetiology, medication useage, BMI, NYHA class, NT-pro-BNP, LVEF. Comparable for outcome at baseline (2 points difference); Blinding details: Bag and IV tubing were covered in black material so that neither patient nor physician was able to identify the content. nurses who prepared the solution were different to those who later administered the infusion. ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Unplanned hospitalisation (all-cause)
- Actual outcome: Hospitalisations due to heart failure at 6 months; Group 1: 0/20, Group 2: 5/20
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Comments - Note: analysis on first 40 patients recruited into the study only. Analysis of hospitalisations in subsequent paper incompletely and inaccurately reported so could not be extracted. Outcome measured and reported unclear whether hospitalisations or CHF hospitalisations and unclear whether it was number of patients or number of events (differs in table and text) ; Indirectness of outcome: Serious indirectness, Comments: Hospitalisations due to heart failure, not the protocol outcome of all cause hospitalisations; Baseline details: Comparable for age, gender, aetiology, medication useage, BMI, NYHA class, NT-pro-BNP, LVEF; Blinding details: Bag and IV tubing were covered in black material so that neither patient nor physician was able to identify the content. nurses who prepared the solution were different to those who later administered the infusion. ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Improvement in exercise tolerance at 12 months
- Actual outcome: Six minute walk test, distance at 6 months; Group 1: mean 240.1 metres (SD 51.2); n=20, Group 2: mean 184.5 metres (SD 58.5); n=20
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - Note: analysis on first 40 patients recruited into the study only. ; Indirectness of outcome: No indirectness ; Baseline details: Comparable for age, gender, aetiology, medication useage, BMI, NYHA class, NT-pro-BNP, LVEF. Comparable for outcome at baseline (1.6 m difference); Blinding details: Bag and IV tubing were covered in black material so that neither patient nor physician was able to identify the content. nurses who prepared the solution were different to those who later administered the infusion. ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: Change in haemoglobin in anaemic patients at 12 months

- Actual outcome: Haemoglobin at 6 months; Group 1: mean 11.7 g/dL (SD 0.6); n=30, Group 2: mean 9.6 g/dL (SD 0.6); n=30 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable for age, gender, aetiology, medication useage, BMI, NYHA class, NT-pro-BNP, LVEF. Comparable for outcome at baseline (no difference); Blinding details: Bag and IV tubing were covered in black material so that neither patient nor physician was able to identify the content. nurses who prepared the solution were different to those who later administered the infusion. ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 6: Adverse events - hypertension - Actual outcome: Systolic blood pressure at 6 months; Group 1: mean 135.8 mmHg (SD 5.9); n=30, Group 2: mean 134.5 mmHg (SD 6.9); n=30 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable for age, gender, aetiology, medication useage, BMI, NYHA class, NT-pro-BNP, LVEF. Comparable for outcome at baseline (0.3 mmHg difference); Blinding details: Bag and IV tubing were covered in black material so that neither patient nor physician was able to identify the content. nurses who prepared the solution were different to those who later administered the infusion. ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 7: Adverse events - gastrointestinal - Actual outcome: Nausea at 6 months; Group 1: 1/30, Group 2: 1/30 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable for age, gender, aetiology, medication useage, BMI, NYHA class, NT-pro-BNP, LVEF; Blinding details: Bag and IV tubing were covered in black material so that neither patient nor physician was able to identify the content. nurses who prepared the solution were different to those who later administered the infusion. ; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Abdominal pain at 6 months; Group 1: 0/30, Group 2: 1/30 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable for age, gender, aetiology, medication useage, BMI, NYHA class, NT-pro-BNP, LVEF; Blinding details: Bag and IV tubing were covered in black material so that neither patient nor physician was able to identify the content. nurses who prepared the solution were different to those who later administered the infusion. ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Withdrawal due to adverse events/tolerability; Adverse events - stroke; Adverse events - anaphylaxis/hypersensitivity

1

Study	IRONOUT HF trial: Lewis 2017[875]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=225)
Countries and setting	Conducted in USA; Setting: Multicentre (23 sites), Duke Clinical Research Institute served as the coordinating center.
Line of therapy	1st line

Study	IRONOUT HF trial: Lewis 2017[875]
Duration of study	Intervention + follow up: 16 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with reduced left ventricular ejection fraction (≤40%) and heart failure (NYHA class II-IV) (HFrEF) who were stable while receiving medical therapy were eligible to participate if they had objective evidence of iron deficiency (ferritin 15-100 ng/mL or between 100-299 ng/mL with a transferrin saturation [Tsat] level <20%) and hemoglobin levels between 9 and 15 g/dL (men) or 9 and 13.5 g/dL (women).
Exclusion criteria	Individuals were excluded if a neuromuscular, orthopedic, or other noncardiac condition prevented cardiopulmonary exercise testing (CPET). Inability to achieve a respiratory exchange ratio greater than or equal to 1.0 on baseline screening CPET was also an exclusion criteria.
Recruitment/selection of patients	Screening was conducted in outpatients with chronic symptomatic HFrEF. Willing participants who were found to have iron deficiency and met the other entry criteria were enrolled between September 3, 2014 and November 18, 2015.
Age, gender and ethnicity	Age - Median (IQR): 63 (55-70). Gender (M:F): 64%/36%. Ethnicity: White: 73%; Black: 25%; Asian: 1%; more than 1 race: 1%
Further population details	N/A
Indirectness of population	No indirectness
Interventions	(n=111) Intervention 1: Iron supplementation - Oral iron. oral iron polysaccharide 150 mg twice daily (Instructions are provided to take pills separately from meals and to avoid taking antacids, dairy products, tea, or coffee within 2 hours before or after this medication because they will decrease effectiveness. Drug administration with orange juice or other products rich in Vitamin C may enhance absorption and, therefore, is encouraged). Duration 16 weeks. Concurrent medication/care: Receiving medical therapy for HFrEF. Indirectness: No indirectness (n=114) Intervention 2: Placebo. Oral placebo. Duration 16 weeks. Concurrent medication/care: Receiving medical therapy for HFrEF. Indirectness: No indirectness
Funding	Other (The research was supported by the NHLBI Heart Failure Clinical Research Network)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL IRON versus PLACEBO	

Study	IRONOUT HF trial: Lewis 2017[875]
Protocol outcome 1: Mortality - Actual outcome: Deaths at 16 weeks; Oral iron: 3/111; placebo: 1/114 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 19 Protocol outcome 2: Quality of life - Actual outcome: Change in KCCQ clinical summary score at 16 weeks; reported as median and IQR: Oral iron: 80.7 (67.7-91.6); placebo: 77.1 (65.1-89.6) Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 19 Protocol outcome 3: Improvement in exercise tolerance - Actual outcome: Change in peak VO2 ml/kg/min at 16 weeks; reported as median and IQR: Oral iron: 13.5 (11.7 to 16.3); placebo: 13 (10.2 to 15.9) Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 19 - Actual outcome: Change in 6 minute walk distance (m) at 16 weeks; Oral iron: 366 (315-456); placebo: 397 (299-472) Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 19 Protocol outcome 4: Withdrawal due to adverse events/tolerability at during study - Actual outcome: Permanent study drug discontinuation at 16 weeks; Oral iron: 15/111, placebo: 17/114 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: 0 Protocol outcome 5: Adverse events - Actual outcome: Adverse events (not described) at 16 weeks; Oral iron: 39/111; placebo: 45/114 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 19 - Actual outcome: Serious adverse events (not described) at 16 weeks; Oral iron: 11/111; placebo: 10/114 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 19	
Protocol outcomes not reported by the study	Unplanned hospitalisation (all-cause); Change in haemoglobin in anaemic patients; Adverse events - stroke; Adverse events - gastrointestinal; Adverse events - hypertension

F.7 Pharmacological treatment for heart failure in people with heart failure and chronic kidney disease

Study (subsidiary papers)	**Assessment and Treatment with Lisinopril and Survival (ATLAS) trial: Ryden 2000[1233] (Massie 2001[952], Cleland 1999[286]))**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=988)
Countries and setting	Conducted in Multiple countries; Setting: 291 centres in 19 countries
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 4y average (median 46m, range 36-60m)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: NYHA class III or IV (or class II if admission for acute decompensation of heart failure in last 6 months)
Stratum	CKD stage 3b/4/5: Group defined by creatinine between 1.5 and 2.5 mg/dl = between 133 and 139 umol/l, which equates to eGFR approx 45-26, therefore mostly stage 3b
Subgroup analysis within study	Post-hoc subgroup analysis: Not one of specified sub-groups, but in a list of 13 subgroups of "cardiovascular risk". Defined as Cr=>1.5mg/dl
Inclusion criteria	NYHA class III or IV (or class II if admission for acute decompensation of heart failure in last 6 months) with ejection fraction ≤30%, who had received diuretics for at least 60 days. Could tolerate ACE-I at low dose: a run-in tolerability test was included before randomisation for those naive to ACE-I.

Exclusion criteria	Could not tolerate or did not comply (≤80%) during run-in phase. Serum creatinine >2.5mg/dl. Cardiovascular event (ACS or surgery) in last 2 months, current instability (needing inortropes or ventilator assistance in last 48h), hypotension, taking NSAIDs. A non-cardiac disorder that meant that expected survival was less than the study period.
Recruitment/selection of patients	Recruited Oct 1992 - June 1994. 3793 screened, 3164 randomised. 988 had CKD.
Age, gender and ethnicity	Age - Mean (SD): 64 for larger study. Gender (M:F): 79:21 for larger study. Ethnicity: Not stated
Further population details	1. Diabetes: Not stated / Unclear (611 (19%) of larger study defined with diabetes at baseline (taking hypoglycaemics)). 2. Ejection fraction: All patients reduced EF (=<30% at baseline). 3. Ethnicity: Not stated / Unclear 4. Hypertension: Not stated / Unclear (1272 (40%) of larger study had hypertension (SBP>120mmHg)). 5. NYHA class: Not applicable (II - IV, although 77% of larger study class III).
Extra comments	Severity in larger study: NYHA II - 16%, III - 77%, IV - 7% . 56 were excluded due to "abnormal laboratory values", which will include creatinine >2.5mg/dl
Indirectness of population	Serious indirectness: Uses creatinine, not eGFR, to define CKD
Interventions	(n=494) Intervention 1: Angiotensin converting enzyme (ACE) inhibitors. Lisinopril 32.5-35mg per day, titrated up from 12.5mg in two steps over two weeks after randomisation.. Duration 4y average (median 46 months). Concurrent medication/care: To continue all other treatment (except ACE-I if prescribed) (n=494) Intervention 2: Angiotensin converting enzyme (ACE) inhibitors. Lisinopril 2.5-5mg per day, titrated down from 12.5mg in two steps over two weeks after randomisation using dummy pills for blinding.. Duration 4y average (median 46 months). Concurrent medication/care: To continue all other treatment (except ACE-I if prescribed)
Funding	Study funded by industry (Supported by a grant from Zeneca Pharmaceuticals (later AstraZeneca))

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ACE-I HIGH DOSE versus ACE-I LOW DOSE Protocol outcome 1: Mortality - Actual outcome for CKD stage 3b/4/5: All-cause mortality at median 46 months; HR 1.021 (95%CI 0.86 to 1.212) Reported; Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Very high, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - One of 13 post-hoc subgroups. Only overall HR. Dont know numbers in each group. ; Indirectness of outcome: No indirectness ; Baseline details: Baseline for larger study reported as largely balanced; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Unplanned hospitalisation (all-cause) - Actual outcome for CKD stage 3b/4/5: All-cause mortality and all-cause hospitalisation at median 46 months; HR 1.018 (95%CI 0.89 to 1.164) Reported Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Very high, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - One of 13 post-hoc subgroups. Only overall HR. dont know numbers in each group; Indirectness of outcome: Serious indirectness, Comments: Includes mortality. Cannot derive numbers of admissions; Baseline details: Baseline for larger study reported as largely balanced; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Adverse events - hypotension - Actual outcome for CKD stage 3b/4/5: Hypotension/Dizziness at median 46 months; Group 1: 182/494, Group 2: 117/494 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Very high, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - One of 13 post-hoc subgroups. Raw numbers not reported. Appears to be error in total numbers in subgroup in report (switched subgroup v non subgroup numbers); Indirectness of outcome: Serious indirectness; Baseline details: Baseline for larger study reported as largely balanced; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Adverse events - hyperkalaemia - Actual outcome for CKD stage 3b/4/5: Renal dysfunction/hyperkalaemia at median 46 months; Group 1: 199/494, Group 2: 157/494 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Very high, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - One of 13 post-hoc subgroups. Raw numbers not reported. Appears to be error in total numbers in subgroup in report (switched subgroup v non subgroup numbers); Indirectness of outcome: Serious indirectness, Comments: Compound outcome, cannot derive incidence hyperkalaemia; Baseline details: Baseline for larger study reported as largely balanced; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at 12 months ; Renal function ; Adverse events - bradycardia; Adverse events - progression to stage 5 CKD / unplanned dialysis; Adverse events - arrhythmic

Study (subsidiary papers)	CHARM-Overall trial: Desai 2007[375] (Pfeffer 2003[1139])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	3 (n=154)
Countries and setting	Conducted in Multiple countries; Setting: Not stated
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: ave 3y (at least 2y, median 38 months)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Classified according to NYHA criteria
Stratum	CKD stage 3a/3b: Creatinine between 2 and 3 mg/dl, which is 177-265umol/l, equating approximately to GFR 22-34
Subgroup analysis within study	Not stratified but pre-specified
Inclusion criteria	Adults with symptomatic HF (NYHA II-IV) for at least four weeks
Exclusion criteria	Drug contra-indicated, including renal dysfunction with Cr>3mg/dl or K>5.5mmol/l or hx of life-threatening adverse event or significant hyperkalaemia with ACE-inhibitor, bilateral renal artery stenosis. Also symptomatic hypotension or significant valvular disease, and use of ARB in last two weeks
Recruitment/selection of patients	Not specified for wider trial. 2% of participants had Creatinine >2.0 and classified as CKD
Age, gender and ethnicity	Age - Mean (SD): 66(11) for wider study. Gender (M:F): 69% male in wider study. Ethnicity: In wider study, 90% European, 4% white, 6% other
Further population details	1. Diabetes: Not applicable (mix). 2. Ejection fraction: Not applicable/mixed (mix). 3. Ethnicity: Not applicable

	(mix). 4. Hypertension: Not applicable (mix). 5. NYHA class: Not applicable (II-IV).
Extra comments	. Amalgamation of three related trials, CHARM-Preserve, CHARM-Added, and CHARM-Alternative, therefore mixture of single and dual RAAS inhibition, and mixture of HFREF and HFPEF.
Indirectness of population	Serious indirectness: Using creatinine rather than GFR to classify CKD
Interventions	(n=84) Intervention 1: Angiotensin receptor antagonists/blockers (ARB) - Angiotensin receptor antagonists. Candesartan up to 32mg (as tolerated), started at 4-8mg daily and doubled every two weeks as tolerated. Duration Ave 3.2y (range 2-4y). Concurrent medication/care: Visits at 2 weeks, 4 weeks, 6 weeks, 6 months and every 4 months thereafter. If receiving ACE-I, this was maintained at evidenced-based therapeutic levels. Serum creatinine and potassium measured within two weeks of dose escalation. Reaction to high creatinine or potassium left to discretion of investigator. (n=70) Intervention 2: Placebo. Placebo, titrated in same way as Candesartan. Duration Ave 3.2y (range 2-4y). Concurrent medication/care: Visits at 2 weeks, 4 weeks, 6 weeks, 6 months and every 4 months thereafter. If receiving ACE-I, this was maintained at evidenced-based therapeutic levels. Serum creatinine and potassium measured within two weeks of dose escalation. Reaction to high creatinine or potassium left to discretion of investigator.
Funding	Study funded by industry (Study funded by AstraZeneca R&D, and investigators received grants from AstraZeneca (as well as other major cardiovascular pharmaceutical companies))
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ANGIOTENSIN RECEPTOR ANTAGONISTS versus PLACEBO Protocol outcome 1: Unplanned hospitalisation (all-cause) - Actual outcome for CKD stage 3b/4/5: Cardiovascular death or heart failure hospitalization (pre-specified primary outcome) at Ave 3.2y; HR 0.92 (95%CI 0.79 to 1.08) Reported Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Very high, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Baseline not reported. Low missing overall, no details	

<table>
<tr><td colspan="2">about subgroup. Unplanned subgroup analysis; Indirectness of outcome: Serious indirectness, Comments: Compound outcome, cannot identify numbers of admissions; Baseline details: Baseline for sub-group not reported; Number missing: 12 of 7601 in wider trial missing primary end-point

Protocol outcome 2: Adverse events - hyperkalaemia
- Actual outcome for CKD stage 3b/4/5: Clinically relevant hyperkalaemia at Ave 3.2y; Group 1: 14/84, Group 2: 7/70
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Very high, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Vague definition of outcome. Baseline not reported. Low missing overall, no details about subgroup. Unplanned subgroup analysis; Indirectness of outcome: No indirectness; Baseline details: Baseline for sub-group not reported; Number missing: 12 of 7601 in wider trial missing primary end-point</td></tr>
<tr><td>Protocol outcomes not reported by the study</td><td>Mortality; Quality of life; Renal function ; Adverse events - bradycardia; Adverse events - progression to stage 5 CKD / unplanned dialysis; Adverse events - hypotension; Adverse events - arrhythmic</td></tr>
</table>

Study	**CIBIS-2 trial: Castagno 2010-1[250] (Dargie 1999 [345])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=450)
Countries and setting	Conducted in Multiple countries; Setting: 274 hospitals in 18 countries in western and eastern Europe
Line of therapy	1st line
Duration of study	Intervention + follow up: Mean 1.3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: CKD diagnosed using Cockcroft-Gault formula, HF assessed by NYHA and ejection fraction
Stratum	CKD stage 3b/4/5: eGFR < 45 mL/min per 1.73m^2. Study excludes if Creatinine >300, which equates to eGFR approximately 20. Therefore stage 3b and early stage 4.
Subgroup analysis within study	Post-hoc subgroup analysis: Sub-group report over 10 years post-original study
Inclusion criteria	Eligible patients were ambulatory, aged 18-80 years, and had a left-ventricular ejection fraction, measured within 6 weeks of randomisation, of 35% or less. Symptoms had to include dyspnoea on exertion, orthopnoea, or paroxysmal nocturnal dyspnoea, with or without oedema, and fatigue, corresponding to class III or IV of the New York Heart Association (NYHA). Patients had to have a diagnosis of chronic heart failure, made at least 3 months previously, with clinical stability during the preceding 6 weeks for heart failure or 3 months for acute myocardial infarction or unstable angina. Cardiovascular therapy had to have been unchanged in the 2weeks before randomisation. Treatment had to include a diuretic and an angiotensin-converting-enzyme (ACE) inhibitor, although other vasodilators were allowed if patients were intolerant of ACE inhibitors; the use of digoxin was optional.
Exclusion criteria	The main exclusion criteria were uncontrolled hypertension, myocardial infarction or unstable angina pectoris in the previous 3 months, percutaneous transluminal coronary angioplasty or coronary-artery

	bypass graftin the previous 6 months, previous or scheduled heart transplant, atrioventricular block greater than first degree without a chronically implanted pacemaker, resting heart rate of less than 60 beats per min, systolic blood pressure at rest of less than 100 mm Hg, renal failure (serum creatinine≥300 µmol/L), reversible obstructive lung disease, or preexisting or planned therapy with β-adrenoreceptor blockers.
Recruitment/selection of patients	Original study reported in 1999
Age, gender and ethnicity	Age - Median (IQR): 71 (66, 75). Gender (M:F): 246M:204F. Ethnicity: Not stated
Further population details	1. Diabetes: Not applicable (Mixed). 2. Ejection fraction: All patients reduced EF (< 35%). 3. Ethnicity: Not stated / Unclear 4. Hypertension: Not applicable (Mixed). 5. NYHA class: All patients class III or IV
Indirectness of population	No indirectness
Interventions	(n=215) Intervention 1: Beta-blockers (BB). Bisoprolol 1.25mg daily, the dose increased progressively to 2.5, 3.75, 5.0, 7.5 and 10.0mg according to tolerance. Duration Mean 1.3 years. Concurrent medication/care: Treatment with β-blockers (including eye drops), calcium antagonists, inotropic agents except digitalis, and antiarrhythmic drugs other than amiodarone was not allowed during the trial. Patients were treated with a diuretic and an angiotensin-converting-enzyme (ACE) inhibitor, although allowed other vasodilators if patients were intolerant of ACE inhibitors; the use of digoxin was optional for at least 2 weeks prior to randomisation. (n=235) Intervention 2: Placebo. Placebo once daily. Duration Mean 1.3 years. Concurrent medication/care: Treatment with β-blockers (including eye drops), calcium antagonists, inotropic agents except digitalis, and antiarrhythmic drugs other than amiodarone was not allowed during the trial. Patients were treated with a diuretic and an angiotensin-converting-enzyme (ACE) inhibitor, although allowed other vasodilators if patients were intolerant of ACE inhibitors; the use of digoxin was optional for at least 2 weeks prior to randomisation.
Funding	Study funded by industry (Study was sponsored by E Merck. Role of study sponsor in design and conduct of the study not explicitly defined)

<table>
<tr><td colspan="2">RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BETA-BLOCKERS (BB) versus PLACEBO

Protocol outcome 1: Mortality
- Actual outcome for CKD stage 3b/4/5: All-cause mortality at Mean 1.3 years; HR 0.71 (95%CI 0.48 to 1.05) Reported
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Very high, Other 1 - High, Other 2 - Low, Other 3 - Low, Comments - Study reports that this group (stage 3b/4/5) had a substantially higher rate of permanent discontinuation of bisoprolol than placebo, but missing data isn't reported and study reports that all participants have outcome data. Early stopping. Late sub-group report.; Indirectness of outcome: No indirectness ; Baseline details: Baseline only reported for overall group, not for drug/placebo groups; Group 1 Number missing: 0; Group 2 Number missing: 0
Protocol outcome 2: Unplanned hospitalisation (all-cause)
- Actual outcome for CKD stage 3b/4/5: Heart failure hospitalisation at Mean 1.3 years; HR 0.76 (95%CI 0.51 to 1.14) Reported
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Very high, Other 1 - High, Other 2 - Low, Other 3 - Low, Comments - Study reports that this group (stage 3b/4/5) had a substantially higher rate of permanent discontinuation of bisoprolol than placebo, but missing data isn't reported and study reports that all participants have outcome data. Early stopping. Late sub-group report.; Indirectness of outcome: Serious indirectness ; Baseline details: Baseline only reported for overall group, not for drug/placebo groups; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for CKD stage 3b/4/5: All cause mortality or all-cause hospitalisation at Mean 1.3 years; HR 0.82 (95%CI 0.64 to 1.05) Reported
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Very high, Other 1 - High, Other 2 - Low, Other 3 - Low, Comments - Study reports that this group (stage 3b/4/5) had a substantially higher rate of permanent discontinuation of bisoprolol than placebo, but missing data isn't reported and study reports that all participants have outcome data. Early stopping. Late sub-group report.; Indirectness of outcome: Serious indirectness ; Baseline details: Baseline only reported for overall group, not for drug/placebo groups; Group 1 Number missing: 0; Group 2 Number missing: 0</td></tr>
<tr><td>Protocol outcomes not reported by the study</td><td>Quality of life at 12 months ; Renal function ; Adverse events - bradycardia; Adverse events - progression to stage 5 CKD / unplanned dialysis; Adverse events - hypotension; Adverse events - hyperkalaemia; Adverse events - arrhythmic</td></tr>
</table>

Study	CIBIS-2 trial: Castagno 2010-2[250] (Dargie 1999 [345])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=669)
Countries and setting	Conducted in Multiple countries; Setting: 274 hospitals in 18 countries in western and eastern Europe
Line of therapy	Unclear
Duration of study	Intervention + follow up: Mean 1.3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: CKD diagnosed using Cockcroft-Gault formula, HF assessed by NYHA and ejection fraction
Stratum	CKD stage 3a: eGFR 45.0-59.9 mL/min per 1.73m^2
Subgroup analysis within study	Post-hoc subgroup analysis: Subgroup analysis published over 10 years after main study published
Inclusion criteria	Eligible patients were ambulatory, aged 18-80 years, and had a left-ventricular ejection fraction, measured within 6 weeks of randomisation, of 35% or less. Symptoms had to include dyspnoea on exertion, orthopnoea, or paroxysmal nocturnal dyspnoea, with or without oedema, and fatigue, corresponding to class III or IV of the New York Heart Association (NYHA). Patients had to have a diagnosis of chronic heart failure, made at least 3 months previously, with clinical stability during the preceding 6 weeks. Cardiovascular therapy had to have been unchanged in the 2weeks before randomisation. Treatment had to include a diuretic and an angiotensin-converting-enzyme (ACE) inhibitor, although other vasodilators were allowed if patients were intolerant of ACE inhibitors; the use of digoxin was optional.
Exclusion criteria	The main exclusion criteria were uncontrolled hypertension, myocardial infarction or unstable angina pectoris in the previous 3 months, percutaneous transluminal coronary angioplasty or coronary-artery bypass graft in the previous 6 months, previous or scheduled heart transplant, atrioventricular block greater than first degree without a chronically implanted pacemaker, resting heart rate of less than 60 beats per

	min, systolic blood pressure at rest of less than 100 mm Hg, renal failure (serum creatinine≥300 µmol/L), reversible obstructive lung disease, or preexisting or planned therapy with β-adrenoreceptor blockers.
Recruitment/selection of patients	Not stated. Recruited prior 1999
Age, gender and ethnicity	Age - Median (IQR): 67 (61, 72). Gender (M:F): 492M:177F. Ethnicity: Not stated
Further population details	1. Diabetes: Not applicable (Mixed). 2. Ejection fraction: All patients reduced EF (< 35%). 3. Ethnicity: Not stated / Unclear 4. Hypertension: Not applicable (Mixed). 5. NYHA class: All patients class III or IV
Indirectness of population	No indirectness
Interventions	(n=361) Intervention 1: Beta-blockers (BB). Bisoprolol 1.25mg daily, the dose increased progressively to 2.5, 3.75, 5.0, 7.5 and 10.0mg according to tolerance. Duration Mean 1.3 years. Concurrent medication/care: Treatment with β-blockers (including eye drops), calcium antagonists, inotropic agents except digitalis, and antiarrhythmic drugs other than amiodarone was not allowed during the trial. Patients were treated with a diuretic and an angiotensin-converting-enzyme (ACE) inhibitor, although we allowed other vasodilators if patients were intolerant of ACE inhibitors; the use of digoxin was optional for at least 2 weeks prior to randomisation. (n=308) Intervention 2: Placebo. Placebo once daily. Duration Mean 1.3 years. Concurrent medication/care: Treatment with β-blockers (including eye drops), calcium antagonists, inotropic agents except digitalis, and antiarrhythmic drugs other than amiodarone was not allowed during the trial. Patients were treated with a diuretic and an angiotensin-converting-enzyme (ACE) inhibitor, although we allowed other vasodilators if patients were intolerant of ACE inhibitors; the use of digoxin was optional for at least 2 weeks prior to randomisation.
Funding	Study funded by industry

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BETA-BLOCKERS (BB) versus PLACEBO

Protocol outcome 1: Mortality - Actual outcome for CKD stage 3a: All-cause mortality at Mean 1.3 years; HR 0.69 (95%CI 0.46 to 1.04) Reported Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Very high, Other 1 - High, Other 2 - Low, Other 3 - Low, Comments - 114 participants had permanent treatment withdrawal overall but doesn't provide information on which group participants were in. Early stopping and late sub-group analysis.; Indirectness of outcome: No indirectness ; Baseline details: Baseline only reported for overall group, not for drug/placebo groups; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Unplanned hospitalisation (all-cause) - Actual outcome for CKD stage 3a: All-cause mortality or all-cause hospitalisation at Mean 1.3 years; HR 0.72 (95%CI 0.57 to 0.92) Reported Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Very high, Other 1 - High, Other 2 - Low, Other 3 - Low, Comments - 114 participants had permanent treatment withdrawal overall but doesn't provide information on which group participants were in. Early stopping and late sub-group analysis.; Indirectness of outcome: Serious indirectness ; Baseline details: Baseline only reported for overall group, not for drug/placebo groups; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for CKD stage 3a: Heart failure hospitalisation at Mean 1.3 years; HR 0.66 (95%CI 0.45 to 0.97) Reported Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Very high, Other 1 - High, Other 2 - Low, Other 3 - Low, Comments - 114 participants had permanent treatment withdrawal overall but doesn't provide information on which group participants were in. Early stopping and late sub-group analysis.; Indirectness of outcome: Serious indirectness ; Baseline details: Baseline only reported for overall group, not for drug/placebo groups; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at 12 months ; Renal function ; Adverse events - bradycardia; Adverse events - progression to stage 5 CKD / unplanned dialysis; Adverse events - hypotension; Adverse events - hyperkalaemia; Adverse events - arrhythmic

Study	DIG trial: Shlipak 2004-1[1287] (DIG Group, 1997 [386])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	2 (n=218)
Countries and setting	Conducted in Canada, USA; Setting: 302 centres in the US or Canada
Line of therapy	1st line
Duration of study	Intervention + follow up: Mean follow up 3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Heart disease NYHA class 1-4, CKD eGFR using the simplified modification of diet in renal disease equation
Stratum	CKD stage 3b/4/5: GFR <30 ml/min/1.73m^2, study excludes Cr>3.0, which is approximately GFR<20. Therefore stage 4.
Subgroup analysis within study	Post-hoc subgroup analysis: Subgroup analysis published seven years after original publication
Inclusion criteria	Stable heart failure and left ventricular ejection fraction <45% and were in sinus rhythm to assess the efficacy of digoxin therapy. Required to be on ACE-I and diuretic.
Exclusion criteria	Creatinine levels >3.0 mg/dl, abnormal potassium levels, listed for transplantation or recent MI / revascularisation
Recruitment/selection of patients	Recruited August 1991 - March 1993
Age, gender and ethnicity	Age - Median (range): 72. Gender (M:F): 54% male. Ethnicity: 94% white
Further population details	1. Diabetes: Not applicable (Mixed). 2. Ejection fraction: All patients reduced EF (<45%). 3. Ethnicity: Not applicable (Mixed). 4. Hypertension: Systematic review: mixed (Mixed). 5. NYHA class: Not applicable (Mixed).

Indirectness of population	No indirectness
Interventions	(n=102) Intervention 1: Digoxin. An algorithm based on age, gender, weight and creatinine levels determined doses of digoxin . Duration Mean 3 years . Concurrent medication/care: Not stated (n=116) Intervention 2: Placebo. Placebo . Duration Mean 3 years. Concurrent medication/care: Not stated
Funding	Academic or government funding (Supported by the National Heart, Lung, and Blood Institute)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DIGOXIN versus PLACEBO Protocol outcome 1: Mortality - Actual outcome for CKD stage 4/5: Mortality at Mean 3 years; HR 0.93 (95%CI 0.65 to 1.35) Reported Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High; Indirectness of outcome: No indirectness ; Baseline details: Only reported baseline for overall group, not different interventions ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Unplanned hospitalisation (all-cause) - Actual outcome for CKD stage 4/5: Hospitalisation/mortality at Mean 3 years; HR 0.77 (95%CI 0.55 to 1.08) Reported Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High; Indirectness of outcome: Serious indirectness ; Baseline details: Only reported baseline for overall group, not different interventions ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at 12 months ; Renal function ; Adverse events - bradycardia; Adverse events - progression to stage 5 CKD / unplanned dialysis; Adverse events - hypotension; Adverse events - hyperkalaemia; Adverse events - arrhythmic

Study	DIG trial: Shlipak 2004-2[1287] (DIG Group, 1997 [386])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=2939)
Countries and setting	Conducted in Canada, USA; Setting: 302 centres in the US or Canada
Line of therapy	1st line
Duration of study	Intervention + follow up: Mean follow up 3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Heart failure by NYHA stages 1-4, LVEF <45%; CKD by eGFR
Stratum	CKD stage 3a/3b: GFR 30 to 60 ml/min/1.73m^2
Subgroup analysis within study	Post-hoc subgroup analysis: Analysis published seven years after original publication for DIG study
Inclusion criteria	Stable heart failure and left ventricular ejection fraction <45% and were in sinus rhythm to assess the efficacy of digoxin therapy. Required to be on ACE-I and diuretic.
Exclusion criteria	Creatinine levels >3.0 mg/dl, abnormal potassium levels, listed for transplantation or recent MI/revascularisation
Recruitment/selection of patients	Recruited August 1991 - March 1993. 46% of enrolled patients met criteria for CKD
Age, gender and ethnicity	Age - Median (range): 68. Gender (M:F): 73% male. Ethnicity: 94% white
Further population details	1. Diabetes: Not applicable (Mixed). 2. Ejection fraction: All patients reduced EF (<45%). 3. Ethnicity: Not applicable (Mixed). 4. Hypertension: Not applicable (Mixed). 5. NYHA class: Not applicable (Mixed).

Indirectness of population	No indirectness
Interventions	(n=1468) Intervention 1: Digoxin. An algorithm based on age, gender, weight and creatinine levels determined doses of digoxin. Duration Mean 3 years. Concurrent medication/care: Not stated (n=1471) Intervention 2: Placebo. Placebo . Duration Mean 3 years. Concurrent medication/care: Not stated
Funding	Academic or government funding (Supported by the National Heart, Lung, and Blood Institute)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DIGOXIN versus PLACEBO Protocol outcome 1: Mortality - Actual outcome for CKD stage 3a/3b: Mortality at Mean 3 years; HR 0.95 (95%CI 0.85 to 1.07) Reported Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Only reported baseline for overall group, not different interventions; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Unplanned hospitalisation (all-cause) - Actual outcome for CKD stage 3a/3b: Hospitalisation/mortality at Mean 3 years; HR 0.84 (95%CI 0.76 to 0.93) Reported Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High, Comments - Follow up period of 3 years is assumed; Indirectness of outcome: Serious indirectness ; Baseline details: Only reported baseline for overall group, not different interventions; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at 12 months ; Renal function ; Adverse events - bradycardia; Adverse events - progression to stage 5 CKD / unplanned dialysis; Adverse events - hypotension; Adverse events - hyperkalaemia; Adverse events - arrhythmic

Study (subsidiary papers)	Eplerenone in Mild Patients Hospitalization and Suvrvival Study in Heart Failure (EMPHASIS-HF) trial: Eschalier 2013[441] (Zannad 2011[1522])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=912)
Countries and setting	Conducted in Multiple countries; Setting: Multi-centre, over 30 countries, no detail given. Of 2737 recruited to larger study, these regions contributed: Asia, middle east and Africa 380; eastern Europe 911; north and south America 346; western Europe and Australia 1100.
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: ave 2y (median 22 months, range 0-50m [double blind] followed by 12 months open-label)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical diagnosis meeting inclusion criteria
Stratum	CKD stage 3a/3b: eGFR between 60 and 30 ml/min/1.73m^2
Subgroup analysis within study	Not stratified but pre-specified: CKD based on eGFR<60ml/min/1.73m^2
Inclusion criteria	NYHA functional class II symptoms, age of ≥55y, an EF≤30% (or 30-35% with QRS duration of >130 msec on electrocardiography). Admission for cardiovascular reason within last six months or BNP) ≥250 pg per milliliter. Existing tx with ACE-I and/or ARB, and a B-blocker (unless contraindicated) at recommended/maximal tolerated dose. Additionally for CKD group on eGFR<60ml/min/1.73m^2 at baseline.
Exclusion criteria	Acute myocardial infarction in last 28 days, a serum potassium level exceeding 5.0 mmol/l, an eGFR <30 ml/min/1.73 m2, a need for a potassium-sparing diuretic, and any other clinically significant, coexisting condition.

Recruitment/selection of patients	Recruitment from March 2006 to May 2010, when study stopped. Of the patients in the larger study, 33% were included in CKD group.
Age, gender and ethnicity	Age - Mean (SD): 71.1 (7.5) in treatment group. Gender (M:F): 119:320 (27.1% female) in treatment group, 2127:610 (22.3% female) for larger study. Ethnicity: For larger study: White 83%, Black 2.5%, Asian 11.5%, Other 3%
Further population details	1. Diabetes: Not applicable (mixed). 2. Ejection fraction: All patients reduced EF (<30 or 30-35 with QRS prolongation). 3. Ethnicity: Not applicable (mixed). 4. Hypertension: Not applicable (mixed). 5. NYHA class: All patients class I or II (All II).
Extra comments	In wider study, most felt to have ischaemic HF . In wider study, average GFR 71.2(21.9). In CKD treatment group average GFR 48.6(20.7), serum creatinine 1.4(0.3) potassium 4.4(0.4). Other medication: diuretic 91%, ACE-I/ARB 95%, B-blocker 88%. Comorbid hypertension 69%, DM 38%. LVEF% ave 26.39(4.7), hospitalised for HF 58%.
Indirectness of population	No indirectness
Interventions	(n=439) Intervention 1: Mineralocorticoid receptor antagonists (MRA). Eplerenone 50mg once daily, started at 25mg daily (or every other day if eGFR<50) and doubled after four weeks provided serum potassium ≤5.0mmol. Duration ave 2y (median 21 months, range 0-60 months). Concurrent medication/care: Serum potassium monitored every 4 months, with protocol-driven reduction or cessation if potassium above 5.5mmol and 6mmol respectively. To continue other medication, including mandated ACE-I/ARB. Comments: Average dose at month 5 = 32.4mg (39.5mg for all participants) (n=473) Intervention 2: Placebo. Placebo at blinded dose of 50mg daily, started at "25mg" daily (every other day if eGFR<50) and doubled after four weeks unless potassium >5.0mml/l. Duration ave 2y (median 21 months, range 0-60 months). Concurrent medication/care: Serum potassium monitored every 4 months, with protocol-driven reduction or cessation if potassium above 5.5mmol and 6mmol respectively. To continue other medication, including mandated ACE-I/ARB. Comments: Ave blinded dose = 34.7mg (41.1mg for wider placebo)

Funding	Study funded by industry (Funded and overseen by Pfizer)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MINERALOCORTICOID RECEPTOR ANTAGONISTS (MRA) versus PLACEBO Protocol outcome 1: Unplanned hospitalisation (all-cause) - Actual outcome for CKD stage 3a/3b: Hospitalization for HF or death for cardiovascular at average 2y; Group 1: 107/439, Group 2: 163/473 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High, Other 1 - High, Other 2 - Low, Other 3 - Low, Comments - Compound outcome, but as described in protocol. Subgroup analysis predefined in protocol (one of 19) with no stratification. Stopped early due to overwhelming evidence of benefit (pre-defined by drug company); Indirectness of outcome: Very serious indirectness, Comments: Compound outcome, cannot calculate deaths or hospitalization; Baseline details: Baseline characteristics for placebo arm not reported; Group 1 Number missing: 17, Reason: not stated; Group 2 Number missing: 12, Reason: not stated Protocol outcome 2: Renal function - Actual outcome for CKD stage 3a/3b: Change in eGFR from baseline to final visit at average 2y; Group 1: mean 2.04 ml/min/1.73m^2 (SD 17); n=422, Group 2: mean 4.15 ml/min/1.73m^2 (SD 14.9); n=461 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High, Other 1 - High, Other 2 - Low, Other 3 - Low, Comments - Subgroup analysis predefined in protocol (one of 19) with no stratification. Stopped early due to overwhelming evidence of benefit (pre-defined by drug company); Indirectness of outcome: No indirectness; Baseline details: Baseline characteristics for placebo arm not reported; Group 1 Number missing: 17, Reason: not stated; Group 2 Number missing: 12, Reason: not stated Protocol outcome 3: Adverse events - hyperkalaemia - Actual outcome for CKD stage 3a/3b: Serum potassium >5.5mmol/l at average 2y; Group 1: 70/422, Group 2: 43/461 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High, Other 1 - High, Other 2 - Low, Other 3 - Low, Comments - Subgroup analysis predefined in protocol (one of 19) with no stratification. Stopped early due to overwhelming evidence of benefit (pre-defined by drug company); Indirectness of outcome: No indirectness ; Baseline details: Baseline characteristics for placebo arm not reported; Group 1 Number missing: 17, Reason: not stated; Group 2 Number missing: 12, Reason: not stated	
Protocol outcomes not reported by the study	Mortality; Quality of life at 12 months ; Adverse events - bradycardia; Adverse events - progression to stage 5 CKD / unplanned dialysis; Adverse events - hypotension; Adverse events - arrhythmic

Study	HEAAL trial: Konstam 2009[783]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=945)
Countries and setting	Conducted in Multiple countries; Setting: No stated
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: Median 4.7 years, IQR 3.5-5.5y (for wider study)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical diagnosis >2 weeks
Stratum	CKD stage 3a/3b: Defined eGFR<60, exclusion Cr>220 (approximates to eGFR<28)
Subgroup analysis within study	Not stratified but pre-specified
Inclusion criteria	Adults with HF MYHA class II-IV, with LVEF≤40%, intolerant to ACE-inhibitors. Intolerance had to be due to documented cough, hypotension, azotaemia (ie renal dysfunction), hyperkalaemia, taste disturbance, gastrointestinal upset or rash. Needed to have been on stable cardiovascular medication for two weeks prior to enrolment.
Exclusion criteria	Intolerance to ARBs, SBP<90mmHg, significant valvular stenosis, active myo- or peri-carditis, planned heart transplant within 6 months, CV event in last 12 wks, significant renal artery stenosis, contraindication to vasodilator, life-limiting disease other than heart failure, drug or alcohol misuse in last 2y, and participation in other drug study in last 4w. Lab value exclusions: Cr>220umol/l, K<3.5 or >5.7, hepatic enzymes >3x normal, Hb<6.2
Recruitment/selection of patients	Recruited 3834 into wider study, of which 945 (20%) had eGFR<60

Age, gender and ethnicity	Age - Mean (SD): 66.0 (56-72.5) in wider study. Gender (M:F): 70:30 in wider study. Ethnicity: For wider study, White 60%, Asian 22%, Other 11%, Hispanic 6%, Black 1%
Further population details	1. Diabetes: Not applicable (mixed). 2. Ejection fraction: All patients reduced EF (All =<40%, average 33%). 3. Ethnicity: Not applicable (mixed, most white). 4. Hypertension: Not applicable (mixed, average SBP 124). 5. NYHA class: Not applicable (mixed, most class II).
Extra comments	. Baseline data for wider study: Clinical history - AF 28%, IHD 64%, HTN 60%, DM 31% Severity - NYHA II 69%, III 30%, IV 1%, LVEF average 33% Drug use - ARB at screening 77%, B-blocker 72%, digoxin 42%, diuretic 77%
Indirectness of population	No indirectness
Interventions	(n=495) Intervention 1: Angiotensin receptor antagonists/blockers (ARB) - Angiotensin receptor antagonists. Losartan 150mg per day, titrated up from 50mg over a 3-week period. Duration Ave 4.7y. Concurrent medication/care: Pre-randomisation: if not on ARB, titrated up to 25mg over two weeks, if on ARB this was discontinued and receive 25mg daily for one week, or start directly on study medication. During titration, investigators were encouraged to also titrate beta-blockers to target dose in any subjects not already taking. Comments: In wider study, 94% achieved target Losartan dose and average dose over follow-up 129mg/day (n=450) Intervention 2: Angiotensin receptor antagonists/blockers (ARB) - Angiotensin receptor antagonists. Losartan 50mg, started at this dose, with "up-titration" using dummy pills. Duration Ave 4.7y. Concurrent medication/care: Pre-randomisation: if not on ARB, titrated up to 25mg over two weeks, if on ARB this was discontinued and receive 25mg daily for one week, or start directly on study medication. During titration, investigators were encouraged to also titrate beta-blockers to target dose in any subjects not already taking. Comments: In wider study, 95% achieved target dose and average dose over entire follow-up, 46mg/day.
Funding	Study funded by industry (Supported by Merck & Co, three authors employed by Merck, other authors supported by Merck)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ARB - HIGH DOSE versus ARB - LOW DOSE Protocol outcome 1: Unplanned hospitalisation (all-cause) - Actual outcome for CKD stage 3a/3b: Death or admission for heart failure at Ave 4.7y; HR 0.98 (95%CI 0.85 to 1.13) Reported Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Baseline data for subgroup not given. Numbers missing for subgroup not given, 3% overall; Indirectness of outcome: Serious indirectness, Comments: Compound end-point, cannot extract admission data alone; Baseline details: Not reported for subgroup; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Mortality; Quality of life at 12 months ; Renal function ; Adverse events - bradycardia; Adverse events - progression to stage 5 CKD / unplanned dialysis; Adverse events - hypotension; Adverse events - hyperkalaemia; Adverse events - arrhythmic

Study	MERIT-HF trial: Ghali 2009-1[515] (MERIT-HF group 1999[992])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=976)
Countries and setting	Conducted in Multiple countries; Setting: Clinical trial at 313 investigational sites in European countries and in the USA.
Line of therapy	1st line
Duration of study	Intervention + follow up: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	CKD stage 3a: 45 to 60 eGFR (ml/min/1.73m^2)
Subgroup analysis within study	Post-hoc subgroup analysis: Analysis published ten years after original trial
Inclusion criteria	Patients were aged 40-80 years old, with HF class II-IV and an ejection fraction class <40% for at least 3 months before enrolment, with a heart rate of ≥68 beats/min at the enrolment visit. Required to be taking ACE-I unless not tolerated and diuretics.
Exclusion criteria	There were no exclusion criteria relating to the level of serum creatinine at baseline. Cardiovascular event in last 28 days, severe decompensated HF, standing SBP<100mmHg.
Recruitment/selection of patients	Recruited Feb 1997 - April 1998
Age, gender and ethnicity	Age - Mean (SD): 67.4 (8.4). Gender (M:F): 70:30. Ethnicity: Not stated
Further population details	1. Diabetes: Not applicable (Mixed). 2. Ejection fraction: All patients reduced EF (<40%). 3. Ethnicity: Not

	stated / Unclear 4. Hypertension: Not applicable (Mixed). 5. NYHA class: Not applicable (Mixed).
Extra comments	Baseline characteristics for wider study: NYHA class II 39%, class III 56%, class IV 5%. Mean LVEF 27%. Prior MI 51%, ACE/ARB tx 96%, average furosemide dose 66mg/day.
Indirectness of population	No indirectness
Interventions	(n=466) Intervention 1: Beta-blockers (BB). Metoprolol CR/XL. The starting dose was 12·5 mg or 25 mg once daily (half a 25mg tablet was recommended for patients who were in NYHA III-IV). After 2 weeks the dose increased to the recommended 50 mg once daily for 2 weeks, then 100mg once daily for 2 weeks, and finally up to the target dose of 200 mg once daily. Dose regimen could be modified according to the judgement of the investigator.. Duration 1 year. Concurrent medication/care: To continue ACE/ARB, diuretics and other medication (n=510) Intervention 2: Placebo. Placebo titrated up using dummy pills. Duration 1 year. Concurrent medication/care: To continue ACE/ARB, diuretics and other medication
Funding	Study funded by industry (Study was supported by a grant from AstraZeneca, Dr Wedel received consulting and advisory board fees from AstraZeneca)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BETA-BLOCKERS (BB) versus PLACEBO

Protocol outcome 1: Mortality
- Actual outcome for CKD stage 3a: All-cause mortality at 1 year; HR 0.68 (95%CI 0.45 to 1.02) Reported
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High, Other 1 - High, Other 2 - Low, Other 3 - Low, Comments - Number of patients analysed has been assumed as the same as the number of patients randomised as no details are given about number analysed. Therefore, amount of missing data is unknown! The follow up period was assumed to be one year based on follow up reported in the main study, however it is not reported in this study. Early stopping due to results.; Indirectness of outcome: No indirectness ; Baseline details: Baseline details only provided for group overall, not in terms of intervention groups; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Unplanned hospitalisation (all-cause) - Actual outcome for CKD stage 3a: All cause hospitalisation at 1 year; HR 0.9 (95%CI 0.73 to 1.11) Reported Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High, Other 1 - High, Other 2 - Low, Other 3 - Low, Comments - Number of patients analysed has been assumed as the same as the number of patients randomised as no details are given about number analysed. Therefore, amount of missing data is unknown! Early stopping due to results; Indirectness of outcome: No indirectness ; Baseline details: Baseline details only provided for group overall, not in terms of intervention groups; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at 12 months ; Renal function ; Adverse events - bradycardia; Adverse events - progression to stage 5 CKD / unplanned dialysis; Adverse events - hypotension; Adverse events - hyperkalaemia; Adverse events - arrhythmic

Study	MERIT-HF trial: Ghali 2009-2[515]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=493)
Countries and setting	Conducted in Multiple countries; Setting: Clinical trial at 313 investigational sites in European countries and in the USA.
Line of therapy	1st line
Duration of study	Intervention + follow up: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	CKD stage 3b/4/5: GFR<45ml/min/1.73m^2. No maximum creatinine level.
Subgroup analysis within study	Post-hoc subgroup analysis: Ten years between original study publication and subgroup analysis
Inclusion criteria	Patients were aged 40-80 years old, with HF class II-IV and an ejection fraction <40% for at least 3 months before enrolment, with a heart rate of ≥68 beats/min at the enrolment visit. Required to be taking ACE-I unless not tolerated and diuretics. For CKD subgroup, eGFR<45ml/min/1.73m^2
Exclusion criteria	There were no exclusion criteria relating to the level of serum creatinine at baseline. Cardiovascular event in last 28 days, severe decompensated HF, standing SBP<100mmHg.
Recruitment/selection of patients	Recruited Feb 1997 - April 1998
Age, gender and ethnicity	Age - Mean (SD): 69.6 (7.7). Gender (M:F): 35% female. Ethnicity: Not stated
Further population details	1. Diabetes: Not applicable (Mixed). 2. Ejection fraction: All patients reduced EF 3. Ethnicity: Not stated /

	Unclear 4. Hypertension: Not applicable (Mixed). 5. NYHA class: Not applicable (Mixed).
Extra comments	. Baseline characteristics for wider study: NYHA class II 39%, class III 56%, class IV 5%. Mean LVEF 27%. Prior MI 51%, ACE/ARB tx 96%, average furosemide dose 66mg/day.
Indirectness of population	No indirectness
Interventions	(n=269) Intervention 1: Beta-blockers (BB). Metoprolol CR/XL. The starting dose was 12·5 mg or 25 mg once daily (half a 25 mg tablet was recommended for patients who were in NYHA III-IV). After 2 weeks we increased the dose to the commended 50 mg once daily for 2 weeks, then 100 mg once daily for 2 weeks, and finally up to the target dose of 200 mg once daily. Dose regimen could be modified according to the judgement of the investigator. If a patient did not tolerate increases in dose, temporary decrease in study drug or increase in diuretic dose was recommended. Duration 1 year. Concurrent medication/care: To continue ACE/ARB, diuretic and other medications (n=224) Intervention 2: Placebo. Placebo. Used dummy pills: the starting dose was 12·5 mg or 25 mg once daily (half a 25 mg tablet was recommended for patients who were in NYHA III-IV). After 2 weeks we increased the dose to 50 mg once daily for 2 weeks, then 100 mg once daily for 2 weeks, and finally up to the target dose of 200 mg once daily. Dose regimen could be modified according to the judgement of the investigator. If a patient did not tolerate increases in dose, temporary decrease in study drug or increase in diuretic dose was recommended. Duration 1 year. Concurrent medication/care: To continue ACE/ARB, diuretic and other medications
Funding	Study funded by industry (Study was supported by a grant from AstraZeneca, Dr Wedel received consulting and advisory board fees from AstraZeneca)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BETA-BLOCKERS (BB) versus PLACEBO

Protocol outcome 1: Mortality
- Actual outcome for CKD stage 3b/4/5: All-cause mortality at 1 year; HR 0.41 (95%CI 0.25 to 0.68) Reported

<table>
<tr><td colspan="2">Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High, Other 1 - High, Other 2 - Low, Other 3 - Low, Comments - Number of patients analysed has been assumed as the same as the number of patients randomised as no details are given about number analysed. Therefore, amount of missing data is unknown! Follow up is assumed to be one year based on follow up times reported in the main study, as it is not specified in this paper. ; Indirectness of outcome: No indirectness ; Baseline details: Baseline details only provided for group overall, not in terms of intervention groups; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Unplanned hospitalisation (all-cause)
- Actual outcome for CKD stage 3b/4/5: All cause hospitalisation at 1 year; HR 0.61 (95%CI 0.47 to 0.79) Reported
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - High, Other 1 - High, Other 2 - Low, Other 3 - Low, Comments - Number of patients analysed has been assumed as the same as the number of patients randomised as no details are given about number analysed. Therefore, amount of missing data is unknown! Follow up is assumed to be one year based on follow up times reported in the main study, as it is not specified in this paper. ; Indirectness of outcome: No indirectness ; Baseline details: Baseline details only provided for group overall, not in terms of intervention groups; Group 1 Number missing: 0; Group 2 Number missing: 0</td></tr>
<tr><td>Protocol outcomes not reported by the study</td><td>Quality of life at 12 months ; Renal function ; Adverse events - bradycardia; Adverse events - progression to stage 5 CKD / unplanned dialysis; Adverse events - hypotension; Adverse events - hyperkalaemia; Adverse events - arrhythmic</td></tr>
</table>

Study (subsidiary papers)	RALES trial: Vardeny 2012[1433] (Pitt 1999[1159], Vardeny 2014[1432])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=792)
Countries and setting	Conducted in Multiple countries; Setting: 195 centres in 15 countries
Line of therapy	Unclear
Duration of study	Intervention + follow up: 24 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: NYHA class 3 or 4, eGFR <60 ml/min/1.73m^2
Stratum	CKD stage 3a/3b: CKD defined as eGFR<60 ml/min/1.73m^2. Study excludes serum Creatinine >2.5mg/dl, which equates to approximate eGFR of 26. Therefore includes mostly class 3.
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients were eligibile for enrolment had been given a diagnosis of heart failure at least 6 weeks before enrolment, were NYHA class III-IV and had been NYHA IV at some point in the previous 6 months, were being treated with an ACE inhibitor (if tolerated) and a loop diuretic, and had a left ventricular ejection fraction of no more than 35% within 6 months before enrolment.
Exclusion criteria	Patients were excluded if they had primary operable valvular heart disease (other than mitral or tricuspid regurgitation with clinical symptoms due to the left ventricular systolic heart failure), congenital heart disease, unstable angina, primary hepatic failure, active cancer or any life-threatening disease (other than heart failure). Patients who had undergone heart transplantation or were awaiting the procedure were also ineligible. Other exclusion criteria were a serum creatinine concentration of more than 2.5 mg per decilitre and a serum potassium concentration of more than 5.0mmol per litre.

Recruitment/selection of patients	Recruited March 1995-December 1996
Age, gender and ethnicity	Age - Mean (SD): 70.0 (9.4). Gender (M:F): 69.4% men. Ethnicity: 93.5% Caucasian
Further population details	1. Diabetes: Not applicable (Mixed). 2. Ejection fraction: All patients reduced EF (<35%). 3. Ethnicity: Not applicable (Mixed). 4. Hypertension: Not applicable (Mixed). 5. NYHA class: All patients class III or IV
Extra comments	In wider study, severity was III in 70% and IV in 30%. LVEF 25%. ACE-I in 95%, digoxin in 72%, beta blockers in 10%
Indirectness of population	No indirectness
Interventions	(n=390) Intervention 1: Mineralocorticoid receptor antagonists (MRA). Spironolactone 25mg once daily. After 8 weeks of treatment the dose could be increased to 50mg once daily if the patient showed signs or symptoms of progression of heart failure without evidence of hyperkalemia. If hyperkalemia developed at any time, the dose could be decreased to 25mg every other day. Duration 24 months. Concurrent medication/care: Treatment with digitalis and vasodilators was allowed but potassium-sparing diuretics were not permitted (n=402) Intervention 2: Placebo. Matching placebo. Duration 24 months. Concurrent medication/care: Treatment with digitalis and vasodilators was allowed but potassium-sparing diuretics were not permitted
Funding	Study funded by industry (Supported by a grant from Searle)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MINERALOCORTICOID RECEPTOR ANTAGONISTS (MRA) versus PLACEBO

Protocol outcome 1: Mortality
- Actual outcome for CKD stage 3a/3b: Mortality at 24 months; RR 0.68 (CI 0.56-0.84)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High; Indirectness of outcome: No indirectness ; Baseline details: Baseline characteristics only reported for overall group ; Group 1

Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Unplanned hospitalisation (all-cause) - Actual outcome for CKD stage 3a/3b: Death or heart failure hospital stay at 24 months; RR 0.67 (CI 0.56-0.81) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High; Indirectness of outcome: Serious indirectness, Comments: Compound outcome, unable to extract hospitalisation; Baseline details: Baseline characteristics only reported for overall group ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Adverse events - hyperkalaemia - Actual outcome for CKD stage 3a/3b: Hyperkalaemia at 24 months; Group 1: 100/390, Group 2: 34/402 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High; Indirectness of outcome: No indirectness ; Baseline details: Baseline characteristics only reported for overall group ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at 12 months ; Renal function; Adverse events - bradycardia; Adverse events - progression to stage 5 CKD / unplanned dialysis; Adverse events - hypotension; Adverse events - arrhythmic

Study	SENIORS trial: Cohen-solal 2009[296] (Flather 2005[467])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=704)
Countries and setting	Conducted in Multiple countries; Setting: Outpatient setting
Line of therapy	1st line
Duration of study	Follow up (post intervention): Mean follow up 20.89 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis:
Stratum	Overall (CKD any stage): eGFR <55.5 mL/min/1.73m^2. Study excludes Creatinine>250, which equates to eGFR approximately 20. Therefore late stage 2, stage 3, and early stage 4.
Subgroup analysis within study	Post-hoc subgroup analysis: Not one of four pre-specified subgroups
Inclusion criteria	Aged 70 years or over. Documented heart failure of any severity, plus either: LVEF of <35% in last 6 months; or hospitalisation for decompensated HF in the previous year. CKD defined as eGFR in lowest quartile, which is 55.5ml/l/1.73m^2.
Exclusion criteria	Serum creatinine ≥250µmol/L as well as recent change in drug therapy and contraindication/intolerance to beta-blockers
Recruitment/selection of patients	Recruited 2000-2002. Patients were screened for eligibility at participating centres by checking hospital outpatient lists and admissions for heart failure within the previous year.
Age, gender and ethnicity	Age - Mean (SD): NEB group 77.3 (5), PLC group 77.4 (5.1). Gender (M:F): Neb group 41.7% female, PLC group 39.9% female. Ethnicity: Not stated

Further population details	1. Diabetes: Not applicable (Mixed). 2. Ejection fraction: Not applicable/mixed (LVEF reduction not required, but 64% had LVEF<35% in wider study). 3. Ethnicity: Not applicable 4. Hypertension: Not applicable 5. NYHA class: Not applicable (Mixed - in wider study class I 3%, II 57%, III 39%, IV 2%).
Extra comments	In wider study class I 3%, II 57%, III 39%, IV 2%; medication use, diuretic 86%, ACE-I 82%, digoxin 39%
Indirectness of population	Serious indirectness: eGFR <55.5 rather than <60
Interventions	(n=348) Intervention 1: Beta-blockers (BB). Nebivolol initial dose 1.25 mg once daily, and if tolerated, this was increased to 2.5 and 5mg respectively, every 1-2 weeks, reaching a target of 10mg once daily over a maximum of 16 weeks. . Duration Mean 20.89 (9.2) months. Concurrent medication/care: Not stated. Regular scheduled visits. Comments: In wider trial, 68% achieved dose of 10mg, 65% were on study drug at the end of the trial (n=356) Intervention 2: Placebo. Placebo in identical packaging and tablet appearance, uptitrated in same manner. Duration Mean 20.89 (9.2) months. Concurrent medication/care: Not stated. Regular scheduled visits. Comments: In wider study, by end of titration 80% were on 10mg placebo, and at end of study 64% were still taking study medication
Funding	Study funded by industry (Funded by a grant from Menarini Ricerche SpA)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BETA-BLOCKERS (BB) versus PLACEBO

Protocol outcome 1: Mortality
- Actual outcome for Overall (CKD any stage): All-cause mortality at Mean 20.89 months; HR 0.76 (95%CI 0.56 to 1.03) Reported
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Unplanned hospitalisation (all-cause)
- Actual outcome for Overall (CKD any stage): CV hospitalisation at Mean 20.89 months; HR 0.93 (95%CI 0.7 to 1.22) Reported
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Subgroups - High; Indirectness of outcome: Serious indirectness, Comments: Not all-cause; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Renal function
- Actual outcome for Overall (CKD any stage): Renal failure at Mean 20.89 months; Group 1: 0/440, Group 2: 0/446
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Subgroups - High, Comments - Study used different eGFR cut off for this outcome; Indirectness of outcome: No indirectness ; Baseline details: Some participants not included in baseline comparison for this outcome as different cut off was used for eGFR; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Adverse events - bradycardia
- Actual outcome for Overall (CKD any stage): Bradycardia at Mean 20.89 months; Group 1: 12/440, Group 2: 9/446
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Subgroups - High, Comments - Study used different eGFR cut off for this outcome; Indirectness of outcome: No indirectness ; Baseline details: Some participants not included in baseline comparison for this outcome as different cut off was used for eGFR; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: Adverse events - hypotension
- Actual outcome for Overall (CKD any stage): Hypotension at Mean 20.89 months; Group 1: 2/440, Group 2: 0/446
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Subgroups - High, Comments - Study used different eGFR cut off for this outcome; Indirectness of outcome: No indirectness; Baseline details: Some participants not included in baseline comparison for this outcome as different cut off was used for eGFR; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life at 12 months ; Adverse events - progression to stage 5 CKD / unplanned dialysis; Adverse events - hyperkalaemia; Adverse events - arrhythmic

Study	SHIFT trial: Voors 2014[1451] (Swedberg 2010[1349])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1579)
Countries and setting	Conducted in Multiple countries; Setting: Not stated
Line of therapy	1st line
Duration of study	Intervention + follow up: Median 22.9 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	CKD stage 3a/3b: CKD defined as eGFR<60ml/min. Pts with Creatinine >220umol/l excl., which approximates to eGFR<30, so will be mainly stage 3.
Subgroup analysis within study	Not stratified but pre-specified
Inclusion criteria	Men or women aged 18 or older who were in sinus rhythm and had a resting heart rate of ≥70 bpm. These patients had stable symptomatic chronic systolic heart failure, a previous admission to hospital for worsening heart failure within the previous 12 months, and an LVEF of ≤35%. Patients needed to be on stable, guideline recommended background treatment for at least 4 weeks. Eligibility for CKD subgroup was eGFR<60. Patients needed to be on stable, guideline recommended background treatment (including beta blockers unless not tolerated)
Exclusion criteria	Patients with known severe renal disease (serum creatinine >220µmol/L) were excluded, along with anyone with congenital heart disease, severe primary valvular heart disease, MI within preceding 2 months, symptomatic hypotension or SBP < 85mmHg, stroke or cerebral ischemia within preceding month, ICD shock within previous 6 months, severe or uncontrolled hypertension (SBP > 180mmHg or DBP > 110mmHg), moderate or severe liver disease, or anaemia. Certain heart rhythms were contraindicated: ventricular or

	atrioventricular pacing requirement ≥ 40%, atrial fibrillation or flutter, sick sinus syndrome, sinoatrial block, or second-degree or greater atrioventricular block
Recruitment/selection of patients	Recruitment 2006-2010
Age, gender and ethnicity	Age - Mean (SD): 66.7 (9.6). Gender (M:F): 63% male. Ethnicity: 92% Caucasian
Further population details	1. Diabetes: Not applicable (Mixed). 2. Ejection fraction: All patients reduced EF (Less than 35%). 3. Ethnicity: Not applicable (Mixed). 4. Hypertension: Not applicable (Mixed). 5. NYHA class: Not applicable (Mixed).
Extra comments	Baseline medication (CKD group): BB 87%, ACE-I 76%, diuretics 89%, MRA 59%, device (CRT/ICD) 5%. Severity: NYHA class II 43%, years of HF 4, LVEF average 29%. Comorbidity: IHD 73%, previous MI 61%, HTN 76%, DM 38%, AF 11%.. Ave creatinine 237.4 (26.2)
Indirectness of population	No indirectness
Interventions	(n=780) Intervention 1: Ivabradine. The starting dose of study drug on day 0 was 5 mg twice daily of ivabradine. After a 14-day titration period, the ivabradine dose was increased to 7·5 mg twice daily, unless the resting heart rate was 60 bpm or lower. If heart rate was between 50bpm and 60 bpm, the dose was maintained at 5 mg twice daily. If the resting heart rate was lower than 50 bpm or the patient had signs or symptoms related to bradycardia, the dose was reduced to 2·5 mg twice daily. Starting at day 28, visits took place every 4 months until study closure. At each follow-up visit, investigators could maintain the study drug dose, or adjust the dose to the next highest dose, if the resting heart rate was higher than 60 bpm (up to 7·5mg twice daily). If resting heart rate was lower than 50 bpm or if the patient had signs or symptoms related to bradycardia, investigators could adjust the study drug dose to the next lowest dose, unless patients were on 2·5 mg twice daily, in which case study treatment was stopped. Duration Median 22.9 months. Concurrent medication/care: On top of optimal guidelines-based treatment Comments: Ave dose in CKD group 6.27mg bd (n=799) Intervention 2: Placebo. The starting dose on day 0 was 5 mg twice daily of matching placebo. After a 14-day titration period, the placebo dose was increased to 7·5 mg twice daily, unless the resting heart rate was 60 bpm or lower. If heart rate was between 50bpm and 60 bpm, the dose was maintained at 5 mg twice

	daily. If the resting heart rate was lower than 50 bpm or the patient had signs or symptoms related to bradycardia, the dose was reduced to 2·5 mg twice daily. Starting at day 28, visits took place every 4 months until study closure. At each follow-up visit, investigators could maintain the study drug dose, or adjust the dose to the next highest dose, if the resting heart rate was higher than 60 bpm (up to 7·5mg twice daily). Duration Median 22.9 months. Concurrent medication/care: On top of optimal guidelines-based treatment
Funding	Study funded by industry (Funded by Servier, France)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IVABRADINE versus PLACEBO

Protocol outcome 1: Renal function
- Actual outcome for CKD stage 3a/3b: eGFR at 24 months; Group 1: mean 53.9 (SD 17.3); n=437
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High; Indirectness of outcome: No indirectness ; Baseline details: Baseline details only given for overall groups, not for the different interventions; Group 1 Number missing: 343, Reason: Not stated ; Group 2 Number missing: 371, Reason: Not stated
- Actual outcome for CKD stage 3a/3b: Renal failure - not defined in text or study site at Median 22.9 months; Group 1: 79/780, Group 2: 85/799
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - High, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Baseline details only given for overall groups, not for the different interventions; Group 1 Number missing: 343, Reason: Not known if missing due to adverse events; Group 2 Number missing: 371, Reason: Not known if missing due to adverse events

Protocol outcome 2: Adverse events - bradycardia
- Actual outcome for CKD stage 3a/3b: Symptomatic bradycardia at Median 22.9 months; Group 1: 35/780, Group 2: 14/799
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High, Comments - Follow up of 24 months assumed as this is not stated. ; Indirectness of outcome: No indirectness ; Baseline details: Baseline details only given for overall groups, not for the different interventions; Group 1 Number missing: 343, Reason: Not known if missing due to adverse events; Group 2 Number missing: 371, Reason: Not known if missing due to adverse events
- Actual outcome for CKD stage 3a/3b: Asymptomatic bradycardia at Median 22.9 months; Group 1: 52/780, Group 2: 18/799
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High, Comments - Follow up of 24 months assumed as this is not stated. ; Indirectness of outcome: No indirectness ; Baseline details:

<table>
<tr><td colspan="2">Baseline details only given for overall groups, not for the different interventions; Group 1 Number missing: 343, Reason: Not known if missing due to adverse events; Group 2 Number missing: 371, Reason: Not known if missing due to adverse events

Protocol outcome 3: Adverse events - hyperkalaemia
- Actual outcome for CKD stage 3a/3b: Hyperkalaemia at Median 22.9 months; Group 1: 14/780, Group 2: 27/799
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High, Comments - Follow up of 24 months assumed as this is not stated. ; Indirectness of outcome: No indirectness ; Baseline details: Baseline details only given for overall groups, not for the different interventions; Group 1 Number missing: 343, Reason: Not known if missing due to adverse events; Group 2 Number missing: 371, Reason: Not known if missing due to adverse events</td></tr>
<tr><td>Protocol outcomes not reported by the study</td><td>Mortality; Quality of life at 12 months ; Unplanned hospitalisation (all-cause); Adverse events - progression to stage 5 CKD / unplanned dialysis; Adverse events - hypotension; Adverse events - arrhythmic</td></tr>
</table>

Study (subsidiary papers)	SOLVD trial: Bowling 2013[196] (Bohm 2014[179], SOLVD investigators 1991 [1311])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1036)
Countries and setting	Conducted in Multiple countries; Setting: 89 hospitals in the US, Canada and Belgium
Line of therapy	1st line
Duration of study	Intervention + follow up: Mean follow up 41.4 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: LVEF <35%, eGFR <60 ml/min/1.73m^2
Stratum	CKD stage 3a/3b: Defines CKD as eGFR<60, with separate analysis of subgroup with eGFR<45. Original study paper states exclusion Cr>177umol/l, the paper with sub-group analysis states the upper limit for Cr was higher at 221 - equates to eGFR around 34 and 26 respectively.
Subgroup analysis within study	Post-hoc subgroup analysis: Analysis took place many years after original study
Inclusion criteria	LVEF <35% who were not currently receiving ACEIs
Exclusion criteria	Patients aged >80 years and those with serum creatinine level >221 umol/l (elsewhere quoted 177umol/l). Hemodynamically serious valvular disease requiring surgery, unstable angina, angina requiring revascularization, MI during prior month, severe pulmonary disease, other disease that would shorten survival or otherwise impede participation in long-term trial
Recruitment/selection of patients	Recruitment 1986 - 1989. Of 2569 in wider study, 1036 had CKD (40%) and 268 had CKD stage 3B or worse (10%)
Age, gender and ethnicity	Age - Mean (SD): Placebo group 64.5 (7.6), drug group 64.1 (8.3). Gender (M:F): Placebo group 25% female,

	drug group 24% female. Ethnicity: Placebo group 84% white, 11% African American, 5% other; drug group 79% white, 17% African American, 6% other
Further population details	1. Diabetes: Not applicable (Mixed). 2. Ejection fraction: All patients reduced EF (<35%). 3. Ethnicity: Not applicable (Mixed). 4. Hypertension: Not applicable (Mixed). 5. NYHA class: Not applicable (NYHA I 11%, II 52%, III 36%, IV 1%).
Extra comments	Other medication at baseline: BB 7%, digoxin 64%, diuretics 89%. Ejection fraction average 25%. Comorbidities: IHD 73%, prev MI 67%, HTN 47%, DM 29%, AF 8%. Ave creatinine mg/dL - ACE group: 1.49 (0.27) , placebo group 1.50 (0.27)
Indirectness of population	No indirectness:
Interventions	(n=498) Intervention 1: Angiotensin converting enzyme (ACE) inhibitors. Enalapril 2.5 to 20mg/day . Duration Mean 41.4 months. Concurrent medication/care: To continue current medication (n=538) Intervention 2: Placebo. No details given . Duration Mean 41.4 months. Concurrent medication/care: Not stated
Funding	Equipment / drugs provided by industry (Supported by Academic grants. Original study received medication from Merck Sharp)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITORS versus PLACEBO

Protocol outcome 1: Mortality
- Actual outcome for CKD stage 3a/3b: All-cause mortality at Mean 41.4 months; HR 0.88 (95%CI 0.73 to 1.06) Reported
Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Very high, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Unsure if there is missing data/reasons; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for CKD stage 3b/4/5: All-cause mortality at Mean 41.4 months; HR 0.76 (95%CI 0.54 to 1.08) Reported

Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Very high, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Unsure if there is missing data/reasons; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Unplanned hospitalisation (all-cause) - Actual outcome for CKD stage 3a/3b: All-cause hospitalisation at Mean 41.4 months; HR 0.83 (95%CI 0.72 to 0.96) Reported Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Very high, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Unsure if there is missing data/reasons; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Renal function - Actual outcome for CKD stage 3a/3b: Serum creatinine at 12 months; Group 1: mean 0.04 mg/dl (SD 0.28); n=466, Group 2: mean -0.02 mg/dl (SD 0.28); n=501 Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Very high, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 32; Group 2 Number missing: 37 Protocol outcome 4: Adverse events - hyperkalaemia - Actual outcome for CKD stage 3a/3b: Serum potassium ≥5.5mEq/l at any time point at mean 41.4 months; Group 1: 9/467, Group 2: 6/503 Risk of bias: All domain - Very high, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Very high, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Relatively small drop out (6%), but small rate (1%) so might be affected; Indirectness of outcome: No indirectness ; Group 1 Number missing: 31, Reason: not stated; Group 2 Number missing: 35	
Protocol outcomes not reported by the study	Quality of life at 12 months ; Adverse events - bradycardia; Adverse events - progression to stage 5 CKD / unplanned dialysis; Adverse events - hypotension; Adverse events - arrhythmic

Study (subsidiary papers)	Valsartan in Heart Failure Trial (Val-HeFT) trial: Anand 2009[65] (Lesogor 2013[864]; Cohn 2001[297])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=2890 (2185 had at least 12 months follow-up))
Countries and setting	Conducted in Australia, Italy, Multiple countries, United Kingdom, USA; Setting: 302 centres in 16 countries. Site monitoring, data collection, and data analysis were performed by Novartis Pharmaceuticals.
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 2y (mean follow up 23 months, range 0 to 38m, 76% followed for at least 12m)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: History and clinical findings of heart failure of New York Heart Association (NYHA) class II, III, or IV for at least three months
Stratum	CKD stage 3a/3b: CKD group, defined as eGFR<60ml/min, further subdivided by those with and without proteinuria. Note excl of Creatinine >2.5mg/dl, which equates to approximate eGFR of 26. Therefore will include mostly class 3, possible early 4.
Subgroup analysis within study	Post-hoc subgroup analysis: "secondary analysis" not mentioned in protocol paper
Inclusion criteria	Stable, symptomatic HF, LVSD on echo. On HF medication.
Exclusion criteria	Standing SBP<90mmHg, creatinine >2.5mg/dl, cardiovascular event in last three months. HF caused by postpartum cardiomyopathy, pulmonary disease, valvular disease, hypertrophic cardiomyopathy. Sustained, untreated, symptomatic ventricular tachycardia. Hepatic dysfunction, or any other disease with life expectancy less than 5 years. Treatment with interacting drugs, or participation in any drug trial within last 30 days. Previous treatment failure with Valsartan.
Recruitment/selection of patients	Recruitment to main study not described. Of 4957 with data, 2890 (58%) had eGFR<60, of which 289 also had proteinuria. Randomisation stratified for b-blocker use

Age, gender and ethnicity	Age - Mean (SD): 66(9). Gender (M:F): 2543:347 (88% male). Ethnicity: 91% white
Further population details	1. Diabetes: Not applicable (685/2601 (26%) of those without proteinuria and 156/289 (54%) with proteinuria have diabetes). 2. Ejection fraction: All patients reduced EF 3. Ethnicity: Not applicable 4. Hypertension: Not applicable (mean SBP 123mmHg). 5. NYHA class: Not applicable (1060/2601 (41%) of those without proteinuria are in NYHA class III or IV).
Extra comments	Most patients taking ACE-inhibitor (92%). LVSD defined from echo as: documented left ventricular dysfunction with an ejection fraction of less than 40 percent and left ventricular dilatation with an echocardiographically measured short-axis internal dimension at end diastole greater than 2.9 cm per square meter of body-surface area, by approved readers, with quality control during the study.
Indirectness of population	No indirectness: CHF diagnosis and low eGFR at baseline
Interventions	(n=1478) Intervention 1: Angiotensin receptor antagonists/blockers (ARB) - Angiotensin receptor antagonists. Valsartan, target dose 160mg twice a day - started at 40mg twice a day and doubled every two weeks unless hypotension and/or creatinine level >150% of baseline or >2.0mg/dl. Duration 2y average (mean 23 months, range 0-38 months). Concurrent medication/care: Continued medication from baseline Comments: Numbers randomised calculated from results given in Anand et al. Differs from that given in Lesogar et al, which are around 300 lower (n=1441) Intervention 2: Placebo. Placebo, dose doubled every 2 weeks unless hypotension of creatinine increases >150% baseline. Duration 2y average (mean 23 months, range 0-38 months). Concurrent medication/care: Continue all other treatment Comments: Numbers randomised, calculated from results given in Anand et al, differs from that given in Lesogar et al, which are around 300 lower
Funding	Study funded by industry (Supported by a grant from Novartis Pharmaceuticals, Dr Anand and Dr Cohn supported by grants from Novartis. Also received funding from Veterans Affairs R&D grants.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ARB - VALSARTAN versus PLACEBO

Protocol outcome 1: Mortality
- Actual outcome for CKD stage 3a/3b: Death at mean 23 months; HR 1.01 (95%CI 0.85 to 1.2) Reported
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Post-hoc sub-group; Indirectness of outcome: No indirectness ; Baseline details: Ethnicity, severity, renal function, comorbidities, medication use fairly comparable; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Unplanned hospitalisation (all-cause)
- Actual outcome for CKD stage 3a/3b: First morbid event (death, cardiac arrest with resuscitation, hospitalization for heart failure, or administration of intravenous inotropic or vasodilator drugs for four hours or more without hospitalization) at mean 23 months; HR 0.86 (95%CI 0.74 to 0.99) Reported
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - High, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Post-hoc sub-group, compound end-point; Indirectness of outcome: Serious indirectness, Comments: Cannot calculate numbers of hospitalisations; Baseline details: Ethnicity, severity, renal function, comorbidities, medication use fairly comparable; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Renal function
- Actual outcome for CKD stage 3a/3b: eGFR change at 12 months; Group 1: mean -4.8 ml/min (SD 10.0); n=1105, Group 2: mean -1.2 ml/min (SD 6.6); n=1074
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Post-hoc sub-group, 25% missing but unclear if equal between groups; Indirectness of outcome: No indirectness; Baseline details: Ethnicity, severity, renal function, comorbidities, medication use fairly comparable; Group 1 Number missing: 373, Reason: not followed for 12 months / missing; Group 2 Number missing: 367, Reason: not followed for 12 months / missing

Protocol outcome 4: Adverse events - progression to stage 5 CKD / unplanned dialysis
- Actual outcome for CKD stage 3a/3b: Initiation of dialysis at mean 23 months; Group 1: 0/1476, Group 2: 0/1435
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - High, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Post-hoc sub-group, reported as "no cases started dialysis"; Indirectness of outcome: Serious indirectness, Comments: Only initiating dialysis reported, not other end-stage renal disease; Baseline details: Ethnicity, severity, renal function, comorbidities, medication use fairly comparable; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: Adverse events - hyperkalaemia - Actual outcome for CKD stage 3a/3b: Hyperkalaemia (cut-off not given) at mean 23 months; Group 1: 125/1476, Group 2: 65/1435 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - High, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Post-hoc sub-group, reported as "no cases started dialysis"; Indirectness of outcome: No indirectness ; Baseline details: Ethnicity, severity, renal function, comorbidities, medication use fairly comparable; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at 12 months ; Adverse events - bradycardia; Adverse events - hypotension; Adverse events - arrhythmic

F.8 Coronary revascularisation

Study	HEART trial: Cleland 2011[287]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=138)
Countries and setting	Conducted in United Kingdom; Setting: Secondary care.
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 4.9 years
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: Study reports that patients had heart failure, a wall motion index of <1.2, equivalent to an LVEFV< 35%, and evidence of a substantial amount of viable myocardium with impaired contractility.
Stratum	Mixed
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with persistent heart failure of at least 6 weeks duration who were receiving diuretics and who had evidence of coronary artery disease on angiography, or who had a prior history of myocardial infarction, an LVEF ≤ 35%, and who had at least five viable segments with reduced contractility in a 17-segment model could be enrolled.
Exclusion criteria	Patients with a recent acute coronary or stroke syndrome, those requiring revascularization for angina or valve surgery, and those with ventricular arrhythmias requiring device therapy were excluded. Patients with life-limiting co-morbidity, those considered too frail for CABG, and those unable to give valid consent were excluded. Patients had to be willing to be contacted directly by staff at the central data monitoring office in Kingston-upon-Hull and to have their relevant hospital records copied and sent to the data centre.
Recruitment/selection of patients	Recruitment of patients not reported.
Age, gender and ethnicity	Age: median (IQR), surgical intervention (SI) - 65 (58 – 70); Medical therapy - 69 (60 – 74). Gender (M:F): SI - 94% Male; Medical therapy - 93% Male. Ethnicity: Not reported.
Further population details	1. Age: Not applicable / Not stated / Unclear 2. Diabetes: Not applicable / Not stated / Unclear
Extra comments	Baseline characteristics: Prior CABG (n): SI - 5, medical therapy - 6; Prior angioplasty (n): SI- 6, medical therapy - 5; NYHA class I, n: SI - 13, medical therapy - 11; NYHA class II, n: SI - 28, medical therapy - 36; NYHA class III/IV, n: SI - 28; medical therapy - 22.
Indirectness of population	No indirectness: Meets protocol.

Interventions	(n=69) Intervention 1: Angiography with intent to perform coronary revascularization – CABG or PCI. Patients assigned to invasive therapy underwent diagnostic angiography, if not already done, and revascularization within the next 6 - 12 weeks. After their angiogram and non-invasive imaging was reviewed by investigators, the investigator could choose to recommend continued medical therapy alone, PCI, or referral for CABG, as they believed appropriate. All patients were on optimum therapy of: ACEIs, beta-blockers, and, if indicated, aldosterone receptor antagonists and warfarin. Duration 4.9 years. Concurrent medication/care: (n) Nitrates - 30; digitalis compounds - 16; aspirin - 42; other anti-thrombotic - 8; anti-arrhythmic agents - 4; and, lipid-regulating drug - 50. (n=69) Intervention 2: Medical management. All patients were on optimum therapy of: ACEIs, beta-blockers, and, if indicated, aldosterone receptor antagonists and warfarin. Duration 4.9 years. Concurrent medication/care: (n) Nitrates - 32; digitalis compounds - 14; aspirin - 42; other anti-thrombotic - 17; anti-arrhythmic agents - 1; and, lipid-regulating drug - 50.
Funding	Academic or government funding (Medical Research Council of the United Kingdom)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INVASIVE STRATEGY versus MEDICAL MANAGEMENT

Protocol outcome 1: All-cause mortality at 5 years
- Actual outcome for coronary revascularization (CABG or PCI): All-cause mortality at 4.9 years; Group 1: 26/68, Group 2: 25/68;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - After randomization to surgical intervention, the clinician was able to choose the most appropriate mode of care. ; Indirectness of outcome: No indirectness, Comments: Study reports all-cause mortality as a dichotomous outcome.; Baseline details: Current smoker: SI: 22%; MT - 10%; Diabetes: SI - 41%; MT - 33%; Prior stroke: SI - 17%, MT - 12%; peripheral vascular disease: SI - 23%, MT - 17%; history of hyperlipidemia: SI - 70%, MT - 54%, NYHA class III/IV: SI - 41%, MT - 32%. SI group generally in worse health ; Blinding details: Study reports that the trial was not blinded, no rationale was given.; Group 1 Number missing: 7, Reason: 6 participants did not receive the angiography needed to assess eligibility for revascularisation (5 died before procedure, 1 refused), 1 patient lost to follow up.; Group 2 Number missing: 6, Reason: 5 patients switched to revascularization, 1 patient lost to follow up

Protocol outcome 2: Quality of life at 12 months
- Actual outcome for Mixed: Quality of life - EQ-5D at 6 months; MD -0.023 (95%CI -0.144 to 0.097) EQ-5D 0 to 1 Top=High is a good outcome;
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Comments - Result reported as difference between the groups (overall statistic). ACA with switching patients analysed in original groups. ; Indirectness of outcome: No indirectness, Comments: Difference between the groups is reported; Baseline details: EQ-5D median (IQR): SI -0.69 (0.52 - 0.88), MT - 0.69 (0.55 - 0.88). ; Blinding details: Study reports that the trial was not blinded, no rationale was given; Group 1 Number missing: 7, Reason: 6 participants did not receive the angiography needed to assess eligibility for revascularisation (5 died before procedure, 1 refused), 1 patient lost to follow up; Group 2 Number missing: 6, Reason: 5 patients switched to revascularization, 1 patient lost to follow up

- Actual outcome for Mixed: Quality of life - MLWHF at 6 months; MD -3.9 (95%CI -11.4 to 3.5) Minnesota Living with Heart Failure questionnaire (MLWHFQ) 0 to 105 Top=High is poor outcome; Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Comments - Result reported as difference between the groups (overall statistic). ACA with switched patients analysed in original groups. ; Indirectness of outcome: No indirectness, Comments: Difference between the groups is reported.; Baseline details: MLWHF median (IQR): SI 39 (19 - 63), MT 32 (18 - 64). ; Blinding details: Study reports that the trial was unblinded, no rationale was given.; Group 1 Number missing: 7, Reason: 6 patients did not receive the angiography necessary to proceed to revasc (5 died before procedure, 1 refused). 1 lost to follow up. ; Group 2 Number missing: 5, Reason: 5 patients switched to revascularization	
Protocol outcomes not reported by the study	All-cause mortality at 30 days; Unplanned hospitalisation at 12 months; Additional revascularisation events at 24 months; Improvement of NYHA class at 12 months; Improvement in ejection fraction at 12 months; Adverse events - stroke at 12 months

Study (subsidiary papers)	**STICH(ES) trial: Velazquez 2011[1439] (Bonow 2015[186], Carson 2013[246], Doenst 2013[390], Feldman 2013[455], Jolicoeur 2015[704], Panza 2013[1106], Stewart 2014[1328], Velazquez 2007[1441], Macdonald 2015[921], Velazquez 2016[1440], Mark 2014[942], Panza 2014[1107])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	13 (n=1212)
Countries and setting	Conducted in Multiple countries; Setting: Secondary care.
Line of therapy	Not applicable
Duration of study	Follow up (post intervention): 9.3 years
Method of assessment of guideline condition	Method of assessment /diagnosis not stated: LVEF ≤ 0.35 measured by contrast magnectic resonance ventriculogram, gated SPECT ventriculogram, echo, or contrast ventriculogram within 3 months of trial entry.
Stratum	Bypass surgery
Subgroup analysis within study	Not applicable
Inclusion criteria	Men or Women not of childbearing potential; aged ≥ 18 years; LVEF ≤ 0.35 measured by contrast magnectic resonance ventriculogram, gated SPECT ventriculogram, echo, or contrast ventriculogram within 3 months of trial entry, CAD suitable for revascularization.
Exclusion criteria	Failure to provide informed consent; aortic valvular heart disease indicating need for aortic valve repair or replacement; cardiogenic shock (within 72 hrs. of randomization), defined by need for IABP support or requirement of IV inotropic support; plan for PCI of CAD; recent acute MI judged to be an important cause of LV dysfunction; history of more than 1

	prior CABG; non-cardiac illness with a life expectancy of < 3 years; non-cardiac illness imposing substantial operative mortality; conditions/circumstance likely to lead to poor treatment adherence (e.g. history of poor compliance, alcohol or drug dependency, psychiatric illness, no fixed abode); prior heart, kidney, liver, or lung transplant; current participation in another clinical trial in which patient is taking an investigational drug or receiving an investigational medical device.
Recruitment/selection of patients	All patients included in this component of the study (described as 'hypothesis 1' of the STICH study) were assessed as eligible for both CABG and medical therapy before randomization.
Age, gender and ethnicity	Age - Median (IQR): CABG - 60 (54-68), MT- 59(53-67). Gender (M:F): CABG - 537/73, MT - 527/75 . Ethnicity: % Hispanic, Latino, or nonwhite: CABG - 36, MT - 33; % White: CABG - 64, MT - 67.
Further population details	1. Age: Not stated 2. Diabetes: Not stated
Extra comments	Baseline characteristics: Medical history of previous PCI, %: CABG - 13, MT - 12; medical history of previous CABG, %: CABG - 4, MT- 2; NYHA class I, %: CABG - 11, MT - 12; NYHA class II, %: CABG - 52, MT - 51; NYHA class III, %: CABG - 34, MT - 34; NYHA IV, %: CABG - 3, MT - 3.
Indirectness of population	No indirectness: Meets protocol.
Interventions	(n=610) Intervention 1: Coronary revascularization - CABG. Patients received the intervention no later than 14 days after randomisation. CABG was performed using at least one internal mammary conduit unless unavailable or inadequate. Use of cardiopulmonary bypass for CABG was left to the discretion of the surgeon. Duration N/A. Concurrent medication/care: All patients also received optimal medical therapy. Concurrent mitral-valve operation was performed in 63 patients (11%). Comments: A lead cardiologist at each center was responsible for recommending the most appropriate medications and devices for the treatment of heart failure and coronary artery disease on the basis of current guidelines. Cardiac surgery was performed by surgeons who had provided data on least 25 patients with an ejection fraction of 40% or less in whom they had performed CABG and among whom the operative death rate was 5% or less. (n=602) Intervention 2: Medical management. Unless contraindicated, optimal medical treatment included: ACEIs and/or angiotensin receptor blocker, beta-blocker, aldosterone antagonist, and antiplatelet agents adjusted to optimal doses within 30 days post-randomization. HMG-CoA reductase inhibitors, diuretics, and digitalis use was individualised to patient-specific indications. The use of implantable defibrillators was encouraged as part of medical therapy and was used in compliance with standard guidelines. Duration 9.3 years. Concurrent medication/care: None reported.
Funding	Academic or government funding (Funding by the National Heart, Lung, and Blood Institute (NHBLI).)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CABG versus MEDICAL MANAGEMENT

Protocol outcome 1: All-cause mortality at 30 days
- Actual outcome for Bypass surgery: Death from any cause at 30 days ; HR 3.12 (95%CI 1.33 to 7.31) Reported
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: N/A; Blinding details: Study reports no blinding of the interventions; Group 1 Number missing: 55, Reason: Patients had not received the intervention by the end of the study.; Group 2 Number missing: 100, Reason: Patients had a surgical intervention by the end of the study.

Protocol outcome 2: All-cause mortality
- Actual outcome for Bypass surgery: Death from any cause at 9.8 years ; HR 0.80 (95%CI 0.7 to 0.93) Reported
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: N/A; Blinding details: Study reports no blinding of the interventions; Group 1 Number missing: 55, Reason: Patients had not received the intervention by the end of the study.; Group 2 Number missing: 100, Reason: Patients had a surgical intervention by the end of the study

Protocol outcome 3: Quality of life at 12 months
- Actual outcome for Bypass surgery: Kansas City Cardiomyopathy Questionnaire - Quality of life domain at 12 months ; MD 8.8 (95%CI 5.4 to 12.2) Kansas City Cardiomyopathy Questionnaire 0-100 Top=High is good outcome; Adjusted mean difference reported, adjusted for patients having repeat assessments
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ITT method of imputation unclear.; Indirectness of outcome: No indirectness; Baseline details: N/A; Blinding details: Study reports no blinding of the interventions; Group 1 Number missing: 138, Reason: Dead - 79, missing - 55 (40-site error, 2 unable to locate, 4 late follow up, 2 unknown, 1 withdrew, 5 patients refused, 1 to ill or deaf). Remaining missing for reasons unknown/not reported.; Group 2 Number missing: 133, Reason: Dead - 71, missing - 58 (46-site error, 3 unable to locate, 5 late follow up, 3 unknown, 1 withdrew). Remaining missing for reasons unknown/not reported
- Actual outcome for Bypass surgery: SF-12 (Mental component) at 12 months ; MD 2.2 (95%CI 0.5 to 4) Short form -12 Scaled to a norm of 50 with a standard deviation of 10 Top=High is good outcome; Adjusted mean difference reported, adjusted for patients having repeat assessments
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ITT method of imputation unclear.; Indirectness of outcome: No indirectness, Comments: Meets protocol.; Baseline details: N/A; Blinding details: Study reports no blinding of the interventions; Group 1 Number missing: 207, Reason: Dead - 79, missing - 55 (40-site error, 2 unable to locate, 4 late follow up, 2 unknown, 1 withdrew, 5 patients refused, 1 to ill or deaf). Remaining missing for reasons unknown/not reported.; Group 2 Number missing: 197, Reason: Dead - 71, missing - 58 (46-site error, 3 unable to locate, 5 late follow up, 3 unknown, 1 withdrew). Remaining missing for reasons unknown/not reported
- Actual outcome for Bypass surgery: SF-12 (Physical component) at 12 months; MD 1.5 (95%CI 0.5 to 2.5) Short form-12 Scaled to a norm of 50 with a standard deviation of 10. Top=High is good outcome; Adjusted mean difference reported, adjusted for patients having repeat assessments
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ITT method of imputation unclear.; Indirectness of outcome: No indirectness; Baseline details: N/A; Blinding details: Study reports no blinding of the interventions; Group 1 Number missing: 207, Reason: Dead - 79, missing - 55 (40-site error, 2 unable to locate, 4 late follow up, 2 unknown, 1 withdrew, 5 patients refused, 1 to ill or deaf). Remaining missing for reasons unknown/not reported.; Group 2 Number missing: 197, Reason: Dead - 71, missing - 58 (46-site error, 3 unable to locate, 5 late follow up, 3 unknown, 1 withdrew). Remaining missing for reasons unknown/not reported
- Actual outcome for Bypass surgery: EQ-5D at 12 months; Mean 0.052 (95%CI 0.018 to 0.086) EQ-5D 0-1 Top=High is good outcome; Adjusted mean difference reported,

adjusted for patients having repeat assessments
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ITT method of imputation unclear.; Indirectness of outcome: No indirectness; Baseline details: N/A; Blinding details: Study reports no blinding of the interventions; Group 1 Number missing: 171, Reason: Dead - 79, missing - 55 (40-site error, 2 unable to locate, 4 late follow up, 2 unknown, 1 withdrew, 5 patients refused, 1 to ill or deaf). Remaining missing for reasons unknown/not reported.; Group 2 Number missing: 100, Reason: Dead - 71, missing - 58 (46-site error, 3 unable to locate, 5 late follow up, 3 unknown, 1 withdrew). Remaining missing for reasons unknown/not reported
- Actual outcome for Bypass surgery: EQ-5D VAS at 12 months; MD 5.9 (95%CI 3.2 to 8.6) EQ-5D 0-100 Top=High is good outcome
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ITT method of imputation unclear.; Indirectness of outcome: No indirectness, Comments: Meets protocol.; Baseline details: N/A; Blinding details: Study reports no blinding of the interventions; Group 1 Number missing: 163, Reason: Dead - 79, missing - 55 (40-site error, 2 unable to locate, 4 late follow up, 2 unknown, 1 withdrew, 5 patients refused, 1 to ill or deaf). Remaining missing for reasons unknown/not reported.; Group 2 Number missing: 147, Reason: Dead - 71, missing - 58 (46-site error, 3 unable to locate, 5 late follow up, 3 unknown, 1 withdrew). Remaining missing for reasons unknown/not reported

Protocol outcome 4: Unplanned hospitalisation at 12 months
- Actual outcome for Bypass surgery: All-cause hospitalisation at 4.7 years; Group 1: 290/610, Group 2: 340/602
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: N/A; Blinding details: Study reports no blinding of the interventions; Group 1 Number missing: 55, Reason: Patients had not received the intervention by the end of the study.; Group 2 Number missing: 100, Reason: Patients had a surgical intervention by the end of the study

Protocol outcome 5: Additional revascularisation events at 24 months
- Actual outcome for Bypass surgery: Subsequent procedures - CABG surgery at 4.7 years; Group 1: 1/610, Group 2: 100/602
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: Meets protocol.; Baseline details: N/A; Blinding details: Study reports no blinding of the interventions; Group 1 Number missing: 55, Reason: Patients had not received the intervention by the end of the study.; Group 2 Number missing: 100, Reason: Patients had a surgical intervention by the end of the study
- Actual outcome for Bypass surgery: Subsequent procedure - percutaneous coronary intervention at 4.7 years; Group 1: 26/610, Group 2: 37/602
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: Meets protocol.; Baseline details: N/A; Blinding details: Study reports no blinding of the interventions; Group 1 Number missing: 55, Reason: Patients had not received the intervention by the end of the study.; Group 2 Number missing: 100, Reason: Patients had a surgical intervention by the end of the study

Protocol outcome 6: Improvement of NYHA class at 12 months
- Actual outcome for Bypass surgery: Number NYHA class I at 12 months ; Group 1: 255/610, Group 2: 206/602
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: protocol outcome – improvement in NYHA class; extracted outcome no. in NYHA class I; Baseline details: N/A; Blinding details: Study reports no blinding of the interventions; Group 1 Number missing: 55, Reason: Patients had not received the intervention by the end of the study.;

Group 2 Number missing: 100, Reason: Patients had a surgical intervention by the end of the study Protocol outcome 7: Adverse events - stroke at 12 months - Actual outcome for Bypass surgery: Stroke at 9.8 years; Group 1: 47/610, Group 2: 41/602 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Baseline details: N/A; Blinding details: Study reports no blinding of the interventions; Group 1 Number missing: 55, Reason: Patients had not received the intervention by the end of the study.; Group 2 Number missing: 100, Reason: Patients had a surgical intervention by the end of the study	
Protocol outcomes not reported by the study	Improvement in ejection fraction at 12 months; Adverse events - stroke at 12 months

F.9 Home-based versus centre-based rehabilitation

Study (subsidiary papers)	Cowie 2012[329] (Cowie 2014[327] Cowie 2011[328])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=60)
Countries and setting	Conducted in UK; Setting: Single centre
Line of therapy	Adjunctive to current care
Duration of study	Maximum length of follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of CHF, echocardiography, NYHA class II-III
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with: (1) left ventricular systolic dysfunction on echocardiography, (2) clinically stable for at least one month, and (3) on optimised medication dosages.
Exclusion criteria	(1) significant ischaemic symptoms at low workloads, (2) uncontrollable diabetes, (3) acute systematic illness or fever, (4) recent embolism, (5) acute pericarditis, (6) moderate to severe aortic stenosis, (7) regurgitant valvular heart disease requiring surgery, (8) myocardial infarction within the past three weeks, (9) new onset of atrial fibrillation, (10) signs and symptoms of decompensation, (11) other co-morbidities (life-threatening, uncontrolled, infectious, or exacerbated by exercise).

Study (subsidiary papers)	Cowie 2012[329] (Cowie 2014[327] Cowie 2011[328])
Recruitment/selection of patients	Selection not reported; participants were randomised using concealed envelopes
Age, gender and ethnicity	Age - Mean (range): Home-based CR – 65.5 (35-82), Centre-based – 71.2 (59-85). Gender (M:F):85:15. Ethnicity: NR
Further population details	
Extra comments	3-arm trial but the third arm (control group: usual care without CR) has not been extracted
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Home-based cardiac rehabilitation. Twice a week 1-hour aerobic-based exercise session (DVD and booklet), started with a 15-minute warm-up, and ended with a 15-minute cool-down. Aerobic overload: 2 x 15 minute circuits (10 simple, functional aerobic exercises e.g. knee lifts, side steps); interspersed with low-paced 'active recovery' (toe tapping or slow walking; 90 seconds for each exercise). Gradually increasing the proportion of time spent on aerobic overload in relation to active recovery provided interval training, which was individually tailored and progressed. Physiotherapist telephoned every two weeks to modify exercise prescriptions where appropriate. Duration 8 weeks. Concurrent medication/care: Educated on symptoms of unstable heart failure. Use of heart rate monitors to guide training intensity. Encouraged to work at 12-13 on the Borg RPE. Advised to adhere to usual heart failure nursing care and daily routines. (n=20) Intervention 2: Centre-based cardiac rehabilitation. The same as above home-based intervention: twice a week 1-hour aerobic based exercise session but in a rehabilitation centre and physiotherapist-led. Duration 8 weeks. Concurrent medication/care: Educated on symptoms of unstable heart failure. Use of heart rate monitors to guide training intensity. Encouraged to work at 12-13 on the Borg RPE. Advised to adhere to usual heart failure nursing care and daily routines.
Funding	This work was supported by NHS Ayrshire & Arran's coronary heart disease Managed Clinical Network.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HOME-BASED versus CENTRE-BASED CARDIAC REHABILITATION

Protocol outcome 1: All-cause mortality
- Actual outcome: Mortality at 2 months, Group 1: 3/15, Group 2: 3/15; Risk of bias: All domain –High, Random sequence generation - High, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - High, Selective reporting – Low, Groups balanced at baseline – High, Groups received same co-interventions - Low; Indirectness of outcome: No indirectness

Study (subsidiary papers)	Cowie 2012[329] (Cowie 2014[327] Cowie 2011[328])
Protocol outcome 2: Quality of life - Actual outcome: SF-36 physical summary scale at 2 months; Group 1: mean 34.01 (SD 11.04); n=15, Group 2: mean 33.83 (SD 10.00); n=15; SF-36 Questionnaire physical component 0-100 Top=High is good outcome; Risk of bias: All domain –High, Random sequence generation - High, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - High, Selective reporting – Low, Groups balanced at baseline – High, Groups received same co-interventions - Low; Indirectness of outcome: No indirectness Protocol outcome 3: Quality of life - Actual outcome: SF-36 mental summary scale at 2 months; Group 1: mean 44.44 (SD 12.23); n=15, Group 2: mean 48.25 (SD 11.21); n=15; SF-36 Questionnaire mental component 0-100 Top=High is good outcome; Risk of bias: All domain –High, Random sequence generation - High, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - High, Selective reporting – Low, Groups balanced at baseline – High, Groups received same co-interventions - Low; Indirectness of outcome: No indirectness Protocol outcome 4: Exercise capacity - Actual outcome: Incremental shuttle walking test at 2 months; Group 1: mean 318 (SD 153); n=15, Group 2: mean 312 (SD 155); n=15; Risk of bias: All domain –High, Random sequence generation - High, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - High, Selective reporting – Low, Groups balanced at baseline – High, Groups received same co-interventions - Low; Indirectness of outcome: No indirectness Protocol outcome 5: Withdrawals - Actual outcome: Study completers at 2 months; Group 1: 15/20, Group 2: 15/20; Risk of bias: All domain –High, Random sequence generation - High, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - High, Selective reporting – Low, Groups balanced at baseline – High, Groups received same co-interventions - Low; Indirectness of outcome: No indirectness Protocol outcome 6: Adherence - Actual outcome: Percentage completion of 16 exercise sessions at 2 months; Group 1: 77%; n=11; Group 2: 86%; n=12; 11 Risk of bias: All domain –High, Random sequence generation - High, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - High, Selective reporting – Low, Groups balanced at baseline – High, Groups received same co-interventions - Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	CV mortality, all cause hospitalisation, HF-related hospitalisation, health service use

Study	Daskapan 2005[347]

Study	Daskapan 2005[347]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=29)
Countries and setting	Conducted in Turkey; Single centre
Line of therapy	Adjunctive to current care
Duration of study	Intervention: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Patients fulfilled criteria of the New York Heart Association; class II or III CHF with ischaemic or idiopathic dilated cardiomyopathy
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with heart failure of > 3 month duration
Exclusion criteria	Valvular heart disease, exercise-induced cardiac arrhythmias, symptomatic myocardial ischemia within 3 months, taking beta-blockers
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Home-based CR – 49 (11), Centre-based – 52 (8). Gender (M:F) 3:1. Ethnicity: NR
Further population details	
Extra comments	
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: Home-based cardiac rehabilitation. The home-based exercise training group (HETG) performed 12 weeks of physical training by themselves. Follow up logs completed daily/returned biweekly. Outdoor walking. 3 sessions/week, 45 min/session (including warm-up, cool-down, recovery). Intensity of up to 60% peak heart rate (RPE 12-16) Weekly phone calls from staff monitoring adherence and progress, monthly phone calls from patients for control purposes Duration 12 weeks. Concurrent medication/care: not reported (n=14) Intervention 2: Centre-based cardiac rehabilitation. The supervised exercise training group (SETG) performed 12 weeks of physical training of treadmill walking at the laboratory. 3 sessions/week, 45 min/session (including warm-up, cool-down, recovery). Intensity of up to 60% peak heart rate (RPE 12-16)

Study	Daskapan 2005[347]
	Duration 12 weeks. Concurrent medication/care: not reported
Funding	Not reported

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HOME-BASED versus CENTRE-BASED CARDIAC REHABILITATION

Protocol outcome 1: All-cause mortality
- Actual outcome: Mortality at 3 months; Group 1: 0/14, Group 2: 1/15; Risk of bias: All domain –Very high, Random sequence generation - High, Allocation concealment – High, Blinding of outcome assessment - High, Incomplete outcome data - High, Selective reporting – Low, Groups balanced at baseline – Low, Groups received same co-interventions - Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Exercise capacity
- Actual outcome: exercise capacity VO2 max (ml/kg/min) at 3 months; Group 1: mean 23.6 (SD 7.4); n=11, Group 2: mean 23.3 (SD 6.8); n=11; Risk of bias: All domain –High, Random sequence generation - High, Allocation concealment – High, Blinding of outcome assessment - Very high, Incomplete outcome data - High, Selective reporting – Low, Groups balanced at baseline – Low, Groups received same co-interventions - Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Withdrawal
- Actual outcome: completers at 3 months; Group 1: 11/15, Group 2: 11/14; Risk of bias: All domain –Very high, Random sequence generation - High, Allocation concealment – High, Blinding of outcome assessment - High, Incomplete outcome data - High, Selective reporting – Low, Groups balanced at baseline – Low, Groups received same co-interventions - Low; Indirectness of outcome: No indirectness

Protocol outcome 4: Adherence
- Actual outcome: percentage of sessions attended at 3 months; Group 1: 97%, n=14, Group 2: 81%, n=11 ; Risk of bias: All domain –Very high, Random sequence generation - High, Allocation concealment – High, Blinding of outcome assessment - High, Incomplete outcome data - High, Selective reporting – Low, Groups balanced at baseline – Low, Groups received same co-interventions - Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Health-related quality of life, all cause hospitalisation, HF-related hospitalisation, health service use

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Study	Hwang 2017[660]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=53)
Countries and setting	Conducted in Australia; Setting: cardiology and general medical wards of two tertiary hospitals in Brisbane, Australia

Study	Hwang 2017[660]
Line of therapy	Adjunctive to current care
Duration of study	Intervention: 12 weeks (total follow-up 24 weeks)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: all patients with heart failure, Standard echocardiography
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with a diagnosis of chronic heart failure confirmed by an echocardiogram (heart failure with reduced or preserved ejection fraction), presenting with clinical heart failure symptoms and over 18 years of age.
Exclusion criteria	People were excluded if they did not meet safety screening criteria as outlined by the Australian exercise guidelines for patients with chronic heart failure, such as symptomatic severe aortic stenosis and significant ischaemia at low exercise intensity; liven in an institution such as a nursing home; lived more than an hour driving distance from the treating hospital; or had no support person at home, which was important for those recruited to the home-based telerehabilitation program for safety reasons.
Recruitment/selection of patients	People who had a recent hospital admission for heart failure and were referred to heart failure services were recruited between July 2013 and February 2016.
Age, gender and ethnicity	Age - Mean (SD): 68 (14). Gender (% M) 79. Ethnicity: 92% Caucasian
Further population details	
Extra comments	
Indirectness of population	No indirectness
Interventions	(n=24) Intervention 1: Home-based cardiac telerehabilitation: The telerehabilitation program was delivered via a synchronous videoconferencing platform across the internet to groups of up to four participants within the home. Two-way audio-visual communication enabled interaction of all parties, and the physiotherapist guided participants through an exercise program similar to the control group. This approach enabled the physiotherapist to watch participants performing the exercises and provide real-time feedback and modification, as required, as well as facilitating peer support from other participants. A group-based program was selected because many people undertaking cardiac rehabilitation value the guidance from healthcare professionals and enjoy the group interaction and social support.4 Participants were provided with additional home exercises similar to the control group. Educational topics were delivered as electronic slide presentations with embedded audio files which were recorded from the education sessions delivered for a centre-based program. Participants were encouraged to watch the designated presentation individually or with their support person, in their own time in preparation for subsequent online group discussions. A 15-minute interaction period was held at the start of each telerehabilitation session to facilitate these discussions. A range of resources were accessed through the videoconferencing platform to facilitate

Study	Hwang 2017[660]
	these discussions, such as screen and document sharing, collaborative drawing and chat functions. Telerehabilitation equipment was loaned to participants as required, including a laptop computer, a mobile broadband device connected to 3G wireless broadband internet, an automatic sphygmomanometer, a finger pulse oximeter, free weights and resistance bands. Participants received an equipment familiarisation session either in-person at the hospital or during a home visit, which covered operating the laptop, accessing the online videoconferencing software and using the monitoring equipment. An equipment manual with written and pictorial instructions was also supplied. Telephone contact details to access technical support were included in the event that participants needed additional assistance or encountered technical difficulties. Participants were guided to self-monitor and verbally report their blood pressure, heart rate and oxygen saturation levels at the start of each rehabilitation session. Other measurements such as weight, blood sugar level, extent of peripheral oedema and general wellbeing were also undertaken, where relevant. (n=29) Intervention 2: Centre-based cardiac rehabilitation: The control group received a centre-based rehabilitation program based on current recommended guidelines encompassing education, aerobic and strength training exercise. This traditional heart failure rehabilitation program was led by physiotherapists over a 12-week period; it consisted of 60 minutes of exercise per session, two sessions per week, at the treating hospital. Each session consisted of a 10-minute warm-up, 40-minutes of aerobic and strength exercises, and a 10-minute cool-down. Exercise intensity commenced at 9 (very light) and gradually progressed towards 13 (somewhat hard) on the rate of perceived exertion scale.10 Exercise prescription was tailored to the participant's goal and the treating physiotherapist continuously reviewed it to ensure appropriate progression. The control group attended education sessions at the hospital on the same day as the exercise sessions. These sessions were delivered by a multidisciplinary team including the nurse, dietitian, physiotherapist, occupational therapist, social worker and pharmacist. The topics that were covered included self-management, nutritional counselling, physical activity counselling, psychological interventions, medications and risk factor management, where appropriate. Participants were provided with additional home exercises to be undertaken three times per week, at a similar intensity as prescribed for the supervised exercise sessions.
Funding	The study was supported by the Princess Alexandra Hospital Research Support Scheme Small Grant 2013; The Prince Charles Hospital Foundation Novice Researcher Grant 2012; and the Queensland Health, Health Practitioner Research Scheme 2012-2013.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HOME-BASED CARDIAC TELEREHABILITATION versus CENTRE-BASED CARDIAC REHABILITATION

Protocol outcome 1: All-cause mortality
- Actual outcome: Mortality at 12 weeks; Group 1: 0/24, Group 2: 0/26;   Risk of bias: All domain –Low, Random sequence generation - Low, Allocation concealment –

Study	Hwang 2017[660]
Low, Blinding of outcome assessment - Low, Incomplete outcome data - Low, Selective reporting – Low, Groups balanced at baseline – Low, Groups received same co-interventions - Low; Indirectness of outcome: No indirectness Protocol outcome 2: Exercise capacity - Actual outcome: 6-minute walk distance at 24 weeks; Between group difference (CI): 2 (-36 to 41); Risk of bias: All domain –Low, Random sequence generation - Low, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - Low, Selective reporting – Low, Groups balanced at baseline – Low, Groups received same co-interventions - Low; Indirectness of outcome: No indirectness - Actual outcome: 10m walk test (fast) at 24 weeks; Between group difference (CI): 1 (0.9 to 1.1); Risk of bias: All domain –Low, Random sequence generation - Low, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - Low, Selective reporting – Low, Groups balanced at baseline – Low, Groups received same co-interventions - Low; Indirectness of outcome: No indirectness - Actual outcome: Grip strength (kg) at 24 weeks; Between group difference (CI): 1 (-2 to 4); Risk of bias: All domain –Low, Random sequence generation - Low, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - Low, Selective reporting – Low, Groups balanced at baseline – Low, Groups received same co-interventions - Low; Indirectness of outcome: No indirectness Protocol outcome 3: Quality of life - Actual outcome: EQ-5D (utility) at 24 weeks; Between group difference (CI): -0.06 (-0.16 to 0.03); Risk of bias: All domain –Low, Random sequence generation - Low, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - Low, Selective reporting – Low, Groups balanced at baseline – Low, Groups received same co-interventions - Low; Indirectness of outcome: No indirectness - Actual outcome: MLWHFQ at 24 weeks; Between group difference (CI): -4 (-17 to 10); Risk of bias: All domain –Low, Random sequence generation - Low, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - Low, Selective reporting – Low, Groups balanced at baseline – Low, Groups received same co-interventions - Low; Indirectness of outcome: No indirectness Protocol outcome 4: Adherence - Actual outcome: Attendance at exercise sessions at 12 weeks; Between group difference (CI): 6 (2 to 9); Risk of bias: All domain –Low, Random sequence generation - Low, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - Low, Selective reporting – Low, Groups balanced at baseline – Low, Groups received same co-interventions - Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	CV mortality, all cause hospitalisation, HF-related hospitalisation, health service use, adverse events(withdrawal from the exercise programme)

Study	Karapolat 2009[729]

Study	Karapolat 2009[729]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=74)
Countries and setting	Conducted in Turkey; Setting: Single centre
Line of therapy	Adjunctive to current care
Duration of study	Intervention: 8 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: all patients with heart failure, Standard echocardiography and Tissue Doppler Imaging echocardiography
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with: heart failure as a result of ischaemic and dilated cardiomyopathy, clinical stability for at least 3 months, left ventricular ejection fraction ≤ 40%, NYHA functional class II-III, optimal and standard pharmacological treatment, the ability to speak and understand Turkish, absence of psychiatric disease, the ability to remain stable during exercise tests, and willingness to volunteer to participate in this study.
Exclusion criteria	Neurological orthopaedic, peripheral vascularisation, or severe pulmonary disease; NYHA class IV patients; unstable angina pectoris; poorly controlled or exercise-induced cardiac arrhythmias; recent acute coronary syndrome or revascularisation (≤ 3 months); significant valvular disease; atrial fibrillation; uncontrolled arterial hypertension; and performing exercise training at regular intervals during the previous 6 weeks.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Home-based CR – 44.05 (11.49), Centre-based – 45.16 (13.58). Gender (M:F) 3:2. Ethnicity: NR
Further population details	
Extra comments	
Indirectness of population	No indirectness
Interventions	(n=37) Intervention 1: Home-based cardiac rehabilitation. All sessions were performed at home. A specific program was designed for each patient based on individual muscle strength, joint flexibility, and aerobic endurance. Exercise sessions included flexibility exercises, aerobic exercises, and breathing exercises. The flexibility exercises focused on range of motion and included exercises designed to stretch the cervical and lumbar spine and the upper and lower extremities. Training HR measured by monitor. Walking with a pedometer. No information on length, number and intensity of sessions given. Exercise only. Weekly telephone call.

Study	Karapolat 2009[729]
	Duration 8 weeks. Concurrent medication/care: breathing and flexibility exercises (n=37) Intervention 2: Centre-based cardiac rehabilitation. All rehabilitation sessions were supervised by a physician. A specific program was designed for each patient based on individual muscle strength, joint flexibility, and aerobic endurance. Exercise sessions included flexibility exercises, aerobic exercises, and breathing exercises. The flexibility exercises focused on range of motion and included exercises designed to stretch the cervical and lumbar spine and the upper and lower extremities. Training HR measured by monitor. Treadmill walking. 3 sessions/week of 45-60 min (incl. 5 min warm-up, 30 min aerobic exercise and 5 min cool-down) at an intensity of 60-70% heart rate reserve, level 13-15 on the Borg scale. Duration 8 weeks. Concurrent medication/care: breathing and flexibility exercises
Funding	"We have no support for this study"

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HOME-BASED versus CENTRE-BASED CARDIAC REHABILITATION

Protocol outcome 1: All-cause mortality
- Actual outcome: all-cause mortality at 8 weeks; Group 1: 0/37, Group 2: 0/37; Risk of bias: All domain –High, Random sequence generation - High, Allocation concealment – Low, Blinding of outcome assessment - High, Incomplete outcome data - Low, Selective reporting – Low, Groups balanced at baseline – Low, Groups received same co-interventions - Low; Indirectness of outcome: No indirectness37

Protocol outcome 2: Exercise capacity
- Actual outcome: exercise capacity VO2 at 2 months; Group 1: mean 18.12 (SD 6.00); n=36, Group 2: mean 19.43 (SD 4.59); n=32; Risk of bias: All domain –High, Random sequence generation - High, Allocation concealment – Low, Blinding of outcome assessment - High, Incomplete outcome data - Low, Selective reporting – Low, Groups balanced at baseline – Low, Groups received same co-interventions - Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Withdrawal
- Actual outcome: completers at 2 months; Group 1: 36/37, Group 2: 32/37; Risk of bias: All domain –High, Random sequence generation - High, Allocation concealment – Low, Blinding of outcome assessment - High, Incomplete outcome data - Low, Selective reporting – Low, Groups balanced at baseline – Low, Groups received same co-interventions - Low; Indirectness of outcome: No indirectness

Protocol outcome 4: Adherence
- Actual outcome: attendance at exercise sessions at 2 months; Group 1: 87.5% (n=32/37), Group 2: 90.0% (n=33/37) ; Risk of bias: All domain –High, Random

Study	Karapolat 2009[729]
sequence generation - High, Allocation concealment – Low, Blinding of outcome assessment - High, Incomplete outcome data - Low, Selective reporting – Low, Groups balanced at baseline – Low, Groups received same co-interventions - Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	CV mortality, health-related quality of life, all cause hospitalisation, HF-related hospitalisation, health service use

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Study (subsidiary papers)	Piotrowicz 2010[1151] (Piotrowicz 2015[1152])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=152)
Countries and setting	Conducted in Poland; Setting: Single centre
Line of therapy	Adjunctive to current care
Duration of study	Intervention: 8 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: all patients with heart failure, two-dimensional echocardiography
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	(i) patients of either sex with any aetiology of left ventricular systolic HF (as defined in the European Society of Cardiology (ESC) guidelines) diagnosed for > 3 months; (ii) with a left ventricular ejection fraction ≤ 40% on echocardiography; (iii) in NYHA class II or III; (iv) who were clinically stable and receiving an optimal and stable medication regimen for at least 4 weeks before enrolment; and (v) who were able to exercise using the new model of home-based exercise.
Exclusion criteria	(i) NYHA class I or IV; (ii) unstable angina; (iii) a history of an acute coronary syndrome within the last month, coronary artery bypass grafting within the last 2 months, or initiation of cardiac resynchronization therapy (CRT) within the last year; (iv) symptomatic and/or exercise-induced cardiac arrhythmia or conduction disturbances; (v) valvular or congenital heart disease requiring surgical treatment; (vi) hypertrophic cardiomyopathy; (vii) severe pulmonary hypertension or other severe pulmonary disease; (viii) uncontrolled hypertension; (ix) anaemia (haemoglobin,10.0 g/dL); (x) acute and/or decompensated non-cardiac disease; (xi) physical disability related to severe or neurological problems; (xii) acute or chronic inflammatory disease; (xiii) cancer; (xiv) severe psychiatric disorder; and (xv) patient refusal to participate.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Home-based CR – 56.4 (10.9), Centre-based – 60.5 (8.8). Gender (M:F) 9:1. Ethnicity: NR
Further population details	Ischaemic: Home-based CR: 73.3% Centre-based CR:85.7%

Study (subsidiary papers)	Piotrowicz 2010[1151] (Piotrowicz 2015[1152])
	Non-ischaemic: Home-based CR: 26.7% Centre-based CR: 14.3% MI: Home-based CR: 64.0% Centre-based CR: 78.6%
Extra comments	
Indirectness of population	No indirectness
Interventions	(n=77) Intervention 1: Home-based tele-monitored cardiac rehabilitation**.** In order to make the exercise test (ET) safe for HF patients, the following recommendations were taken into account: (i) special attention was paid to appropriate patient risk stratification before CR; (ii) contraindications to ET were never overlooked; (iii) in patients with an implantable cardioverter defibrillator (ICD), maximal training HR was set at 20 beats/min lower than the defibrillator discharge threshold; and (iv) in patients with a pacemaker, the rate–response function was switched on, enabling HR adjustment to the physical effort which facilitates reaching the desired training HR. Exercise training was planned individually for each patient during hospitalization. The chosen workload reflected individual effort tolerance with regard to: (i) perceived exertion according to the Borg scale and (ii) the training HR range established individually for each patient. In line with the standards, the assumption was that patients should not exceed perceived moderate exertion during the ET (i.e. a score of 11 on the Borg scale). All patients received an EHO 3 device and a mobile phone. The EHO 3 device enabled recording of ECG data from three pre-cordial leads and transmittal via a mobile phone to the monitoring centre. Before beginning a training session, patients used the mobile phone to answer a series of questions regarding their present condition, including fatigue, dyspnoea, blood pressure, body mass and medication taken. Patients then transmitted resting ECG data to the monitoring centre. If no contraindications to training were identified, patients were given permission to start the training session. This could take place where the patient wished to exercise. Continuous walking training on level ground. 3 sessions/week of 20-45 min (i) warm-up: 5-10mins (breathing and light exercises, calisthenics), (ii) basic aerobic endurance training for 10-30 mins (walking), and (iii) a 5 min cooling down (a period when patients could calm down and relax). Individually tailored intensity. Duration 8 weeks. Concurrent medication/care: All patients & partners participated in an education programme: how to measure HR, BP, and body weight; evaluate signs and symptoms; level perceived exertion & how to perform exercise training. Each patient received psychological support. (n=75) Intervention 2: Centre-based cardiac rehabilitation (outpatient-based standard CR). As above apart from: Cycle ergometer. 3 sessions/week of 20-45 min (i) warm-up: 5-10mins (breathing and light exercises, calisthenics), (ii)

Study (subsidiary papers)	Piotrowicz 2010[1151] (Piotrowicz 2015[1152])
	basic aerobic endurance training for 10-30 mins (walking), and (iii) a 5 min cooling down (a period when patients could calm down and relax). Individually tailored intensity. Before each outpatient session, patients in this group answered the same questions as the home-based exercise group. The ECG was analysed, and if no contraindications were identified, patients were given permission to start the training session. ECG, HR and BP were measured during the training session. Duration 8 weeks. Concurrent medication/care: All patients & partners participated in an education programme: how to measure HR, BP, and body weight; evaluate signs and symptoms; level perceived exertion & how to perform exercise training. Each patient received psychological support.
Funding	National Institute of Cardiology, Warsaw, Poland (study number 2.9/I/06)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HOME-BASED versus CENTRE-BASED CARDIAC REHABILITATION

Protocol outcome 1: Mortality
- Actual outcome: Mortality at 2 months; Group 1: 1/75, Group 2: 0/77; Risk of bias: All domain –Very high, Random sequence generation - High, Allocation concealment – High, Blinding of outcome assessment - High, Incomplete outcome data - High, Selective reporting – Low, Groups balanced at baseline – Low, Groups received same co-interventions - Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Quality of life
- Actual outcome: SF-36 physical summary scale at 2 months; Group 1: mean 50.27 (SD 17.06); n=, Group 2: mean 51.37 (SD 19.60); n=; SF-36 Questionnaire physical component 0-100 Top=High is good outcome; All domain –Very high, Random sequence generation - High, Allocation concealment – High, Blinding of outcome assessment - High, Incomplete outcome data - High, Selective reporting – Low, Groups balanced at baseline – Low, Groups received same co-interventions - Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Quality of life
- Actual outcome: SF-36 mental summary scale at 2 months Group 1: mean 21.68 (SD 12.46); n=, Group 2: mean 18.56 (SD 9.18); n=; SF-36 Questionnaire mental component 0-100 Top=High is good outcome; All domain –Very high, Random sequence generation - High, Allocation concealment – High, Blinding of outcome assessment - High, Incomplete outcome data - High, Selective reporting – Low, Groups balanced at baseline – Low, Groups received same co-interventions - Low; Indirectness of outcome: No indirectness

Protocol outcome 4: Exercise capacity
- Actual outcome: exercise capacity (6-MWT) at 2 months; Group 1: mean 462 (SD 91); n=75, Group 2: mean 462 (SD 92); n=56; All domain –Very high, Random sequence generation - High, Allocation concealment – High, Blinding of outcome assessment - High, Incomplete outcome data - High, Selective reporting – Low, Groups

Study (subsidiary papers)	Piotrowicz 2010[1151] (Piotrowicz 2015[1152])
balanced at baseline – Low, Groups received same co-interventions - Low; Indirectness of outcome: No indirectness Protocol outcome 5: Exercise capacity - Actual outcome: exercise capacity VO2 at 2 months; Group 1: mean 19.7 (SD 5.2); n=75, Group 2: mean 19.0 (SD 4.6); n=56; All domain –Very high, Random sequence generation - High, Allocation concealment – High, Blinding of outcome assessment - High, Incomplete outcome data - High, Selective reporting – Low, Groups balanced at baseline – Low, Groups received same co-interventions - Low; Indirectness of outcome: No indirectness Protocol outcome 6: Withdrawal - Actual outcome: completers at 2 months; Group 1: 75/77, Group 2: 56/75; Risk of bias: ?; Indirectness of outcome: No indirectness Protocol outcome 7: Adherence - Actual outcome: number of patients who carried out the prescribed exercise training (home group: daily telephone contacts with monitoring centre; centre group: attendance at supervised sessions) at 2 months; Group 1: 77/77, Group 2: 59/75; All domain –Very high, Random sequence generation - High, Allocation concealment – High, Blinding of outcome assessment - High, Incomplete outcome data - High, Selective reporting – Low, Groups balanced at baseline – Low, Groups received same co-interventions - Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	all cause hospitalisation, HF-related hospitalisation, health service use

F.10 Monitoring

Study (subsidiary papers)	BATTLESCARRED trial: Lainchbury 2009[826] (Lainchbury 2006[825])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=364)
Countries and setting	Conducted in New Zealand; Setting: Recruited in acute hospital
Line of therapy	Adjunctive to current care

Duration of study	Intervention time: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Mixed:
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients hospitalised for heart failure aged > 18 years, symptomatic HF defined by Framingham criteria and satisfying the ESC diagnostic guidelines, precipitating admission, NT-proBNP > 50 pmol/L immediately prior to randomisation. "Recruitment deliberately included elderly patients and patients with preserved LVEF"
Exclusion criteria	Active mycarditis/pericarditis, life expectancy < 24 months due to noncardiovascular disease, severe hepatic or pulmonary disease, severe renal impairment, severe valvular disease, or candidacy for cardiac transplantation.
Recruitment/selection of patients	3,576 patients admitted to Christchurch hospital with heart failure were screened; 823 patients were approached and 448 consented to participate (of whom 84 were subsequently excluded because NT-proBNP levels were < 50 pmol/L); study period: 2001-2006
Age, gender and ethnicity	Age - Mean (range): 75 (31-89). Gender (M:F): 64:36. Ethnicity: Not stated
Further population details	1. Ejection fraction: Mixed 2. Patient risk status: Recruited following acute admission
Extra comments	Severity: NYHA class I - 10%, II - 67%, III - 23%, IV - 2%, LVEF 39% Clinical (mean): SBP 125, DM 22%, HxMI 45%, creatinine 120 umol/l, NT-preBNP 238pmol/l
Indirectness of population	No indirectness
Interventions	(n=121) Intervention 1: Biomarker monitoring - NTproBNP. Target NT-proBNP < 1300pg/mL. Therapy

	intensified according to stepwise algorithm to achieve target NT-proBNP and congestion score < 2. Follow up 2 weekly until treatment target met, then 3 monthly (total 3 years). HF clinic. Duration Intervention 2y, plus further year of follow-up. Concurrent medication/care: Also received instructions on monitoring weight, dietary sodium restriction, rest after diuretic administration, exercise, avoidance of licorice + NSAIDS + alcohol, need for influenza vaccination (n=121) Intervention 2: Usual care - Usual care: clinical monitoring. Clinical target - Framingham HF score of < 2. Therapy intensified to achieve target score. Follow up 2 weekly until treatment target met, then 3 monthly (total 3 years). HF clinic. Duration intervention 2y, plus further year of follow-up. Concurrent medication/care: Also received instructions on monitoring weight, dietary sodium restriction, rest after diuretic administration, exercise, avoidance of licorice + NSAIDS + alcohol, need for influenza vaccination (n=122) Intervention 3: Usual care - Usual care: no monitoring protocol. No contact with research team after randomisation, except for 3-monthly review of outcomes. Duration 3 years. Concurrent medication/care: Management undertaken in primary care with or without additional attendance of hospital cardiology or specialist heart failure clinics at the request of patient's primary care physician
Funding	Other author(s) funded by industry (Supported by grants from Health Research Council of New Zealand and the National Heart Foundation of New Zealand. Two authors receive honoraria from Roche diagnostics)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NTPROBNP versus USUAL CARE: CLINICAL MONITORING

Protocol outcome 1: Quality of life at 12 months
- Actual outcome for Mixed: MLWHFQ at 12 months; Group 1: mean 28.8 pt (SD 21.6); n=121, Group 2: mean 26.5 pt (SD 22); n=121; scored from 0-105 Top=High is poor outcome; No analysed not given.
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Reported in HTA as low risk performance bias, but due to subjective outcome rated 'high' here; missing data not reported and presumed to be negligible; Indirectness of outcome: No indirectness ; Baseline details: age 76/76, male 63/67%, DM 23/20%, NYHA >II 20/27%, multiple HF admissions 31/32%, NT-proBNP 2012/1996; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Adverse events - renal function
- Actual outcome for Mixed: eGFR at 12 months; Group 1: mean 55 ml/min (SD 17); n=121, Group 2: mean 59 ml/min (SD 19); n=121
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Reported in HTA as low risk performance bias; missing data not reported, felt to be more likely for this outcome, and also close scores, therefore downgraded; Indirectness of outcome: No indirectness ; Baseline details: age 76/76, male 63/67%, DM 23/20%, NYHA >II 20/27%, multiple HF admissions 31/32%, NT-proBNP 2012/1996; Group 1 Number missing: 0; Group 2 Number missing: 0

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NTPROBNP versus USUAL CARE: NO MONITORING PROTCOL

Protocol outcome 1: Mortality
- Actual outcome for Age < 75 years: Mortality (relative risk) at 3 years; Group 1: 9/58, Group 2: 20/64
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Reported in HTA as low risk performance bias, missing data not reported and presumed to be negligible; Indirectness of outcome: No indirectness ; Baseline details: age 76/75, male 63/62%, creatinine 120/119, NYHA class >II 20/26%, multiple HF admissions 31/29%, NT-proBNP 238/238; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Age >= 75 years: Mortality (relative risk) at 3 years; Group 1: 31/63, Group 2: 20/58Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Reported in HTA as low risk performance bias, missing data not reported and presumed to be negligible; Indirectness of outcome: No indirectness ; Baseline details: age 76/75, male 63/62%, creatinine 120/119, NYHA class >II 20/26%, multiple HF admissions 31/29%, NT-proBNP 238/238; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Unplanned hospitalisation (all-cause)
- Actual outcome for Age < 75 years: Heart failure admissions (relative risk) at 3 years; Group 1: 17/58, Group 2: 23/64Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Reported in HTA as low risk performance bias, missing data not reported and presumed to be negligible; Indirectness of outcome: Serious indirectness, Comments: HF rather than all-cause admission; Baseline details: age 76/75, male 63/62%, creatinine 120/119, NYHA class >II 20/26%, multiple HF admissions 31/29%, NT-proBNP 238/238; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Age >= 75 years: Heart failure admissions (relative risk) at 3 years; Group 1: 27/63, Group 2: 18/58
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Reported in HTA as low risk performance bias; Indirectness of outcome:

Serious indirectness, Comments: HF rather than all-cause admission; Baseline details: age 76/75, male 63/62%, creatinine 120/119, NYHA class >II 20/26%, multiple HF admissions 31/29%, NT-proBNP 238/238; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Adverse events - hyperkalaemia; Adverse events - hypotension; Adverse events - arrhythmic events; Adverse events - bradycardia

Study (subsidiary papers)	Berger 2010[157] (Adlbrecht 2011[18])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	2 (n=278)
Countries and setting	Conducted in Austria; Setting: Eight Viennese hospitals
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Mixed
Subgroup analysis within study	Not applicable
Inclusion criteria	Clinical signs and symptoms of cardiac decompensation during the present hospitalisation, NYHA class III or IV at admission, cardiothoracic ratio > 0.5 or LVEF < 40% by echo
Exclusion criteria	Nil stated
Recruitment/selection of patients	July 2003 - September 2004, 278 of 441 eligible patients randomised (n=21 ineligible, n=163 refused)
Age, gender and ethnicity	Age - Mean (SD): GP arm 71(13), biomarker 70(12). Gender (M:F): 180:98. Ethnicity: Not stated
Further population details	1. Ejection fraction: Not stated / Unclear 2. Patient risk status: Recruited following acute admission
Extra comments	.

Indirectness of population	No indirectness
Interventions	(n=90) Intervention 1: Usual care - Usual care: no monitoring protocol. After discharge, management plan sent to the appropriate primary care physician, who then became responsible for their HF follow-up. Could be referred to hospital if necessary, but no contact with the research team.. Duration 15 months. Concurrent medication/care: As above (n=96) Intervention 2: Usual care - Usual care: clinical monitoring. Enhanced care including two scheduled doctor visits and four scheduled nurse visits where physical exam performed and functional status documented. Further visits at clinical discretion. Medication up-titrated according to guidelines. . Duration 15 months. Concurrent medication/care: Other management as usual Comments: This arm was considered in the aggregate data of the HTA, and therefore not further extracted here (n=92) Intervention 3: Biomarker monitoring - NTproBNP. Target NT-proBNP < 2200 pg/L. Visits and therapy intensified according to set protocol until reach target NT-proBNP or on maximally tolerated doses of medication. Levels taken at 0 weeks, then 1, 3, 6 and 12 months (total 15 months). HF clinic.. Duration 15 months. Concurrent medication/care: Other care as normal
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: USUAL CARE: NO MONITORING PROTOCOL versus NTPROBNP

Protocol outcome 1: Mortality
- Actual outcome for Mixed: Mortality (relative risk) at 15 months; Group 1: 35/90, Group 2: 20/92
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Only concern is lack of blinding; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Mixed: HF Hospitalisation (relative risk) at 15 months; Group 1: 55/90, Group 2: 26/92
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover -

Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Only concern is lack of blinding; Indirectness of outcome: Serious indirectness, Comments: Not protocol outcome of "all-cause" hospitalisation; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at 12 months ; Unplanned hospitalisation (all-cause); Adverse events - hyperkalaemia; Adverse events - renal function; Adverse events - hypotension; Adverse events - arrhythmic events; Adverse events - bradycardia

Study	Christchurch Pilot: Troughton 2000[1405]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=69)
Countries and setting	Conducted in New Zealand; Setting: recruited after admission for HF decompensation (29%) or from specialist cardiology clinic
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: At least six months, median 9 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Mixed
Subgroup analysis within study	Not applicable
Inclusion criteria	LVEF < 40%, NYHA class II-IV, treatment with ACEi, loop diuretic with or without digoxin
Exclusion criteria	recent acute coronary syndrome (within 3 months), pending cardiac transplant or revasc, severe stenotic

	valvular heart disease, severe pulmonary, hepatic or renal disease
Recruitment/selection of patients	1998-1999
Age, gender and ethnicity	Age - Other: Int 68, control 72 (variance data not given). Gender (M:F): 76:24. Ethnicity: Not stated
Further population details	1. Ejection fraction: Reduced ejection fraction 2. Patient risk status: Not applicable (mixed).
Indirectness of population	No indirectness
Interventions	(n=33) Intervention 1: Biomarker monitoring - BNP. Target NT-proBNP level < 1700 pg/mL. Therapy intensified according to stepwise algorithm to achieve target. Follow up every 3 months unless treatment targets not met, when increased to two-weekly (total 9.5 months). HF clinic. Duration Ave 9.6 months. Concurrent medication/care: Patients were assessed for Framingham score at every visit and blood taken for biochemistry. At baseline they had echo, 6 min walk test and cycle ergonometry, and completed MLWHFQ. Echo was repeated at three months. (n=36) Intervention 2: Usual care - Usual care: clinical monitoring. Clinical target - Framingham HF score of < 2. Therapy intensified according to stepwise algorithm to achieve target score. Follow up every 3 months unless treatment targets not met when increased to every two weeks (total 9.5 months). HF clinic. Duration Ave 9.6 months. Concurrent medication/care: Patients were assessed for Framingham score at every visit and blood taken for biochemistry. At baseline they had echo, 6 min walk test and cycle ergonometry, and completed MLWHFQ. Echo was repeated at three months.
Funding	Academic or government funding (Health Research Council of New Zealand)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BNP versus USUAL CARE: CLINICAL MONITORING

Protocol outcome 1: Unplanned hospitalisation (all-cause)
- Actual outcome for Mixed: All-cause admissions (count rate) at average 9.6 months; rate ratio: 0.74 SE 0.314;

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Insufficient info on randomisation and slight imbalance at baseline characteristics; Indirectness of outcome: No indirectness ; Baseline details: Recruited after inpatient stay 30v28%. Confounders appear similar: Age 68v72, diabetes 12/14, average NYHA class 2.3/2.3; except for BNP 217v251 slightly lower in intervention group (no variance data given - may increase effect); Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Adverse events - hypotension - Actual outcome for Mixed: symptomatic hypotension at average 9.6 months; Group 1: 7/33, Group 2: 4/36 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Insufficient info on randomisation and slight imbalance at baseline characteristics. No clear criteria given for diagnosing symptomatic hypotension; Indirectness of outcome: No indirectness ; Baseline details: 64v67% HTN at baseline. Confounders appear similar: Age 68v72, diabetes 12/14, average NYHA class 2.3/2.3; except for BNP 217v251 slightly lower in intervention group (no variance data given - may increase effect); Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Adverse events - renal function - Actual outcome for Mixed: creatinine clearance at 6 months; Group 1: mean 52.2 ml/min (SD 4.2); n=33, Group 2: mean 51 ml/min (SD 4.2); n=36 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Insufficient info on randomisation and slight imbalance at baseline characteristics; Indirectness of outcome: No indirectness ; Baseline details: CC slightly higher in intervention group 60(4.2)v54(4.2) (may reduce effect). Confounders appear similar: Age 68v72, diabetes 12/14, average NYHA class 2.3/2.3; except for BNP 217v251 slightly lower in intervention group (no variance data given - may increase effect); Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Mortality; Quality of life at 12 months ; Adverse events - hyperkalaemia; Adverse events - arrhythmic events; Adverse events - bradycardia

Study	**GUIDE-IT: Effect of NT-proBNP therapy in patients with HF and reduced ejection fraction trial: Felker 2017[458]**

Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=894)
Countries and setting	Conducted in Canada, USA; Setting: Patients were enrolled at 45 sites in the United States and Canada between January 2013 and July 2016.
Line of therapy	1st line
Duration of study	Intervention and follow-up: between 12 and 24 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Mixed
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with chronic heart failure with reduced ejection fraction (HFrEF) with an ejection fraction of 40% or less, a history of prior HF event (hospitalisation for HF, emergency department visit for HF, or outpatient treatment with intravenous diuretics for HF) within the prior 12 months, and an NT-proBNP level of more than 2000 pg/mL or BNP of more than 400 pg/mL within the prior 30 days.
Exclusion criteria	Patients were excluded if they had an acute coronary syndrome or revascularisation procedure within the prior 30 days, cardiac resynchronisation therapy within the prior 3 months, end-stage renal disease, or anticipated heart transplant or mechanical cardiac support within the next 12 months.
Recruitment/selection of patients	The study enrolled patients with high-risk HF, as characterised by a low ejection fraction (40% or less), significantly elevated NT-proBNP, and a history of prior HF hospitalisation (or equivalent) in the past year.
Age, gender and ethnicity	Age - Median (IQR): NT-proBNP group: 62 (51-70) years, usual care group: 64 (54-72) years. Gender (M:F): 2/1. Ethnicity: NT-proBNP group: White (54%), Black (39%), Hispanic (7%), Other (7%); usual care group:

	White (59%), Black (35%), Hispanic (6%), Other (6%)
Further population details	1. Ejection fraction: Reduced ejection fraction (ejection fraction of 40% or less). 2. Patient risk status: Recruited following acute admission (high risk status: a history of prior HF event (hospitalisation for HF, emergency department visit for HF, or outpatient treatment with intravenous diuretics for HF) within the prior 12 months, and an NT-proBNP level of more than 2000 pg/mL or BNP of more than 400 pg/mL within the prior 30 days.).
Indirectness of population	No indirectness
Interventions	(n=446) Intervention 1: Biomarker monitoring - NTproBNP. Biomarker-guided therapy: clinicians were instructed to titrate HF therapy to target an NT-proBNP level of less than 1000 pg/mL. Specific adjustments of therapy for individual patients were at the discretion of the treating physician, but sites were encouraged to prioritise titration of neurohormonal antagonists over diuretics unless there was clinical evidence of congestion or volume overload. Patients randomised to this group used local laboratory NT-proBNP measurements to make decisions about titration of HF therapy. . Duration intervention and follow-up of between 12-24 months. Concurrent medication/care: All patients in either group also had blinded NT-proBNP concentrations measured in a core laboratory at each study visit. For patients in either group, investigators were provided with the most recent AHA/ACC practice guidelines for the management of HF and specific information on target doses of proven medical therapies. After an initial visit at 2 and 6 weeks,visits occurred every 3 months throughout the remainder of the study. After therapy adjustment for HF (whether driven by NT-proBNP levels or clinical reasoning), patients had a 2-week follow-up visit for reassessment until therapeutic targets were reached. Patients hospitalised for HF during the study had a 2-4 week follow-up study visit post discharge to reassess and adjust medical therapy, which includes all standard follow-up assessments as described above. Indirectness: No indirectness (n=448) Intervention 2: Usual care - Usual care: clinical monitoring. Usual care group: patients received care based on the 2013 AHA/ACC guideline recommendations. Investigators were provided with specific information on evidence-based target doses of neurohormonal antagonists. Diuretics were titrated based on the clinical judgment of the treating physician. Importantly, routine assessment of NPs was not performed in the usual care group except for compelling medical reasons, consistent with current guidelines. . Duration

	intervention and follow-up of between 12-24 months. Concurrent medication/care: All patients in either group also had blinded NT-proBNP concentrations measured in a core laboratory at each study visit. For patients in either group, investigators were provided with the most recent AHA/ACC practice guidelines for the management of HF and specific information on target doses of proven medical therapies. After an initial visit at 2 and 6 weeks, visits occurred every 3 months throughout the remainder of the study. After therapy adjustment for HF (whether driven by NT-proBNP levels or clinical reasoning), patients had a 2-week follow-up visit for reassessment until therapeutic targets are reached. Patients hospitalised for HF during the study had a 2-4 week follow-up study visit post discharge to reassess and adjust medical therapy, which includes all standard follow-up assessments as described above. Indirectness: No indirectness
Funding	Academic or government funding (and support provided by a pharmaceutical company)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NTPROBNP versus USUAL CARE: CLINICAL MONITORING

Protocol outcome 1: Mortality
- Actual outcome for Mixed: all-cause mortality at 24 months; Group 1: 66/446 ; Group 2:77/448;
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 49; Group 2 Number missing: 44

Protocol outcome 2: Unplanned hospitalisation (all-cause)
- Actual outcome for Mixed: HF hospitalisations (count rate) at 24 months; Group 1: 350/446; Group 2: 277/448
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: HF rather than all-cause hospitalisations; Group 1 Number missing: 49; Group 2 Number missing: 44

Protocol outcome 3: Adverse events - hypotension
- Actual outcome for Mixed: Symptomatic hypotension at 12-24 weeks; Group 1: 7/446; Group 2: 2/448
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Adverse events - hyperkalaemia

<table>
<tr><td colspan="2">- Actual outcome for Mixed: Hyperkalaemia at 12-24 weeks; Group 1: 11/446; Group 2: 6/448
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 5: Adverse events - renal function
- Actual outcome for Mixed: Worsening renal function at 12-24 weeks; Group 1: 16/446; Group 2: 9/448
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 6: Adverse events - bradycardia
- Actual outcome for Mixed: Symptomatic bradycardia at 12-24 weeks; Group 1: 0/446; Group 2: 0/448
Risk of bias: All domain - ; Indirectness of outcome: No indirectness</td></tr>
<tr><td>Protocol outcomes not reported by the study</td><td>Quality of life at 12 months; Adverse events - arrhythmic events at during study</td></tr>
</table>

Study	OPTIMA trial: Krupika 2010[806]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=52)
Countries and setting	Conducted in Czech Republic; Setting: Not stated
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Mixed
Subgroup analysis within study	Not applicable
Inclusion criteria	Hospitalised for newly diagnosed or decompensated heart failure (HF) NYHA class III to IV and LVEF ≤45%
Exclusion criteria	Age under 18 or above 90 years old; acute coronary syndrome during the last three months, pulmonary embolism during the last three months, history of hepatic cirrhosis, severe renal insufficiency (creatinine >250 µmol/L), severe chronic lung disease, current malignant disease
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (range): int 71(36-89), 70(45-84). Gender (M:F): 67:33. Ethnicity: Not stated
Further population details	1. Ejection fraction: Reduced ejection fraction 2. Patient risk status: Recruited following acute admission

Extra comments	Severity: average NYHA 2.1 [despite inclusion criteria ?refers to after acute decompensation treated], hx HF int 15/12 control 42/12, LVEF 34% Clinical: CHD 62%, HTN 73%, creatinine 110 umol/l, BNP 680pg/ml
Indirectness of population	No indirectness
Interventions	(n=26) Intervention 1: Biomarker monitoring - BNP. Treatment guided by clinical status and by effort to normalise plasma BNP levels, although specific actions for those who were above target not given. Seen in clinic in tapering manner to a total of nine visits in two years. Duration 2 years. Concurrent medication/care: Not stated (n=26) Intervention 2: Usual care - Usual care: clinical monitoring. Treatment guided clinical assessment according to current guidelines. Seen in clinic in tapering manner to a total of nine visits in two years. Duration 2 years. Concurrent medication/care: Not stated
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BNP versus USUAL CARE: CLINICAL MONITORING

Protocol outcome 1: Mortality
- Actual outcome for Mixed: All-cause mortality at 2 years; Group 1: 4/26, Group 2: 3/26
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High, Other 2 - Low, Other 3 - Low, Comments - Not fully reported (data taken from cochrane review) downgraded under 'other', missing data not stated (plausible very low); Indirectness of outcome: No indirectness, Comments: Note that this result is taken from Cochrane review (McEllen 2016); Baseline details: UC group appear to have had HF for longer, and more have been prescribed ACE/ARB at baseline. Otherwise similar; Blinding details: As reported in Cochrane review "only patients were blind to treatment arm"; Group 1 Number missing: not reported; Group 2 Number missing: not reported
- Actual outcome for Mixed: HF admission at 2 years; Group 1: 6/26, Group 2: 13/26
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - High, Other 2 - Low, Other 3 - Low, Comments - Not fully reported (data taken from cochrane review)

downgraded under 'other', missing data not stated (plausible very low); Indirectness of outcome: Serious indirectness, Comments: Not all-cause admission. Also note that this result is taken from Cochrane review (McEllen 2016); Baseline details: UC group appear to have had HF for longer, and more have been prescribed ACE/ARB at baseline. Otherwise similar; Blinding details: As reported in Cochrane review "only patients were blind to treatment arm"; Group 1 Number missing: not reported; Group 2 Number missing: not reported	
Protocol outcomes not reported by the study	Quality of life at 12 months ; Unplanned hospitalisation (all-cause); Adverse events - hyperkalaemia; Adverse events - renal function; Adverse events - hypotension; Adverse events - arrhythmic events; Adverse events - bradycardia

Study	PRIMA trial: Eurlings 2010[444] Extraction for question 2
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=345 in main study)
Countries and setting	Conducted in Netherlands
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Mixed:
Subgroup analysis within study	Unclear: One of four subgroups is creatinine over the median level of 123umol/L (approximate eGFR 40-53ml/min at age 72y), not clear if pre-specified
Inclusion criteria	Patients hospitalised for decompensated, symptomatic HF, fulfilling the ESC diagnostic guideline criteria for acute HF; NT-proBNP levels at admission ≥ 1700 pg/mL and a decrease in levels of ≥ 10% at discharge.
Exclusion criteria	Life-threatening cardiac arrhythmia during index hospitalisation, urgent invaisve or surgical intervention performed or planned during the index hospitalisation, severe chronic obstructive pulmonary disease with FEV1 of < 1 l/s, pulmonary embolism < 3 months prior to admission, pulmonary hypertension not caused by LVSD, a non-HF related expected survival of < 1 year, patients undergoing hemodialysis or continuous ambulant peritoneal dialysis (a lesser degree of renal dysfunction was not an exclusion criterion)
Recruitment/selection of patients	Patients hospitalised for acute HF were screened and included during hospitalisation; study period 2004-

	2007. 163 patients had a creatinine level above the median of 123umol/L, therefore included in this analysis, as likely eGFR<60
Age, gender and ethnicity	Age - Mean (SD): 72(12) in whole control group. Gender (M:F): 148:197 in whole study. Ethnicity: Not stated
Further population details	1. Ejection fraction: Mixed 2. Patient risk status: Recruited following acute admission
Indirectness of population	No indirectness
Interventions	(n=81) Intervention 1: Biomarker monitoring - NTproBNP. Individual NT-proBNP level (lowest level at discharge or at 2 weeks follow-up). Therapy intensified according to clinical guidelines to maintain target NT-proBNP. Follow up 2 weeks, 1 month, then 3 monthly (total 24 months). HF clinic.. Duration 2 years. Concurrent medication/care: As usual (n=82) Intervention 2: Usual care - Usual care: clinic. Clinical target - clinical assessment. Therapy intensified at clinician discretion. Follow up 2 weeks, 1 month, then 3 monthly (total 24 months). HF clinic.. Duration 2 years. Concurrent medication/care: As usual
Funding	Other (Major funding from public sector, minor funding from variety of industry sources (Pfizer, Astra-Zeneca, Medtronic and Roche diagnostics))

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NTPROBNP versus USUAL CARE: CLINICAL MONITORING

Protocol outcome 1: Unplanned hospitalisation (all-cause)
- Actual outcome for Mixed: Days in hospital at 2 years; Group 1: mean 6.92 (SD 10.2); n=81, Group 2: mean 6.54 (SD 10.6); n=82
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Rated down as insufficient information about selection/randomisation and subgroup planning; Indirectness of outcome: Serious indirectness, Comments: Days in hospital is a proxy for protocol outcome all-cause hospitalisation rate ratio; Baseline details: Baseline details not given for subgroup; Group 1 Number missing: not reported; Group 2

Number missing: not reported	
Protocol outcomes not reported by the study	Mortality at during study; Quality of life at 12 months ; Adverse events - hyperkalaemia; Adverse events - renal function; Adverse events - hypotension; Adverse events - arrhythmic events; Adverse events - bradycardia

Study (subsidiary papers)	**PROTECT trial: Januzzi 2011[691] (Weiner 2013[1470], Mallick 2016[931], Ibrahim 2017[661], Bhardwaj 2010[164], Bhardwaj 2012[165])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=137)
Countries and setting	Conducted in USA
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: range 6-12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Mixed
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients ≥ 21 years; LVEF ≤ 40%; NYHA class II-IV symptoms; hospital admission, emergency department visit or outpatient therapy for destabilised HF at least once in the 6 months before enrollment
Exclusion criteria	Serum creatinine > 2.5 mg/dL, inoperable aortic valvular heart disease, life expectancy < 1 year due to causes other than HF, cardiac transplantation or revascularisation indicated or expected within 6 months, severe obstructive or restrictive pulmonary disease, coronary revasc within previous 3 months
Recruitment/selection of patients	single-centre; study period 2006-2010
Age, gender and ethnicity	Age - Mean (SD): 63(13). Gender (M:F): 85:15. Ethnicity: 87% white

Further population details	1. Ejection fraction: Reduced ejection fraction 2. Patient risk status: Recruited following acute admission
Extra comments	Severity: 55% > NYHA II, EF ave 28% Aetiology: 55% ischaemic Lab: ave eGFR 59ml/min/1.73², ave NT-proBNP 2000
Indirectness of population	No indirectness
Interventions	(n=76) Intervention 1: Biomarker monitoring - NTproBNP. Target NT-proBNP ≤ 1000 pg/mL. Therapy intensified according to clinical guidelines to maintain target NT-proBNP. Follow up as required to meet treatment target and then 3 monthly (total follow up min 6 months and max 12 months). HF clinic.. Duration at least 6 months. Concurrent medication/care: As usual (n=75) Intervention 2: Usual care - Usual care: clinical monitoring. Clinical target - clinical assessment. Therapy intensified at clinician discretion. Follow up as required to meet treatment target and then 3 monthly (total follow up min 6 months and max 12 months). HF clinic.. Duration at least 6 months. Concurrent medication/care: As usual
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NTPROBNP versus USUAL CARE: CLINICAL MONITORING

Protocol outcome 1: Mortality
- Actual outcome for Mixed: Cardiovascular deaths at ave 10 months; Group 1: 4/76, Group 2: 6/75
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Baseline variation unlikely to affect. Unblinded; Indirectness of outcome: Serious indirectness, Comments: Not all-cause mortality; Baseline details: Marginally higher BP and use of nitrates in control. Otherwise similar age, severity, ethnicity, DM, ICD, smoking status, creatinine, baseline ACE or beta-blocker use.; Group 1 Number missing: 0, Reason: not stated; Group 2 Number missing: 0, Reason: not stated

Protocol outcome 2: Quality of life at 12 months
- Actual outcome for Mixed: MLWHFQ follow-up score at across all follow-up visits (3,6,9 and 12 months); MLWHFQ 0-105 Top=High is poor outcome; Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Unblinded and subjective; Indirectness of outcome: No indirectness ; Group 1 Number missing: 8, Reason: not stated; Group 2 Number missing: 6, Reason: not stated

Protocol outcome 3: Adverse events - hyperkalaemia
- Actual outcome for Mixed: Hyperkalaemia/hypokalaemia at average 10 months; Group 1: 3/76, Group 2: 1/75
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Baseline variation unlikely to affect. No definition given.; Indirectness of outcome: Serious indirectness, Comments: Not merely hyperkalaemia; Baseline details: Baseline potassium 4.3(0.4)/4.2(0.4) and use of loop diuretics 89/94% similar. Marginally higher BP and use of nitrates in control. Otherwise similar age, severity, ethnicity, DM, ICD, smoking status, creatinine, baseline ACE use.; Group 1 Number missing: 0, Reason: not stated; Group 2 Number missing: 0, Reason: not stated
- Actual outcome for Mixed: Hypotension at average 10 months; Group 1: 4/76, Group 2: 0/75
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Differences at baseline may affect hypotension. No definition given for outcome; Indirectness of outcome: No indirectness; Baseline details: Marginally higher blood pressure in control group (SBP 108(15)/112(16)) and higher use of nitrates at baseline and follow-up (11/21%) may affect tendency to hypotension. Otherwise similar age, severity, ethnicity, DM, ICD, smoking status, creatinine, baseline ACE use; Group 1 Number missing: 0, Reason: not stated; Group 2 Number missing: 0, Reason: not stated

Protocol outcome 4: Adverse events - renal function
- Actual outcome for Mixed: mean eGFR at follow-up at 6 months; Group 1: mean 49.7 ml/min/1.73m² (SD 24.4); n=65, Group 2: mean 46.1 ml/min/1.73m² (SD 20.5); n=58
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Unblinded, 24% missing data for this outcome in experimental group vs 13% in control group; Indirectness of outcome: No indirectness; Group 1 Number missing: 18, Reason: not stated; Group 2 Number missing: 10, Reason: not stated
- Actual outcome for Mixed: acute renal failure (AKI) at average 10 months; Group 1: 4/76, Group 2: 3/75
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness, Comments: overlapping concept with mean eGFR; Baseline details: Baseline creatinine 1.46(0.5)/1.49(0.43) and use of loop diuretics 89/94% similar. Marginally higher BP and use of nitrates in control. Otherwise similar age, severity, ethnicity, DM, ICD, smoking status, creatinine, baseline ACE use.; Group 1 Number missing: 0, Reason: not stated;

Group 2 Number missing: 0, Reason: not stated Protocol outcome 5: Adverse events - arrhythmic events - Actual outcome for Mixed: Significant ventricular arrhythmia at average 10 months; Group 1: 7/76, Group 2: 4/75; Comments: Considered as part of primary efficacy outcome rather than adverse effect in study Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline AF 41v40%, digoxin use 29v33%. Marginally higher BP and use of nitrates in control. Otherwise similar age, severity, ethnicity, DM, ICD, smoking status, creatinine, baseline ACE use.; Group 1 Number missing: 0, Reason: not stated; Group 2 Number missing: 0, Reason: not stated - Actual outcome for Mixed: atrial fibrillation at average 10 months; Group 1: 2/76, Group 2: 5/75 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness; Baseline details: Baseline AF 41v40%, digoxin use 29v33%. Marginally higher BP and use of nitrates in control. Otherwise similar age, severity, ethnicity, DM, ICD, smoking status, creatinine, baseline ACE use.; Group 1 Number missing: 0, Reason: not stated; Group 2 Number missing: 0, Reason: not stated	
Protocol outcomes not reported by the study	Unplanned hospitalisation (all-cause); Adverse events - hypotension; Adverse events - bradycardia

Study	**Pufulete 2017**[1174]
Study type	Systematic Review
Number of studies (number of participants)	12 (n=2944)
Countries and setting	Conducted in Multiple countries; Setting: 11 studies in HF clinic (2 with additional primary care arms), 1 in primary care

	only
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 6-36 months
Method of assessment of guideline condition	Systematic review: method of assessment mixed
Stratum	Mixed
Subgroup analysis within study	Sys review – pre-specified in protocol: Age, EF%, sex, NYHA class, diabetes status, BNP at baseline
Inclusion criteria	IPD studies: Anguita: NR Northstar: ≥ 18 years, LVEF ≤ 45% at baseline visit, educated in HF, on optimal medical therapy with an ACEi/ARB and BB at recommended maximum or maximum tolerated dose, an ARA, an ICD and/or CRT if indicated, and an NT-proBNP ≥ 1000pg/mL after up-titration. Patients had to be euvolaemic and clinically stable. Shochat: NR Upstep: > 18 years, verified systolic HF and LVEF < 40% within last 6 months, NYHA class II-IV, signs and/or symptoms of worsening HF within the last month (requiring hospitalisation and/or intravenous diuretic treatment, metolazone, or increased daily dosages or diuretics and/or need of intravenous inotropic support), elevated BNP (>150ng/L for those aged < 75 years and > 300 ng/L for those aged > 75 years), standard ongoing HF treatment according to guidelines (ACEi or ARB, BB and diuretics if fluid retention existed). Aggregate studies: Troughton: LVEF < 40%, NYHA class II-IV, treatment with ACEi, loop diuretic with or without digoxin. TIME-CHF: Patients aged 60 years or older with dyspnea (NYHA class ≥ II with current therapy), a history of hospitalisation for heart failure within the last year, and an N-terminal BNP level of 400pg/mL or higher in patients < 75 years or 800 pg/mL or higher in patients ≥ 75 years. Berger: clinical signs and symptoms of cardiac decompensation during the present hospitalisation, NYHA class III or IV at admission, cardiothoracic ratio > 0.5 or LVEF < 40% by echo. PRIMA: patients hospitalised for decompensated, symptomatic HF, fulfilling the ESC diagnostic guideline criteria for acute HF; NT-proBNP levels at admission ≥ 1700 pg/mL and a decrease in levels of ≥ 10% at discharge. SIGNAL-HF: patients in primary care with a diagnosis of CHF and stable NYHA class II-IV, LVEF < 50%, elevated NT-proBNP levels (males > 800, females > 1000 ng/L). BATTLESCARRED: patients hospitalised for heart failure aged > 18 years, symptomatic HF defined by Framingham criteria

	and satisfying the ESC diagnostic guidelines, precipitating admission, NT-proBNP > 50 pmol/L immediately prior to randomisation. "Recruitment deliberately included elderly patients and patients with preserved LVEF". STARS-BNP: patients > 18 years with symptomatic (NYHA class II to III) systolic heart failure with LVEF < 45%, in stable condition (no hospital stay in previous month), treated by optimal medical therapy according to the European guidelines (diuretics, ACEis, or ARBs; and BBs), dosages of medication stable for at least 1 month prior to study. PROTECT: patients ≥ 21 years; LVEF ≤ 40%; NYHA class II-IV symptoms; hospital admission, emergency department visit or outpatient therapy for destabilised HF at least once in the 6 months before enrollment.
Exclusion criteria	IPD studies: Anguita: NR Northstar: plasma creatinine > 200 mmol/L, waiting for a heart transplan, valvular or ischemic heart disease with planned surgery or PCI, withdrawal of ACEi/ARBs, BB and ARAs due to a reversible cause of cardiomyopathy, malignancy with life expectancy < 5 years, and dementia. Shochat: NR Upstep: haemodynamically unstable patients on the waiting list for cardiac surgery/intervention, patients with an MI within the last 3 months, patients with haemodynamically significant valvular heart disease, patients with impaired renal or liver function, patients with severely decreased pulmonary function, patients with a limited life expectancy. Aggregate studies: Troughton: recent acute coronary syndrome (within 3 months), pending cardiac transplant or revasc, severe stenotic valvular heart disease, severe pulmonary, hepatic or renal disease. TIME-CHF: Dyspnea not mainly due to heart failure, valvular disease requiring surgery, acute coronary syndromes within the previous 10 days, angina pectoris higher than class II, revasc within the previous month, BMI > 35, serum creatinine> 2.49 mg/dL, life expectancy of < 3 years for noncardiovascular causes. Berger: N/A PRIMA: life-threatening cariac arrhythmia during index hospitalisation, urgent invaisve or surgical intervention performed or planned during the index hospitalisation, severe chronic obstructive pulmonary disease with FEV1 of < 1 l/s, pulmonary embolism < 3 months prior to admission, pulmonary hypertension not caused by LVSD, a non-HF related expected survival of < 1 year, patients undergoing hemodialysis or continuous ambulant peritoneal dialysis (a lesser degree of renal dysfunction was not an exclusion criterion). SIGNAL-HF: planned CV hospitalisation; stroke, acute MI or open heart surgery within 3 months before enrolment; mitral stenosis, aortic stenosis of clinical significance; patients already receiving optimal pharmacological treatment for CHF according to guidelines, serum creatinine ≥ 265 umol/L. BATTLESCARRED: active mycarditis/pericarditis, life expectancy < 24 months due to noncardiovascular disease, severe hepatic or pulmonary disease, severe renal impairment, severe valvular disease, or candidacy for cardiac transplantation. STARS-BNP: acute coronary syndrome within 3 months, chronic renal failure, documented hepatic cirrhosis, astham, or COPD.

	PROTECT: serum creatinine > 2.5 mg/dL, inoperable aortic valvular heart disease, life expectancy < 1 year due to causes other than HF, cardiac transplantation or revascularisation indicated or expected within 6 months, severe obstructive or restrictive pulmonary disease, coronary revasc within previous 3 months.
Recruitment/selection of patients	IPD studies: Anguita - consecutive patients discharged with a diagnosis of heart failure NYHA class III or IV from one Spanish cardiology department; study period 2006-2008. Northstar - patients recruited from 18 out of 40 public heart failure clinics in Denmark from Nov 2005 to Dec 2009. Shochat: NR; study period 2007-2010. Upstep: NR; study period 2006-2009. Aggregate studies: Troughton: patients recruited after hospital admission with decompensated heart failure or from a specialist cardiology outpatient clinic in New Zealand; study period 1998-1999. Time-CHF: 15 centres in Switzerland and Germany; study period 2003 - 2006. Berger: patients hospitalised for heart failure at 8 Viennese hospitals; study period 2003-2004. PRIMA: patients hospitalised for acute AF were screened and included during hospitalisation; study period 2004-2007. SIGNAL-HF: 45 primary care centres in Sweden; study period 2006-2009. BATTLESCARRED: 3,576 patients admitted to Christchurch hospital with heart failure were screened; 823 patients were approached and 448 consented to participate (of whom 84 were subsequently excluded because NT-proBNP levels were < 50 pmol/L); study period: 2001-2006. STARS-BNP: patients were included by CHF specialists from 17 university hospitals in France; study period NR. PROTECT: single-centre; study period 2006-2010.
Age, gender and ethnicity	Age - Range of means: 69-80. Gender (M:F): % male, range: 57-86. Ethnicity: NR
Further population details	1. Ejection fraction: Systematic review: mixed 2. Patient risk status: Systematic review: mixed
Indirectness of population	No indirectness
Interventions	(n=1471) Intervention 1: Biomarker monitoring - NTproBNP or BNP (mixed). Anguita: Target BNP level < 100 pg/mL. Therapy intensified to achieve target BNP. Follow up at 1, 2, 3, 6, 12 and 18 months (total 18 months). HF clinic. NORTHSTAR: Checklist to evaluate need for further investigation or intensification of therapy when NT-proBNP was > 30% from randomisation visit. Follow up every 1-3 months at the discretion of the investigator (total 2.5 years). HF clinic. Shochat: Therapy intensified if NT-proBNP was higher by > 30% from previous clinic visit. Follow up every 1-2 months

	(median 11 months (IQR 3-22 months)). HF clinic. UPSTEP: < 75 years - target BNP level < 150 pg/mL, ≥ 75 years - target BNP level < 300 pg/mL. Therapy intensified according to stepwise algorithm to achieve maximally tolerated or guideline recommended target doses. Follow up at weeks 2, 6, 10, 16, 24, 36, 48 and then every 6 months (total ≥ 12 months). HF clinic. Troughton: Target NT-proBNP level < 1700 pg/mL. Therapy intensified according to stepwise algorithm to achieve target. Follow up every 3 months unless treatment targets not met (total 9.5 months). HF clinic. TIME-CHF: Target NT-proBNP less than 2x upper limit of normal (<400 pg/mL for patients < 75 years; < 800 pg/mL for patients ≥ 75 years). Therapy intensified according to step-wise algorithm to achieve target NT-proBNP. Follow up 1, 3, 6, 12 and 18 months (total 18 months). HF clinic. Berger: NT-proBNP < 2200 pg/L. Therapy intensified according to set protocol to maintain target NT-proBNP. Follow up at 2 weeks, then 1, 3, 6 and 12 months (total 15 months). HF clinic. PRIMA: Individual NT-proBNp level (lowest level at discharge or at 2 weeks follow-up). Therapy intensified according to clinical guidelines to maintain target NT-proBNP. Follow up 2 weeks, 1 month, then 3 monthly (total 24 months). HF clinic. SIGNAL-HF: Individual NT-proBNP level (reduction 50% from baseline). Stepwise algorithm to increase therapy to achieve target NT-proBNP. Follow up 1, 3, 6 and 9 months (total 9 months). Primary care. BATTLESCARRED: Target NT-proBNP < 1300pg/mL. Therapy intensified according to stepwise algorithm to achieve target NT-proBNP and congestion score < 2. Follow up 2 weekly until treatment target met, then 3 monthly (total 3 years). HF clinic. STARS-BNP: Target BNP level < 100pg/mL. Therapy intensified according to clinical guidelines to maintain BNP. Follow up at months 1, 2 and 3 and then 3 monthly (total 15 months). HF clinic. PROTECT: Target NT-proBNP ≤ 1000 pg/mL. Therapy intensified according to clinical guidelines to maintain target NT-proBNP. Follow up as required to meet treatment target and then 3 monthly (total follow up min 6 months and max 12 months). HF clinic. . Duration 6-36 months. Concurrent medication/care: N/A (n=1413) Intervention 2: Usual care - Usual care: clinical monitoring. Anguita: Clinical target - Framingham HF score < 2. Therapy intensified to achieve target congestion score. Follow up 1, 2, 3, 6, 12 and 18 months (total 18 months). HF clinic. NORTHSTAR: Clinical target - clinical assessment. Therapy evaluated and intensified at clinician discretion. Follow up every 1-3 months at discretion of investigator (total 2.5 years). HF clinic. Shochat: Clinical target (if any) not reported. Treatment algorithm (if any) not reported. Follow up every 1-2 months (total median 11 months (IQR 3-22 months)). HF clinic. UPSTEP: Clinical target - clinical assessment. Therapy intensified at clinician discretion. Follow up weeks 2, 6, 10, 16, 24, 36, 48 and then every 6 months (total ≥ 12 months). HF clinic. Troughton: Clinical target - Framingham HF score of < 2. Therapy intensified according to stepwise algorithm to achieve

	target score. Follow up every 3 months unless treatment targets not met (total 9.5 months). HF clinic. TIME-CHF: Clinical target - NYHA class ≤ II. Therapy intensified according to stepwise algorithm to achieve target. Follow up 1, 3, 6, 12 and 18 months (total 18 months). HF clinic. Berger: Clinical target - clinical assessment. Therapy intensified at clinician discretion. Follow up at 2 weeks, then 1, 3, 6 and 12 months (total 15 months). HF clinic. PRIMA: Clinical target - clinical assessment. Therapy intensified at clinician discretion. Follow up 2 weeks, 1 month, then 3 monthly (total 24 months). HF clinic. SIGNAL-HF: Clinical target - clinical assessment. Therapy intensified at clinician discretion. Follow up 1, 3, 6 and 9 months (total 9 months). Primary care. BATTLESCARRED: Clinical target - Framingham HF score of < 2. Therapy intensified to achieve target score. Follow up 2 weekly until treatment target met, then 3 monthly (total 3 years). HF clinic. STARS-BNP. Clinical target - clinical assessment. Therapy intensified at clinician discretion. Follow up at months 1, 2 and 3 and then 3 monthly (total 15 months). HF clinic. PROTECT: Clinical target - clinical assessment. Therapy intensified at clinician discretion. Follow up as required to meet treatment target and then 3 monthly (total follow up min 6 months and max 12 months). HF clinic. . Duration 6-36 months. Concurrent medication/care: N/A Comments: 1 study out of 12 was a comparison with usual care in primary care (rather than clinic-based care). Also, some of the usual care groups included a clinical target and a protocolised treatment intensification strategy. (n=60) Intervention 3: Usual care - Usual care: mixed. No protocol reported for guiding monitoring and treatment in usual care arm. Duration 3-22 months. Concurrent medication/care: NA
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NTPROBNP OR BNP (MIXED) versus CLINICAL MONITORING

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NTPROBNP OR BNP (MIXED) versus CLINICAL MONITORING

Protocol outcome 1: Mortality
- Actual outcome for Age < 75 years: All-Cause Mortality (results of meta-analysis) at 12 months;(Results from IPD analysis):
Anguita (weight 3%) HR 1.31 (0.22-7.85);
Northstar (25%) HR 0.87 (0.48-1.58)

Aggregate data from Bunner-La Rocca (includes Christcurch, Time CHF, Berger, PRIMA, Signal-HF, BATTLESCARRED and STARS-BNP): (weight 72%)
HR 0.69 (0.50-0.95)));
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Concerns (percentages refer to the weight in the total meta-analysis): Around 20% had unclear sequence generation (including PRIMA) and around 75% had unclear allocation concealment (inc PRIMA, NORTHSTAR and BATTLESCARRED). Most studies unblinded; most larger studies blinded outcome assessors, but not BATTLESCARRED. Authors did not report plan for missing data or rate of missing data in IPD - mainly low in aggregate data.; Indirectness of outcome: No indirectness ; Baseline details: Unable to assess for systematic differences in the baseline groups, but randomisation good, and large numbers; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Age >= 75 years: All-Cause Mortality (results of meta-analysis) at 12 months; (Results from the IPD analysis:
Aguita (weight 3%) 0.68 (0.06-7.52);
Northstar (43%) 1.43 (0.76-2.66);
Aggregate data from Brunner La-Rocca (includes Christcurch, Time CHF, Berger, PRIMA, SIGNAL-HF BATTLESCARRED and STARS-BNP)
Total (54%)
HR 1.11 (0.63-1.95)));
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Concerns (percentages refer to the weight in the total meta-analysis): Around 30% had unclear sequence generation (including PRIMA) and around 70% had unclear allocation concealment (inc PRIMA, NORTHSTAR and BATTLESCARRED). Most studies unblinded; most larger studies blinded outcome assessors, but not BATTLESCARRED. Authors did not report plan for missing data or rate of missing data in IPD - mainly low in aggregate data.; Indirectness of outcome: No indirectness ; Baseline details: Unable to assess for systematic differences in the baseline groups, but randomisation good, and large numbers; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Unplanned hospitalisation (all-cause)
- Actual outcome for Age < 75 years: All-cause hospitalisation (results of meta-analysis) at 12 months; (Results from IPD analysis):
Anguita (weight 5%) HR 1.11 (0.43-2.88);
Northstar (36%) HR 0.84 (0.60-1.19);
UPSTEP (28%) HR 0.88 (0.70-1.09)
Aggregate data from Time-CHF
Total (32%) HR 0.70 (0.49-1.00)));
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Concerns (percentages refer to the weight in the total meta-analysis): Around 70% had unclear allocation concealment (inc NORTHSTAR and UPSTEP). All studies unblinded for participants, but blinded for assessor. Authors did not report plan for missing data or rate of missing data in IPD - mainly low in aggregate data.; Indirectness of outcome: No indirectness ; Baseline details:

Unable to assess for systematic differences in the baseline groups, but randomisation good, and large numbers; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome for Age >= 75 years: All-cause hospitalisation (results of meta-analysis) at 12 months; (Results from IPD analysis):
Anguita (weight 1%) HR 0.31 (0.04-2.81)
Northstar (31%) HR 1.02 (0.71-1.48)
UPSTEP (20%) HR 0.91 (0.62-1.37)
Aggregate results from Time-CHF:
Total (47%) HR 1.10 (0.82-1.47)));
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Concerns (percentages refer to the weight in the total meta-analysis): Around 55% had unclear allocation concealment (inc NORTHSTAR and UPSTEP). All studies unblinded for participants, but blinded for assessor. Authors did not report plan for missing data or rate of missing data in IPD - mainly low in aggregate data.; Indirectness of outcome: No indirectness ; Baseline details: Unable to assess for systematic differences in the baseline groups, but randomisation good, and large numbers; Group 1 Number missing: 0; Group 2 Number missing: 0

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NTPROBNP OR BNP (MIXED) versus NO MONITORING PROTOCOL

Protocol outcome 1: Mortality
- Actual outcome for Age < 75 years: All-cause mortality (IPD results) at 12 months; HR; 0.11 (95%CI 0.01 to 0.86);
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - As per quality assessment in HTA and Cochrane. Marked as either "low", "unclear" or "high" risk. Marked as selective reporting because has not been fully published yet.; Indirectness of outcome: No indirectness ; Group 1 Number missing: not reported; Group 2 Number missing: not reported
- Actual outcome for Age >= 75 years: All-cause mortality (IPD results) at 12 months; HR; 1.48 (95%CI 0.35 to 6.26);
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - As per quality assessment in HTA and Cochrane. Marked as either "low", "unclear" or "high" risk. Marked as selective reporting because has not been fully published yet.; Indirectness of outcome: No indirectness ; Group 1 Number missing: not reported; Group 2 Number missing: not reported

Protocol outcome 2: Unplanned hospitalisation (all-cause)
- Actual outcome for Age < 75 years: All-cause hospitalisation (IPD results) at 12 months; HR; 1.08 (95%CI 0.55 to 2.12);
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low,

Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - As per quality assessment in HTA and Cochrane. Marked as either "low", "unclear" or "high" risk. Marked as selective reporting because has not been fully published yet.; Indirectness of outcome: No indirectness ; Group 1 Number missing: not reported; Group 2 Number missing: not reported - Actual outcome for Age >= 75 years: All-cause hospitalisation (IPD results) at 12 months; HR; 1.66 (95%CI 0.81 to 3.4); Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - As per quality assessment in HTA and Cochrane. Marked as either "low", "unclear" or "high" risk. Marked as selective reporting because has not been fully published yet.; Indirectness of outcome: No indirectness ; Group 1 Number missing: not reported; Group 2 Number missing: not reported	
Protocol outcomes not reported by the study	Quality of life at 12 months ; Adverse events - hyperkalaemia; Adverse events - renal function; Adverse events - hypotension; Adverse events - arrhythmic events; Adverse events - bradycardia

Study	**SIGNAL-HF trial: Persson 2010[1130]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=250)
Countries and setting	Conducted in Sweden
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 9 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Mixed
Subgroup analysis within study	Not applicable
Inclusion criteria	patients in primary care with a diagnosis of CHF and stable NYHA class II-IV, LVEF < 50%, elevated NT-proBNP levels (males > 800, females > 1000 ng/L)
Exclusion criteria	planned CV hospitalisation; stroke, acute MI or open heart surgery within 3 months before enrolment; mitral stenosis, aortic stenosis of clinical significance; patients already receiving optimal pharmacological treatment for CHF according to guidelines, serum creatinine ≥ 265 umol/L
Recruitment/selection of patients	45 primary care centres in Sweden; study period 2006-2009
Age, gender and ethnicity	Age - Mean (SD): int 78(7), control 77(8). Gender (M:F): 71:29. Ethnicity: Not stated
Further population details	1. Ejection fraction: Reduced ejection fraction 2. Patient risk status: Recruited in community

Extra comments	. Severity: NYHA II - 62%, III - 38%, ave EF 31% Serum creatinine ave 105
Indirectness of population	No indirectness
Interventions	(n=126) Intervention 1: Biomarker monitoring - NTproBNP. Individual NT-proBNP level (reduction 50% from baseline). Stepwise algorithm to increase therapy to achieve target NT-proBNP. Follow up 1, 3, 6 and 9 months (total 9 months). Primary care.. Duration 9 months. Concurrent medication/care: As usual (n=124) Intervention 2: Usual care - Usual care: clinical monitoring. Clinical target - clinical assessment. Therapy intensified at clinician discretion. Follow up 1, 3, 6 and 9 months (total 9 months). Primary care.. Duration 9 months. Concurrent medication/care: As usual
Funding	Study funded by industry (Supported by AstraZeneca Sweden)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NTPROBNP versus USUAL CARE: CLINICAL MONITORING Protocol outcome 1: Quality of life at 12 months - Actual outcome for Mixed: Symptoms assessed using KCCQ at 9 months; Group 1: mean 3.6 pt (SD 18.5); n=126, Group 2: mean 6.2 pt (SD 18.5); n=124; KCCQ 0-100 Top=High is good outcome; Comments: Actual numbers analysed not given Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Single blinded, no detail re randomisation. No details for missing values of follow-up. Unclear reporting of outcome (but counted in indirectness so not downgraded here); Indirectness of outcome: Serious indirectness, Comments: Unclear whether this is the full KCCQ, which would count as a protocol outcome for QoL, or s subscale, which would usually be downgraded; Baseline details: Baseline KCCQ is 66.0 v 66.2; Group 1 Number missing: , Reason: no details; Group 2 Number missing: , Reason: no details	
Protocol outcomes not reported by the study	Mortality; Unplanned hospitalisation (all-cause); Adverse events - hyperkalaemia; Adverse events - renal function; Adverse events - hypotension; Adverse events - arrhythmic events; Adverse events - bradycardia

Study	STARS-BNP trial: Jourdain 2007[710]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=220)
Countries and setting	Conducted in France; Setting: The clinics of heart failure specialists in 17 French hospitals
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: ave 15 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Mixed
Subgroup analysis within study	Not applicable
Inclusion criteria	patients > 18 years with symptomatic (NYHA class II to III) systolic heart failure with LVEF < 45%, in stable condition (no hospital stay in previous month), treated by optimal medical therapy according to the European guidelines (diuretics, ACEis, or ARBs; and BBs), dosages of medication stable for at least 1 month prior to study
Exclusion criteria	acute coronary syndrome within 3 months, chronic renal failure (creatinine >250umol/l), documented hepatic cirrhosis, asthma, or COPD
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): int 65(5) cotrol 66(6). Gender (M:F): 127:93. Ethnicity: Not stated
Further population details	1. Ejection fraction: Reduced ejection fraction 2. Patient risk status: Recruited in community ("stable").

Extra comments	. Severity: NYHA class ave 2.25, LVEF ave 30%, ave length of HF 30 months. Comorbid: HTN 30%, DM 17%, IHD 50%
Indirectness of population	No indirectness
Interventions	(n=110) Intervention 1: Biomarker monitoring - BNP. Target BNP level < 100pg/mL. Therapy intensified according to clinical guidelines to maintain BNP. Follow up at months 1, 2 and 3 and then 3 monthly (total 15 months). HF clinic.. Duration ave 15 months. Concurrent medication/care: Physical exam, ECG, serum sodium, renal function and Hb monitored at visits during titration phase (first three months). Physical exam each visit for the remainder. (n=110) Intervention 2: Usual care - Usual care: clinical monitoring. Clinical target - clinical assessment. Therapy intensified at clinician discretion. Follow up at months 1, 2 and 3 and then 3 monthly (total 15 months). HF clinic. Duration ave 15 months. Concurrent medication/care: Physical exam, ECG, serum sodium, renal function and Hb monitored at visits during titration phase (first three months). Physical exam each visit for the remainder.
Funding	Study funded by industry (unrestricted grant from Biosite Inc)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BNP versus USUAL CARE: CLINICAL MONITORING

Protocol outcome 1: Unplanned hospitalisation (all-cause)
- Actual outcome for Mixed: All-cause hospitalisation (risk ratio) at ave 15 months; Group 1: 52/110, Group 2: 60/110
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Not clear on randomisation, allocation or attrition - insufficient concern for a very high rating.; Indirectness of outcome: No indirectness; Baseline details: Reported differences in smoking rates and LVEF between groups; Group 1 Number missing: not reported; Group 2 Number missing: not reported

Protocol outcome 2: Adverse events - renal function
- Actual outcome for Mixed: Creatinine increase by >30% at 3 months; Group 1: 7/110, Group 2: 9/110

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Not clear on randomisation, allocation or attrition - insufficient concern for a very high rating.; Indirectness of outcome: Serious indirectness, Comments: Refers only to the period of medication titration (hence three months) rather than total intervention time, but felt to be relevant as a safety parameter; Baseline details: Reported differences in smoking rates and LVEF between groups; Group 1 Number missing: not reported; Group 2 Number missing: not reported	
Protocol outcomes not reported by the study	Mortality; Quality of life at 12 months ; Adverse events - hyperkalaemia; Adverse events - hypotension; Adverse events - arrhythmic events; Adverse events - bradycardia

Study (subsidiary papers)	TIME-CHF trial: Maeder 2013[926] (Pfisterer 2009[1141], Brunner-la rocca 2006[213], Sanders-van wijk 2013[1242], Sanders-van wijk 2014[1241], Kaufmann 2015[741])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=622)

Countries and setting	Conducted in Germany, Switzerland; Setting: 15 hospitals in Germany and Switzerland
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 6 months active management, with further 12months follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Mixed
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged 60 years or older with dyspnea (NYHA class ≥ II with current therapy), a history of hospitalisation for heart failure within the last year, and an N-terminal BNP level of 400pg/mL or higher in patients < 75 years or 800 pg/mL or higher in patients ≥ 75 years
Exclusion criteria	Dyspnea not mainly due to heart failure, valvular disease requiring surgery, acute coronary syndromes within the previous 10 days, angina pectoris higher than class II, revasc within the previous month, BMI > 35, serum creatinine> 2.49 mg/dL, life expectancy of < 3 years for noncardiovascular causes
Recruitment/selection of patients	study period 2003 - 2006
Age, gender and ethnicity	Age - Mean (SD): pEF: 80(7), rEF 76(7). Gender (M:F): 369:253 (male 59%). Ethnicity: Not stated
Further population details	1. Ejection fraction: Not stated / Unclear 2. Patient risk status: Recruited in community (required to have one admission in last year).
Extra comments	. Severity: NYHA >II 75%, LVEF ave 30% Clinical: AF 32%, NT-proBNP 4200, creatinine 1.33mg/dL Med Hx: DM 35%, HTN 70%, CKD 55%

Indirectness of population	No indirectness
Interventions	(n=207) Intervention 1: Biomarker monitoring - NTproBNP. Target NT-proBNP less than 2x upper limit of normal (<400 pg/mL for patients < 75 years; < 800 pg/mL for patients ≥75 years). Therapy intensified according to step-wise algorithm to achieve target NT-proBNP. Follow up 1, 3, 6, 12 and 18 months (total 18 months). HF clinic. Duration 18 months. Concurrent medication/care: All pt had full examination, ECG, plasma sodium, renal function and Hb measure every visit for first six months, and physical examination at every visit therafter. (n=185) Intervention 2: Usual care - Usual care: clinical monitoring. Clinical target - NYHA class ≤ II. Therapy intensified according to stepwise algorithm to achieve target. Follow up 1, 3, 6, 12 and 18 months (total 18 months). HF clinic. Duration 18 months. Concurrent medication/care: All pt had full examination, ECG, plasma sodium, renal function and Hb measure every visit for first six months, and physical examination at every visit therafter.
Funding	Other (Mixed: 55% study budget from Horton Research Foundation (Lugano, Switzerland), remainder from multiple industry grants from AstraZeneca Pharma, Novartis Pharma, Menarini Pharma, Pfiza Pharma, Servier, Roche Diagnostics, Roche Pharma and Merck Pharma. In addition, one author has received grants from Roche Diagnostics)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NTPROBNP versus USUAL CARE: CLINICAL MONITORING

Protocol outcome 1: Quality of life at 12 months
- Actual outcome for Mixed: MLWHFQ at 12 months; Group 1: mean 27.7 pt (SD 17.9); n=110, Group 2: mean 27 pt (SD 18.6); n=110; MLWHFQ 0-105 Top=High is poor outcome;
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low,; Indirectness of outcome: No indirectness ; Baseline details: Creatinine 1.33/1.32; Group 1 Number missing: not reported; Group 2 Number missing: not reported
- Actual outcome for Mixed: SF-12 Physical Composite Score at 12 months; Group 1: mean 37.9 pt (SD 10.1); n=110, Group 2: mean 40.6 pt (SD 10.3); n=110; SF-12 PCS 0-100 Top=High is good outcome

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Creatinine 1.33/1.32; Group 1 Number missing: not reported; Group 2 Number missing: not reported
- Actual outcome for Mixed: SF-12 Mental Composite Score at 12 months; Group 1: mean 50.8 pt (SD 10.4); n=110, Group 2: mean 51.1 pt (SD 9.5); n=110; SF-12 MCS 0-100 Top=High is good outcome;
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - HTA rated low risk apart from unblinded; Indirectness of outcome: No indirectness ; Baseline details: Creatinine 1.33/1.32; Group 1 Number missing: not reported; Group 2 Number missing: not reported

Protocol outcome 2: Adverse events - hypotension
- Actual outcome for Age < 75 years: Incidence any hypotension at 18 months; Group 1: 48/108, Group 2: 38/102
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - HTA rated low risk apart from unblinded, missing data unclear but likely low, predefined subgroup, precise definitions of AEs not given.; Indirectness of outcome: No indirectness ; Group 1 Number missing: not reported; Group 2 Number missing: not reported
- Actual outcome for Age >= 75 years: Incidence any hypotension at 18 months; Group 1: 68/143, Group 2: 44/146
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - HTA rated low risk apart from unblinded, missing data unclear but likely low, predefined subgroup, precise definitions of AEs not given.; Indirectness of outcome: No indirectness ; Group 1 Number missing: not reported; Group 2 Number missing: not reported

Protocol outcome 3: Adverse events - hyperkalaemia
- Actual outcome for Age < 75 years: Incidence any hyperkalaemia at 18 months; Group 1: 20/108, Group 2: 15/102
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - HTA rated low risk apart from unblinded, missing data unclear but likely low, predefined subgroup, precise definitions of AEs not given.; Indirectness of outcome: No indirectness ; Group 1 Number missing: not reported; Group 2 Number missing: not reported
- Actual outcome for Age >= 75 years: Incidence any hyperkalaemia at 18 months; Group 1: 34/143, Group 2: 35/146
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - missing data unclear but likely low, predefined subgroup; Indirectness of outcome: No indirectness ; Group 1 Number missing: not reported; Group 2 Number missing: not reported

<table>
<tr><td colspan="2">Protocol outcome 4: Adverse events - renal function
- Actual outcome for Mixed: Creatinine at 12 months; Group 1: mean 1.44 mg/dl (SD 0.5); n=110, Group 2: mean 1.41 mg/dl (SD 0.53); n=110
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Creatinine 1.33/1.32; Group 1 Number missing: not reported; Group 2 Number missing: not reported
- Actual outcome for Age < 75 years: Incidence any renal failure at 18 months; Group 1: 32/108, Group 2: 28/102
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - missing data unclear but likely low, predefined subgroup, precise definition of AEs not given; Indirectness of outcome: No indirectness ; Group 1 Number missing: not reported; Group 2 Number missing: not reported
- Actual outcome for Age >= 75 years: Incidence any renal failure at 18 months; Group 1: 42/146, Group 2: 47/143
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - missing data unclear but likely low, predefined subgroup, precise definition of AE not given; Indirectness of outcome: No indirectness ; Group 1 Number missing: not reported; Group 2 Number missing: not reported

Protocol outcome 5: Adverse events - bradycardia
- Actual outcome for Age < 75 years: Incidence any bradycardia at 18 months; Group 1: 13/108, Group 2: 8/102
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - missing data unclear but likely low, predefined subgroup; Indirectness of outcome: No indirectness ; Group 1 Number missing: not reported; Group 2 Number missing: not reported
- Actual outcome for Age >= 75 years: Incidence any bradycardia at 18 months; Group 1: 21/143, Group 2: 18/146
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - missing data unclear but likely low, predefined subgroup, precise definitions of AEs not given.; Indirectness of outcome: No indirectness ; Group 1 Number missing: not reported; Group 2 Number missing: not reported</td></tr>
<tr><td>Protocol outcomes not reported by the study</td><td>Mortality; Unplanned hospitalisation (all-cause); Adverse events - arrhythmic events</td></tr>
</table>

Study (subsidiary papers)	Troughton 2014[1404] (Brunner-la rocca 2015[214]) Extraction for question 1 (for CKD – specific extraction see below)
Study type	Systematic Review
Number of studies (number of participants)	10 (n=1515)
Countries and setting	Conducted in Multiple countries; Setting: Troughton: patients recruited after hospital admission with decompensated heart failure or from a specialist cardiology outpatient clinic in New Zealand; study period 1998-1999. Berger: patients hospitalised for heart failure at 8 Viennese hospitals; study period 2003-2004. PRIMA: patients hospitalised for acute AF were screened and included during hospitalisation; study period 2004-2007. SIGNAL-HF: 45 primary care centres in Sweden; study period 2006-2009. BATTLESCARRED: 3,576 patients admitted to Christchurch hospital with heart failure were screened; 823 patients were approached and 448 consented to participate (of whom 84 were subsequently excluded because NT-proBNP levels were < 50 pmol/L); study period: 2001-2006. STARS-BNP: patients were included by CHF specialists from 17 university hospitals in France; study period NR. PROTECT: single-centre; study period 2006-2010.
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 9 - 18 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Mixed
Subgroup analysis within study	Not applicable

Inclusion criteria	Troughton: LVEF < 40%, NYHA class II-IV, treatment with ACEi, loop diuretic with or without digoxin. Berger: clinical signs and symptoms of cardiac decompensation during the present hospitalisation, NYHA class III or IV at admission, cardiothoracic ratio > 0.5 or LVEF < 40% by echo. PRIMA: patients hospitalised for decompensated, symptomatic HF, fulfilling the ESC diagnostic guideline criteria for acute HF; NT-proBNP levels at admission ≥ 1700 pg/mL and a decrease in levels of ≥ 10% at discharge. SIGNAL-HF: patients in primary care with a diagnosis of CHF and stable NYHA class II-IV, LVEF < 50%, elevated NT-proBNP levels (males > 800, females > 1000 ng/L). BATTLESCARRED: patients hospitalised for heart failure aged > 18 years, symptomatic HF defined by Framingham criteria and satisfying the ESC diagnostic guidelines, precipitating admission, NT-proBNP > 50 pmol/L immediately prior to randomisation. "Recruitment deliberately included elderly patients and patients with preserved LVEF". STARS-BNP: patients > 18 years with symptomatic (NYHA class II to III) systolic heart failure with LVEF < 45%, in stable condition (no hospital stay in previous month), treated by optimal medical therapy according to the European guidelines (diuretics, ACEis, or ARBs; and BBs), dosages of medication stable for at least 1 month prior to study. PROTECT: patients ≥ 21 years; LVEF ≤ 40%; NYHA class II-IV symptoms; hospital admission, emergency department visit or outpatient therapy for destabilised HF at least once in the 6 months before enrollment.
Exclusion criteria	Troughton: recent acute coronary syndrome (within 3 months), pending cardiac transplant or revasc, severe stenotic valvular heart disease, severe pulmonary, hepatic or renal disease. Berger: N/A PRIMA: life-threatening cariac arrhythmia during index hospitalisation, urgent invaisve or surgical intervention performed or planned during the index hospitalisation, severe chronic obstructive pulmonary disease with FEV1 of < 1 l/s, pulmonary embolism < 3 months prior to admission, pulmonary hypertension not caused by LVSD, a non-HF related expected survival of < 1 year, patients undergoing hemodialysis or continuous ambulant peritoneal dialysis (a lesser degree of renal dysfunction was not an exclusion criterion). SIGNAL-HF: planned CV hospitalisation; stroke, acute MI or open heart surgery within 3 months before enrolment; mitral stenosis, aortic stenosis of clinical significance; patients already receiving optimal pharmacological treatment for CHF according to guidelines, serum creatinine ≥ 265 umol/L. BATTLESCARRED: active mycarditis/pericarditis, life expectancy < 24 months due to noncardiovascular disease, severe hepatic or pulmonary disease, severe renal impairment, severe valvular disease, or

	candidacy for cardiac transplantation. STARS-BNP: acute coronary syndrome within 3 months, chronic renal failure, documented hepatic cirrhosis, astham, or COPD. PROTECT: serum creatinine > 2.5 mg/dL, inoperable aortic valvular heart disease, life expectancy < 1 year due to causes other than HF, cardiac transplantation or revascularisation indicated or expected within 6 months, severe obstructive or restrictive pulmonary disease, coronary revasc within previous 3 months.
Age, gender and ethnicity	Age - Range of means: 60-78y. Gender (M:F): NR. Ethnicity: Not reported
Further population details	1. Ejection fraction: Systematic review: mixed (range of means of LVEF: 20-39%). 2. Patient risk status: Systematic review: mixed
Indirectness of population	No indirectness
Interventions	(n=762) Intervention 1: Biomarker monitoring - NTproBNP or BNP (mixed). Troughton: Target NT-proBNP level < 1700 pg/mL. Therapy intensified according to stepwise algorithm to achieve target. Follow up every 3 months unless treatment targets not met (total 9.5 months). HF clinic. Berger: NT-proBNP < 2200 pg/L. Therapy intensified according to set protocol to maintain target NT-proBNP. Follow up at 2 weeks, then 1, 3, 6 and 12 months (total 15 months). HF clinic. PRIMA: Individual NT-proBNp level (lowest level at discharge or at 2 weeks follow-up). Therapy intensified according to clinical guidelines to maintain target NT-proBNP. Follow up 2 weeks, 1 month, then 3 monthly (total 24 months). HF clinic. SIGNAL-HF: Individual NT-proBNP level (reduction 50% from baseline). Stepwise algorithm to increase therapy to achieve target NT-proBNP. Follow up 1, 3, 6 and 9 months (total 9 months). Primary care. BATTLESCARRED: Target NT-proBNP < 1300pg/mL. Therapy intensified according to stepwise algorithm to achieve target NT-proBNP and congestion score < 2. Follow up 2 weekly until treatment target met, then 3 monthly (total 3 years). HF clinic. STARS-BNP: Target BNP level < 100pg/mL. Therapy intensified according to clinical guidelines to maintain BNP. Follow up at months 1, 2 and 3 and then 3 monthly (total 15 months). HF clinic. PROTECT: Target NT-proBNP ≤ 1000 pg/mL. Therapy intensified according to clinical guidelines to maintain target NT-proBNP. Follow up as required to meet treatment target and then 3 monthly (total follow up min 6 months and max 12 months). HF clinic.. Duration 9.5-18 months. Concurrent medication/care: NA

	(n=753) Intervention 2: Usual care - Usual care: clinical monitoring. Troughton: Clinical target - Framingham HF score of < 2. Therapy intensified according to stepwise algorithm to achieve target score. Follow up every 3 months unless treatment targets not met (total 9.5 months). HF clinic. Berger: Clinical target - clinical assessment. Therapy intensified at clinician discretion. Follow up at 2 weeks, then 1, 3, 6 and 12 months (total 15 months). HF clinic. PRIMA: Clinical target - clinical assessment. Therapy intensified at clinician discretion. Follow up 2 weeks, 1 month, then 3 monthly (total 24 months). HF clinic. SIGNAL-HF: Clinical target - clinical assessment. Therapy intensified at clinician discretion. Follow up 1, 3, 6 and 9 months (total 9 months). Primary care. BATTLESCARRED: Clinical target - Framingham HF score of < 2. Therapy intensified to achieve target score. Follow up 2 weekly until treatment target met, then 3 monthly (total 3 years). HF clinic. STARS-BNP. Clinical target - clinical assessment. Therapy intensified at clinician discretion. Follow up at months 1, 2 and 3 and then 3 monthly (total 15 months). HF clinic. PROTECT: Clinical target - clinical assessment. Therapy intensified at clinician discretion. Follow up as required to meet treatment target and then 3 monthly (total follow up min 6 months and max 12 months). HF clinic.. Duration 9.5-18 months. Concurrent medication/care: NA
Funding	No funding (No funding specific to review. Individual studies in review funded by mixture of academic and industry sources)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NTPROBNP OR BNP (MIXED) versus USUAL CARE: CLINICAL MONITORING Protocol outcome 1: Unplanned hospitalisation (all-cause) - Actual outcome for Mixed: HF hospitalisation at 9.5-18 months; HR; (Studies contributing to IPD): Christchurch pilot (5%) HR 0.71 (0.23-2.26) Berger (19%) HR 0.62 (0.38-1.03) PRIMA (27%) HR 1.00 (0.68-1.47) SIGNAL-HF (7%) HR 0.53 (0.21-1.32) BATTLESCARRED (20%) HR 0.78 (0.48-1.27)	

<table>
<tr><td colspan="2">PROTECT (9%) HR 0.65 (0.29-1.44)
Studies contributing aggregate data:
STARS-BNP (14%) HR 0.32 (0.18-0.59)));
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Sequence generation unclear in four (weight 54%), low risk in three. Allocation concealment unclear in six (weight 81%), low risk in one.
Blinding of participants was low risk in two (25%), high risk in five. Blinding of assessor unclear in four, low risk in two (36%) and high risk in one (7%). Rated low overall as fairly objective outcome.
Attrition was unclear in three (32%), low risk in four. Reporting was unclear in three, low risk in three (56%) and high risk in one (7%). Three studies had no "other" concerns about bias (64%), while four studies had uncertain rating for "other" concerns;Indirectness of outcome: Serious indirectness, Comments: Not protocol outcome of all-cause admission; Group 1 Number missing: not reported; Group 2 Number missing: not reported</td></tr>
<tr><td>Protocol outcomes not reported by the study</td><td>Mortality; Quality of life at 12 months ; Adverse events - hyperkalaemia; Adverse events - renal function; Adverse events - hypotension; Adverse events - arrhythmic events; Adverse events - bradycardia</td></tr>
</table>

Study (subsidiary papers)	Troughton review trial: Troughton 2014[1404] (Brunner-la rocca 2015[214]) Extraction for question 2
Study type	Systematic Review
Number of studies (number of participants)	9 (n=1147)
Countries and setting	Conducted in Multiple countries; Setting: Christchurch pilot: patients recruited after hospital admission with decompensated heart failure or from a specialist cardiology outpatient clinic in New Zealand; study period 1998-1999. Berger: patients hospitalised for heart failure at 8 Viennese hospitals; study period 2003-2004. PRIMA: patients hospitalised for acute AF were screened and included during hospitalisation; study period 2004-2007. SIGNAL-HF: 45 primary care centres in Sweden; study period 2006-2009. BATTLESCARRED: 3,576 patients admitted to Christchurch hospital with heart failure were screened; 823 patients were approached and 448 consented to participate (of whom 84 were subsequently excluded because NT-proBNP levels were < 50 pmol/L); study period: 2001-2006. PROTECT: single-centre; study period 2006-2010.
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 6-36 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Mixed
Subgroup analysis within study	Post-hoc subgroup analysis: People with GFR 60 or less by MDRD formula
Inclusion criteria	As per individual studies, with addition of GFR 60 or less at IPD level:

	Christchurch pilot: LVEF < 40%, NYHA class II-IV, treatment with ACEi, loop diuretic. Berger: clinical signs and symptoms of cardiac decompensation during the present hospitalisation, NYHA class III or IV at admission, cardiothoracic ratio > 0.5 or LVEF < 40% by echo. PRIMA: patients hospitalised for decompensated, symptomatic HF, fulfilling the ESC diagnostic guideline criteria for acute HF; NT-proBNP levels at admission ≥1700 pg/mL and a decrease in levels of ≥ 10% at discharge. SIGNAL-HF: patients in primary care with a diagnosis of CHF and stable NYHA class II-IV, LVEF < 50%, elevated NT-proBNP levels (males > 800, females > 1000 ng/L). BATTLESCARRED: patients hospitalised for heart failure aged > 18 years, symptomatic HF defined by Framingham criteria and satisfying the ESC diagnostic guidelines, precipitating admission, NT-proBNP > 50 pmol/L immediately prior to randomisation. PROTECT: patients ≥ 21 years; LVEF ≤ 40%; NYHA class II-IV symptoms; hospital admission, emergency department visit or outpatient therapy for destabilised HF at least once in the 6 months before enrollment.
Exclusion criteria	Christchurch pilot: recent acute coronary syndrome (within 3 months), pending cardiac transplant or revasc, severe stenotic valvular heart disease, severe pulmonary, hepatic or renal disease. Berger: N/A PRIMA: life-threatening cariac arrhythmia during index hospitalisation, urgent invaisve or surgical intervention performed or planned during the index hospitalisation, severe chronic obstructive pulmonary disease with FEV1 of <1 l/s, pulmonary embolism < 3 months prior to admission, pulmonary hypertension not caused by LVSD, a non-HF related expected survival of < 1 year, patients undergoing hemodialysis or continuous ambulant peritoneal dialysis (a lesser degree of renal dysfunction was not an exclusion criterion). SIGNAL-HF: planned CV hospitalisation; stroke, acute MI or open heart surgery within 3 months before enrolment; mitral stenosis, aortic stenosis of clinical significance; patients already receiving optimal pharmacological treatment for CHF according to guidelines, serum creatinine ≥ 265 umol/L. BATTLESCARRED: active mycarditis/pericarditis, life expectancy < 24 months due to noncardiovascular disease, severe hepatic or pulmonary disease, severe renal impairment, severe valvular disease, or candidacy for cardiac transplantation. PROTECT: serum creatinine > 2.5 mg/dL, inoperable aortic valvular heart disease, life expectancy < 1 year due to causes other than HF, cardiac transplantation or revascularisation indicated or expected within 6 months, severe obstructive or restrictive pulmonary disease, coronary revasc within previous 3 months.

Recruitment/selection of patients	Of the 2021 patients for whom a GFR was calculated, 1147 fell into the CKD level of 60ml/min/1.73sa or less (57%)
Age, gender and ethnicity	Age - Mean (SD): 73.5(10.6) in whole cohort. Gender (M:F): 66:34 in whole cohort (CKD and non-CKD). Ethnicity: not stated
Further population details	1. Ejection fraction: Systematic review: mixed (Analysed separately in this paper as HFrEF and HFpEF). 2. Patient risk status: Systematic review: mixed
Indirectness of population	No indirectness: Note that people with severe renal failure may have been excluded from original trials, but those with CKD level III are likely to have been included
Interventions	(n=573) Intervention 1: Biomarker monitoring - NTproBNP or BNP (mixed). Christchurch pilot: Target NT-proBNP level < 1700pg/mL. Therapy intensified according to stepwise algorithm to achieve target. Follow up every 3 months unless treatment targets not met (total 9.5 months). HF clinic. Berger: NT-proBNP < 2200 pg/L. Therapy intensified according to set protocol to maintain target NT-proBNP. Follow up at 2 weeks, then 1, 3, 6 and 12 months (total 15 months). HF clinic. PRIMA: Individual NT-proBNp level (lowest level at discharge or at 2 weeks follow-up). Therapy intensified according to clinical guidelines to maintain target NT-proBNP. Follow up 2 weeks, 1 month, then 3 monthly (total 24 months). HF clinic. SIGNAL-HF: Individual NT-proBNP level (reduction 50% from baseline). Stepwise algorithm to increase therapy to achieve target NT-proBNP. Follow up 1, 3, 6 and 9 months (total 9 months). Primary care. BATTLESCARRED: Target NT-proBNP < 1300pg/mL. Therapy intensified according to stepwise algorithm to achieve target NT-proBNP and congestion score < 2. Follow up 2 weekly until treatment target met, then 3 monthly (total 3 years). HF clinic. PROTECT: Target NT-proBNP ≤ 1000 pg/mL. Therapy intensified according to clinical guidelines to maintain target NT-proBNP. Follow up as required to meet treatment target and then 3 monthly (total follow up min 6 months and max 12 months). HF clinic. Duration 9.5-36 months. Concurrent medication/care: NA Comments: number in treatment group not given, estimated as 50% of total (n=574) Intervention 2: Usual care - Usual care: mixed. Christchurch pilot: Clinical target - Framingham HF

	score of < 2. Therapy intensified according to stepwise algorithm to achieve target score. Follow up every 3 months unless treatment targets not met (total 9.5 months). HF clinic. Berger: Clinical target - clinical assessment. Therapy intensified at clinician discretion. Follow up at 2 weeks, then 1, 3, 6 and 12 months (total 15 months). HF clinic. PRIMA: Clinical target - clinical assessment. Therapy intensified at clinician discretion. Follow up 2 weeks, 1 month, then 3 monthly (total 24 months). HF clinic. SIGNAL-HF: Clinical target - clinical assessment. Therapy intensified at clinician discretion. Follow up 1, 3, 6 and 9 months (total 9 months). Primary care. BATTLESCARRED: Clinical target - Framingham HF score of < 2. Therapy intensified to achieve target score. Follow up 2 weekly until treatment target met, then 3 monthly (total 3 years). HF clinic. PROTECT: Clinical target - clinical assessment. Therapy intensified at clinician discretion. Follow up as required to meet treatment target and then 3 monthly (total follow up min 6 months and max 12 months). HF clinic.. Duration 9.5-36 months. Concurrent medication/care: NA Comments: Actual number in treatment group not given, assumed half
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NTPROBNP OR BNP (MIXED) versus USUAL CARE: CLINICAL MONITORING

Protocol outcome 1: Mortality
- Actual outcome for Mixed: All-cause mortality (result of meta-analysis) at 3-36 months; HFpEF HR 1.47 (0.85 to 2.54); HFrEF: HR 0.81 (0.63 to 1.04)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - High, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Based on quality assessment in HTA. 74% weight from studies with adequate sequence generation, remainder unclear. 44% weight from studies with adequate allocation concealment, remainder unclear. 12% weight from studies with patient blinding, remainder were not blinded. 74% weight from studies with blinded assessor. 60% weight from studies with low attrition, remainder unclear. 69% weight from studies with low risk reporting, 3% from high risk, remainder unclear. 4% marked as unclear for other sources of bias, remainder low risk. SR marked down for subgroup, as three variants on CKD used in the reporting, and unclear why or how they differed.;
Indirectness of outcome: No indirectness ; Group 1 Number missing: not reported; Group 2 Number missing: not reported

Protocol outcomes not reported by the study	Quality of life at 12 months ; Unplanned hospitalisation (all-cause); Adverse events - hyperkalaemia; Adverse events - renal function; Adverse events - hypotension; Adverse events - arrhythmic events; Adverse events - bradycardia

Study (subsidiary papers)	**UPSTEP trial: Karlstrom 2011[731] (Karlstrom 2016[733], Karlstrom 2015[732])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=279)
Countries and setting	Conducted in Norway, Sweden; Setting: 15 hospitals in Sweden and four in Norway
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: At least 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Mixed: Ratio <75/>75 (sic, not including 75yo): int 84:63 (1:0.75), control 84:48 (1:0.57)
Subgroup analysis within study	Not applicable
Inclusion criteria	> 18 years, verified systolic HF and LVEF < 40% within last 6 months, NYHA class II-IV, signs and/or symptoms of worsening HF within the last month (requiring hospitalisation and/or intravenous diuretic treatment, metolazone, or increased daily dosages or diuretics and/or need of intravenous inotropic support), elevated BNP (>150ng/L for those aged <75 years and > 300 ng/L for those aged > 75 years)

Exclusion criteria	Haemodynamically unstable patients on the waiting list for cardiac surgery/intervention, patients with an MI within the last 3 months, patients with haemodynamically significant valvular heart disease, patients with impaired renal or liver function, patients with severely decreased pulmonary function, patients with a limited life expectancy
Recruitment/selection of patients	recruited by physicians experienced in treating HF, 2006-2009
Age, gender and ethnicity	Age - Mean (SD): int 71.6 (9.7). Gender (M:F): int 107/40, control 93/36. Ethnicity: Not stated
Further population details	1. Ejection fraction: Reduced ejection fraction 2. Patient risk status: Recruited following acute admission (required recent deterioration).
Extra comments	. Severity: NYHA II 30%, III 52%, IV 15%, LVEF<30 57% BNP: int 808 (676), control 899 (915) eGFR ave 61(20)ml/min/1.73^2, <60ml/min 51%
Indirectness of population	No indirectness
Interventions	(n=147) Intervention 1: Biomarker monitoring - NTproBNP. < 75 years - target BNP level < 150 pg/mL, ≥ 75 years - target BNP level < 300 pg/mL. Therapy intensified according to stepwise algorithm to achieve maximally tolerated or guideline recommended target doses. Follow up at weeks 2, 6, 10, 16, 24, 36, 48 and then every 6 months (total ≥ 12 months). HF clinic. Duration At least 12 months. Concurrent medication/care: Not discussed Comments: Seven patients did not complete protocol (n=132) Intervention 2: Usual care - Usual care: clinical monitoring. Clinical target - clinical assessment. Not allowed to measure BNP. Therapy intensified at clinician discretion. Follow up weeks 2, 6, 10, 16, 24, 36, 48 and then every 6 months (total ≥ 12 months). HF clinic . Duration At least 12 months. Concurrent medication/care: Not discussed Comments: Four did not complete protocol

Funding	Equipment / drugs provided by industry (Mixed funding, from Swedish Heart-Lung Foundation, regional research foundations in Sweden, Biosite International and Infiniti Medical AB (provided BNP testing equipment). One author has lectured for Biosite)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NTPROBNP versus USUAL CARE: CLINIC Protocol outcome 1: Quality of life at 12 months - Actual outcome for Mixed: SF-36 Physical Component Score at 12 months; Group 1: mean 37.8 pt (SD 12); n=100, Group 2: mean 35.6 pt (SD 11); n=98; SF-36 PCS 0-100 Top=High is good outcome Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Unblinded and subjective, no statement about comparability of careIndirectness of outcome: No indirectness ; Baseline details: PCS 31.5/32.7, MCS 42.7/43.6; Group 1 Number missing: 47, Reason: 10 had no starting questionnaire, 31 died, 7 dropped out; Group 2 Number missing: 34, Reason: 1 had no starting questionnaire, 29 died, 4 dropped out - Actual outcome for Mixed: SF-36 Mental Component Score at at least 12 months; Group 1: mean 46.5 pt (SD 10); n=100, Group 2: mean 46 pt (SD 11); n=98; SF-36 MCS 0-100 Top=High is good outcome Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Unblinded and subjective, no statement about comparability of care; Indirectness of outcome: No indirectness ; Baseline details: PCS 31.5/32.7, MCS 42.7/43.6; Group 1 Number missing: 47, Reason: 10 had no starting questionnaire, 31 died, 7 dropped out; Group 2 Number missing: 34, Reason: 1 had no starting questionnaire, 29 died, 4 dropped out	
Protocol outcomes not reported by the study	Mortality; Unplanned hospitalisation (all-cause); Adverse events - hyperkalaemia; Adverse events - renal function; Adverse events - hypotension; Adverse events - arrhythmic events; Adverse events - bradycardia

F.11 Telemonitoring and self-monitoring

Study	Al-sutari 2017[45]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=144)
Countries and setting	Conducted in Jordan; Setting: Cardiac clinic at an educational hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Community
Subgroup analysis within study	Not applicable
Inclusion criteria	Confirmed diagnosis of heart failure by the attending cardiologist, left ventricular ejection fraction of 40% or less, and NYHA functional class II or III, 18 years of age or older, able to speak arabic, and have a telephone to be accessible for follow-up
Exclusion criteria	Heart failure patients who have dementia
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 64.73 (9.9). Gender (M:F): 86/58. Ethnicity: Not reported
Further population details	NYHA class II: STS: 34 (47.2); UC: 30 (41.7); NHYA class III: STS: 38 (52.8); UC: 42 (58.3)
Extra comments	All patients with heart failure who attended the cardiac clinic at the educational hospital between August and

	November 2014 were invited to participate in the study.
Indirectness of population	No indirectness
Interventions	(n=72) Intervention 1: Structured telephone support - Structured telephone support (monitoring or self-care management using simple telephone technology). Educational programme consisting of 3 parts: a single educational session at the beginning of the study, a self-care manual, and telephone calls. The included participants received one 15 minute phone call every week for the first month of the intervention, then they received phone calls every 2 weeks in the second and third months. In each phone call, the principal investigator (who was a nurse) reviewed the recommended self-care behaviours and asked the participants to describe their self-care activities. The investigator did not change the participants medical regimen but provided feedback and recommendations to go to the emergency department when symptoms of heart failure decompensation were identified. Duration 3 months. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Focus of telephone support: 2. Intensity: 3. Publication year: 4. Technology: (n=72) Intervention 2: Usual care - Usual care (standard post discharge care without intensified attendance at cardiology or HF disease management clinic, or home visiting). . Participants in the control group received the traditional care, which is provided at the target hospital. The traditional care consists of follow-up of the patients with heart failure at the return to the outpatients clinic. During each follow-up appointment, participants were assessed by their cardiologists.. Duration 3 months. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Focus of telephone support: 2. Intensity: 3. Publication year: 4. Technology:
Funding	Academic or government funding (Supported by the University of Jordan)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STRUCTURED TELEPHONE SUPPORT (MONITORING OR SELF-CARE MANAGEMENT USING SIMPLE TELEPHONE TECHNOLOGY) versus USUAL CARE (STANDARD POST DISCHARGE CARE WITHOUT INTENSIFIED ATTENDANCE AT CARDIOLOGY OR HF DISEASE MANAGEMENT CLINIC, OR HOME VISITING).

Protocol outcome 1: All-cause mortality - Actual outcome for Community: Frequency of deaths at 3 months; Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline covariates not fully described; Group 1 Number missing: 2; Group 2 Number missing: 7 Protocol outcome 2: All-cause hospitalisation - Actual outcome for Community: Frequency of hospitalisations at 3 months; Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Baseline covariates not fully described; Group 1 Number missing: 2; Group 2 Number missing: 7	
Protocol outcomes not reported by the study	Quality of life; Adherence to intervention

Study	Dang 2017[341]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=61)
Countries and setting	Conducted in USA; Setting: Patients in the community receiving care from the Heart Failure Clinic at Jackson Memorial Hospital in Miami.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Community
Subgroup analysis within study	Not applicable
Inclusion criteria	Community-dwelling ambulatory patients diagnosed with HF. Other eligibility criteria included age ≥18 years; ability to speak and read English or Spanish; anticipated survival ≥6 months; no previous history of unstable coronary syndromes; no end stage HF; and no heart transplantation.
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 55.3 (9.8). Gender (M:F): 39/22. Ethnicity: Race - Black: 15; white: 46 Ethnicity - Hispanic/Latino: 46; non-hispanic: 15
Further population details	Not reported

Indirectness of population	No indirectness
Interventions	(n=42) Intervention 1: Structured telephone support - Structured telephone support (monitoring or self-care management using simple telephone technology). Participants in the intervention group received a mobile phone (model FG 630) to be used for the 3-month period of the study for daily monitoring. Participants chose their preferred time to receive the daily questions. They were asked to weigh themselves daily and use the mobile phone to answer 10 daily questions about their weight and HF symptoms (yes/no format) for 3 months. Patients received 3 messages, 15 minutes apart, if they did not respond to the first automated message. The transmitted information was stored in the server database and immediately programmatically analyzed for triggers of any deterioration. If responses indicated possible worsening of the HF (based on pre-configured algorithms), the patient received a message asking to contact the study coordinator. The study coordinator was able to view the data on a secure web site and received an alert on his/her mobile phone. He/she contacted the patient to ask additional questions to confirm if there was indeed a decline in the patients status and helped him/her to coordinate his/her care with the Heart Failure Clinic, as needed. Patients were contacted at least once a month to complete the scheduled questionnaires. . Duration 3 months. Concurrent medication/care: Patients also received usual care in the Heart Failure Clinic, which included visits determined by the clinic providers based on HF severity and medication optimization needed.. Indirectness: No indirectness (n=19) Intervention 2: Usual care - Usual care (standard post discharge care without intensified attendance at cardiology or HF disease management clinic, or home visiting). . Patients received usual care in the Heart Failure Clinic which included visits determined by the clinic providers based on HF severity and medication optimization needed. Patients were contacted at least once a month to administer the resource use questionnaire. Duration 3 months. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Academic or government funding (Florida Department of Health's James and Esther King Biomedical Research Program)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STRUCTURED TELEPHONE SUPPORT (MONITORING OR SELF-CARE MANAGEMENT USING SIMPLE TELEPHONE TECHNOLOGY) versus USUAL CARE (STANDARD POST DISCHARGE CARE WITHOUT INTENSIFIED ATTENDANCE AT CARDIOLOGY	

OR HF DISEASE MANAGEMENT CLINIC, OR HOME VISITING). Protocol outcome 1: Quality of life - Actual outcome for Community: Health Distress Score at 3 months; Group 1: mean -0.08 (SD 1.49); n=36, Group 2: mean 1.03 (SD 1.44); n=16 Risk of bias: All domain - Very high, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6; Group 2 Number missing: 3 - Actual outcome for Community: Minnesota Living with Heart Failure Questionnaire at 3 months; Group 1: -3.94 (SD 26.29); n=36, Group 2: mean 0.75 (SD 16.02); n=16 Risk of bias: All domain - Very high, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6; Group 2 Number missing: 3	
Protocol outcomes not reported by the study	All-cause mortality; All-cause hospitalisation; Adherence to intervention

Study (subsidiary papers)	**Inglis 2015[667] (Rainville 1999[1181], Gattis 1999[509], Laramee 2003[834], Bento 2009[154], [77], Baker 2011[113], Villani 2014[1445], Vuorinen 2014[1453], Anon 2005[513], Antonicelli 2008[88], Balk 2008[117], Biannic 2012[167], Blum 2014[177], Brandon 2009[201], Capomolla 2004[236], Chaudhry 2010[262], Cleland 2005[290], De lusignan 2001[357], Debusk 2004[363], Dendale 2012[370], Dewalt 2006[378], Domingues 2011[394], Galbreath 2004[499], Giordano 2009[521], Koehler 2011[776], Krum 2013[800], Lyng† 2012[917], Mortara 2009[1018], Ramachandran 2007[1182], Riegel 2006[1207], Riegel 2002[1208], Scherr 2009[1255], Seto 2012[1271], Sisk 2006[1295], Soran 2008[1314], Tsuyuki 2004[1411], Wakefield 2008[1457], Woodend 2008[1495], Zamanzadeh 2013[1519], [131], [530])**
Study type	Systematic Review
Number of studies (number of participants)	39 (n=13,192)
Countries and setting	Conducted in Multiple countries; Setting: Community and outpatient setting
Line of therapy	Not applicable

Duration of study	Intervention time: 3 months to 24 months
Method of assessment of guideline condition	Systematic review: method of assessment mixed
Stratum	Mixed: This cochrane review included 2 strata: structured telephone support and non-invasive telemonitoring.
Subgroup analysis within study	Sys review – pre-specified in protocol: 1. Categorized by technology: (a) telephone calls; (b) videophone; (c) interactive voice; (d) complex/clinical telemonitoring involving the automatic transmission of physiological data; 2. Telemonitroing intensity: office hours versus 24/7 or 7 day; 3. Publication year: 2000-2007 and ≥2008; 4. Participant age: <70 years and ≥70 years; 5. Focus of telephone support: clinical monitoring and self-management education
Inclusion criteria	Randomized control trials comparing heart failure management delivered via structured telephone support or non-invasive home telemonitoring with usual post discharge care for people aged 18 years and over of either sex with a definitive diagnosis of heart failure living within the community.
Exclusion criteria	Not reported
Recruitment/selection of patients	Angermann 2012: central computer-generated block random assignment; Antonicelli 2008: not reported; Baker 2011: sealed envelope block randomisation; Balk 2008: web-based block randomisation; Barth 2001: not reported; Bento 2009: simple random allocation; Biannic 2012: central randomisation; Blum 2014: web-based randomisation; Capomolla 2004: not reported; Chaudhry 2010: computer generated random number allocation stratified by study site; Cleland 2005 (structured telephone): random permuted block; Cleland 2005 (telemonitoring):random permuted block; De Lusignan 2001: random table allocation; DeBusk 2004: Efron procedure; Dendale 2012: block randomisation by sealed envelopes; DeWalt 2006: random number allocation; Domingues 2011: not reported; Galbreath 2004: not reported; Gattis 1999: computer-generated randomisation; GESICA 2005: permuted block randomisation; Giordano 2009: permuted block randomisation; Goldberg 2003: not reported; Koehler 2011: central computerised randomisation using Pocock's minimization algorithm; Krum 2013: computer-generated random sequence; Laramee 2003: not reported; Lynga 2012: not reported; Mortara 2009 (structured telephone): randomisation list; Mortara 2009

	(telemonitoring): randomisation list; Rainville 1999: not reported; Ramachandran 2007: computer-generated list; Riegel 2002: not reported; Riegel 2006: not reported; Scherr 2009: not reported; Seto 2012: computer-generated stratified four-block randomization; Sisk 2006: computer-generated, random-number sequence without blocking or stratification; Soran 2008: not reported; Tsuyuki 2004: computer-generated sequence using block randomization stratified by study site; Villani 2014: computerized random number generator; Vuorinen 2014: matched pair design randomization; Wakefield 2008: sealed envelopes containing group assignments in blocks of 24; Woodend 2008: not reported;
Age, gender and ethnicity	Age: Mean/median age of participants ranged from 45-75 years in the structured telephone support studies and from 55-78 years in the telemonitoring studies.. Gender (M:F): Mean % of males (range): structured telephone support - 63% (45%-99%); telemonitoring - 72% (35%-85%). Ethnicity: not reported
Further population details	Not reported
Indirectness of population	No indirectness
Interventions	(n=9332) Intervention 1: Structured telephone support (monitoring or self-care management using simple telephone technology): Angermann 2012: Electronic scale and BP at participant's home. Intervention included: 1) in-hospital face-to-face education; 2) telephone-based structured monitoring using 19-item questionnaire (assessing indicators of worsening HF, other cardiac symptoms, medication, health care utilisation, state of mood and general health and well-being; 3) up titration of HF medication in co-operation with GPs; 4) needs-adjusted specialist care, which nurses coordinated with participant's physician. All nurses received supervision by cardiologist (weekly) and a psychologist (bimonthly), and had unrestricted access to their supervisor for questions. Professionals involved: skilled nurses, general practitioners and cardiologist. Frequency of intervention: weekly during the first month, and then individualised according to NYHA class at discharge (weekly or fortnightly for NYHA III - IV, monthly for NYHA I - II) and participant's needs. Baker 2011: Intensive education and self-care training which was based on social cognitive theory and adult learning theory. This included specific instruction using daily weights to guide diuretic self-adjustment and included an individualised plan developed with the participant's clinician. Over 4 weeks, participants were scheduled to receive 5 - 8 phone calls from the study educator to reinforce education and to guide the

	participant towards improved self-care skills. Each call lasted about10 minutes. The calls focused on reviewing the content of the initial education session, assessing the participant's knowledge and behavior and providing additional information and encouragement. Barth 2001: Structured nurse-managed telephonic post-discharge programme involving pre-discharge education plus post-discharge telephone follow-up. Structured interaction at 72 hours, 144hours, and then fortnightly Bento 2009: Conventional medical assistance (not otherwise specified), nursing consultation (fortnightly or monthly depending on participants' needs) and telephone monitoring every 15days (education, recording hospitalisations and emergency treatments). Recommendations on pharmacological treatment, water intake, sodium intake, BP control, bodyweight control. Duration: 6 months. Professionals involved: nurses Capomolla 2004: Daily communication of vital signs (including weight, systolic BP, HR) and symptoms with review by nurses and physicians. Access to medical staff via phone was available as needed. Chaudhry 2010: All study participants received educational materials developed by the Heart Failure Society of America, and if needed, a weighing scale. Participants in the intervention group were also provided with detailed instructions and a demonstration by site coordinators of how to use the system, as well as a touch-tone telephone, if needed. The intervention was performed using a commercial system, Tel-Assurance (Pharos Innovations). The intervention group was instructed to make daily, toll-free calls to the system. During each call, participants, via an interactive voice response system, heard a series of questions about general health and heart-failure symptoms, and entered responses using the telephone keypad. Validated depression screening questions were included monthly. Information from the system was downloaded daily to a secure Internet site and was reviewed every weekday (except on holidays) by site coordinators. All questions had predetermined responses that triggered "variances" to flag clinicians' attention. The protocol required the sites to contact any participant whose response generated variances and document their management of the variances. Clinicians were instructed to treat participants in accordance with national guidelines for the management of heart failure. Cleland 2005: Participants assigned to the nurse telephone support arm received a telephone call each month by a heart failure specialist nurse to assess their symptoms and current medications. Participants

	assigned to telemonitoring received the nurse telephone support and had their weight, BP and ECG monitored twice daily DeBusk 2004: Standardised telephonic physician-directed nurse-managed case management, involving CHF lifestyle education and medication management. Participants contacted weekly for 6 weeks, biweekly for 8 weeks and then monthly and bimonthly. DeWalt 2006: Intervention participants received self-care education, picture-based educational materials with verbal explanation, a digital scale and scheduled follow-up phone calls (days 3,7, 14, 21, 28, 56) and monthly during months 3 – 6 for reinforcement of education and revision of individualised care plan. Domingues 2011: Education in hospital (3 - 5 visits). Systematic telephone contact (by a study nurse) for a3-month period. 1 telephone contact per week during the 1st month, followed by1 every 15 days in the 2nd and 3rd month. Galbreath 2004: All intervention participants received bathroom scales and were assigned a disease manager who administered the disease management programme telephonically. Initial call frequency was weekly then transitioned to monthly for the duration of the study. Call frequency could be adjusted for acuity or need. After each call a call summary was faxed to the participant's primary care provider. An additional randomisation was performed within the intervention arm, with some participants provided within-home technology (BP monitor, pulse oximeter). These measurements were reported by the participant to the disease manager, but the data were not forwarded to the primary care provider. These participants also wore activity monitors at regular intervals and had 6-monthly measurement of thoracic bioimpedance cardiac output; these data were not forwarded to the primary care physician. The authors' state: "because data derived from the technology were not used in clinical management, we combined results from the two treatment groups for the purposes of this analysis." Gattis 1999: Clinical pharmacist-led medication review and patient education. Regularly-scheduled telephone contact (at 2, 12 and 24 weeks) to detect clinical deterioration early GESICA 2005: Nurses trained in the management of people with CHF performed structured telephone follow-up based on adherence to diet and treatment, monitoring of symptoms, control offluid retention and

	daily physical activity. Participants were contacted 4 times in the first fortnight and then as needed Krum 2013: Nurse-led telephone monitoring using the Telewatch System (Baltimore). Participant responded to computer-generated CHF self-monitoring questions by pressing the numbers on the touch-phone key pad. Nurse survey incoming calls daily and responded to preset variations to participant’s parameters Laramee 2003: Telephonic case management performed by 1 CHF nurse case manager, involving 4 major components: early discharge planning, participant and family CHF education, promotion ofoptimal CHF medications and 12 weeks of telephone follow-up. Mortara 2009: Strategy 2 is classed as structured telephone support. Strategy 3 is classed as telemonitoring. Strategy 2 received monthly supportive telephone contacts from a study nurse to check on their clinical status and transmitted their vital signs and other data including details of changes in weight, BP and symptoms weekly by telephone. These participants also performed monthly 24h cardiorespiratory recordings which were not made available to the clinical team. Strategy 3 carried out the same measurements as strategy 2 participants, but the monthly 24h cardiorespiratory recordings were made available for clinical management. Rainville 1999: Usual care plus a pharmacist-led medication review, patient education, medication management prior to discharge and at day 3, day 7, 30 days, 90 days and 12 months via telephone Ramachandran 2007: Intervention group participants were managed in the heart failure clinic and received disease, medication and self-management education and telephonic disease management which consisted of reinforcement of information and drug dose modification Riegel 2002: Telephonic case management by a registered nurse using decision support software, involving patient education and counselling and liaison with primary care physician. Participants were telephoned within 5 days of discharge and thereafter at a frequency guided by the software and case manager (mean 17 calls) Riegel 2006: Education, monitoring and guidance by bilingual-bicultural Mexican-American registered nurses via telephone case management standardised using decision support software. Participants were contacted

	on average within 5 days of discharge and thereafter at a frequency guided by the software and nurse case manager over a 6-month period (mean 13.5 calls to participants and 8.4 additional calls to families). Printed educational material was provided monthly and upon request in the relevant language Sisk 2006: An in-person appointment was arranged for each intervention participant, which included symptom and disease education and referral to additional patient services (if required).Follow-up telephone calls consisted of participant assessment, recording of admission information reinforcement of self monitoring and administration of a food frequency questionnaire (at 2, 4, 8, 12 and 24 weeks and a report sent to participants). Intervention nurses coordinated flow of information between participant and clinician and arranged medication adjustment and required examinations Tsuyuki 2004: Early discharge planning with provision of adherence aids, patient education, regularly scheduled telephone contact with local research coordinator at 2 and 4 weeks then monthly thereafter for 6 months. Recommendations to see primary care physician if not on target dose ACE inhibitor or deterioration Wakefield 2008: Participants allocated to the intervention group were allocated to 1 of 2 interventions: telephone follow-up or videophone follow-up. Intervention participants were contacted by a nurse 3 times in the first week then weekly for 11 weeks. Symptoms and the participant’s discharge plan were reviewed and reinforced as well as referrals made if required. Additionally, the intervention nurses employed behavior skill training strategies to maximise self management, self monitoring and self efficacy (n=3860) Intervention 2: Telemonitoring (digital/broadband/satellite/wireless or Bluetooth transmission of physiological or other non-invasive data): Antonicelli 2008: Participants randomised to home telemonitoring-based care were contacted by telephone at least once a week to collect information on symptoms and treatment adherence as well as BP,HR, weight and 24h urine output on the previous day. A weekly ECG transmission was also obtained. Participants were then evaluated and their regimen altered when necessary based on these data. Additionally, clinic visits were performed when required based on the data collected or telephone interviews. Balk 2008: Participants in the intervention group were provided a MOTIVA system (TV-channel providing educational material, reminders of medication, health-related surveys and motivational messages to encourage the prescribed lifestyle regimen) in addition to scheduled cardiologist appointments. A subgroup

	of intervention participants also received automated BP and weight devices that automatically communicated readings via the telephone (those who had been hospitalised in the prior year for HF). Participant guidance followed a personalised plan. Biannic 2012: TM group: TM during 3 months, after which participants all received usual care up until 1 year. TM: intensity 3 times per week; variables: symptoms, weight and BP. Blum 2014: All participants were given written material about heart failure and self-management activities such as daily weights, medication administration, signs and symptoms of worsening heart failure, and were given an opportunity to ask questions or seek clarification as the handout was discussed. Intervention participants were instructed to use the scale, BP cuff/HR monitor and the heart rhythm strip monitor at the same time each day. The transmitted data were then compared to individually assigned parameters based on the participant's admission and subsequent evaluations. Readings outside these parameters were flagged for the nurse practitioner (NP) who did the monitoring. This NP, who had extensive experience in the management of people with heart failure contacted the participant to gather more information and, if appropriate, adjusted medications, usually diuretics. There were no specific protocols as to the management decisions, and decisions were based on the NP's experience or consultation with the participant's cardiologist, or both. If no flags were noted over the period of 1 month, the participants were called just to maintain contact, provide encouragement and answer any questions they might have. Cleland 2005: Participants assigned to the nurse telephone support arm received a telephone call each month by a heart failure specialist nurse to assess their symptoms and current medications. Participants assigned to telemonitoring received the nurse telephone support and had their weight, BP and ECG monitored twice daily. De Lusignan 2001: Telemonitoring of vital signs (pulse, BP, weight) and clinical status daily assessed daily by nurses along with video consultations with a nurse weekly for 3 months, fortnightly for 3 months, then monthly. Dendale 2012: Daily measurement of weight, BP and HR for 6 months. Participants were seen at the HF clinic 2 weeks after discharge and at 3 and 6 months (but were allowed to visit the clinic sooner or more frequently if necessary). Professionals involved: GP, heart failure clinic (HF nurse and cardiologist).

Giordano 2009: Home-Based Telemanagement (HBT) participants received a 1-lead trace portable device that transferred results via telephone where a nurse was available for interactive teleconsultation. Scheduled standardised telemonitoring appointments were performed every week to15 days depending on HF severity discussing symptomology, medications, self-care and, if required, the transmission of the ECG trace.

Goldberg 2003: Daily transmission
of weight and symptoms using a customised monitor, data was reviewed daily by nurses and concerns reported to the physician.

Koehler 2011: “The telemonitoring system used in the TIM-HF trial is based on a wireless Bluetooth system with a personal digital assistant (PDA) as the central structural element. The only prerequisite for this system to function once installed is the availability of a mobile phone network connection. Three measuring devices are integrated into the system, namely one to collect electrocardiogram (ECG) measurements, one to collect BP measurements, and one to collect body weight. Each device is equipped with a Bluetooth chip and connected to the PDA. The patient performs the daily self-assessment of health status by using the PDA interface. A subgroup of patients in the intervention group performed a 6-min walk test using a telemedical accelerometer once a month starting 3 months after randomization.”

Lyngå 2012: “Patients randomized to the IG were given an electronic scale (Zenicor Medical Systems AB) to install in their homes. A few patients required help to install the electronic scale. The scale could be placed anywhere in the patients’ home and, after weighing, a wireless signal was sent from the scale to a modem plugged into the patient’s telephone. The weight was then automatically transmitted via the telephone network to a central internet-based data server system (Zenicor Medical Systems AB). Hence, the weight could be checked from any computer with internet access. The Zenicor system produces an alarm if patients show a weight gain of .2 kg from the target weight (body weight at discharge from hospital) and also if there is an upward trend with a weight increase of .2 kg in 3 days.”

Mortara 2009: Strategy 2 is classed as structured telephone support. Strategy 3 is classed as telemonitoring. Strategy 2 received monthly supportive telephone contacts from a study nurse to check on their clinical status and transmitted their vital signs and other data including details of changes in weight, BP and

	symptoms weekly by telephone. These participants also performed monthly 24h cardiorespiratory recordings which were not made available to the clinical team. Strategy 3 carried out the same measurements as strategy 2 participants, but the monthly 24h cardiorespiratory recordings were made available for clinical management. Scherr 2009: “Tele group patients were asked to measure vital parameters (blood pressure, heart rate, body weight) on a daily basis at the same time, preferably in the morning after emptying the bladder and before dressing and taking medication. Thereafter, patients were advised to enter these values as well as their dosage of heart failure medication into the mobile phone’s Internet browser and send them to the monitoring center provided by the Austrian Institute of Technology (AIT) - Information Management & eHealth, Graz. Study physicians had access to a secure website providing both numerical and graphical depiction of data for each patient.” Seto 2012: “The participants in the telemonitoring group received the telemonitoring system in addition to standard care. They were asked to use the telemonitoring system for 6 months to take daily morning weight and blood pressure readings as well as weekly single lead electrocardiograms (ECGs) if provided with an ECG recorder. They were also asked to answer daily morning symptom questions on a mobile phone. Only the 17 patients who did not have an implantable cardioverter defibrillator (ICD) were provided with an ECG recorder because the recorder was not certified for use with ICDs. Patients were also told to report their symptoms through the mobile phone if they did not feel well during the day. The patients in the telemonitoring group were given an individual training session on how to use the system during the recruitment session, and were provided with technical support by telephone throughout the study. The daily measurements took about 5 minutes each morning.” Soran 2008: Participants randomised to the Heart Failure Monitoring System (HFMS) cohort received a disease management programme using telecommunication equipment including an electronic scale and individualised symptom response system linked to a database staffed by nurses. Participants weighed themselves and answered questions related to their heart failure. Participants were contacted if any changes were observed in symptoms or weight. Villani 2014: “Integrated Management group, patients and their caregivers had specific training in the use of the dedicated PDA described above. Each day, the PDA acted as a reminder of the correct timing for the pills.

	At a predefined time patients were asked to send their body weight, blood pressure and heart rate data via the PDA. In some cases patients were asked to monitor their diuresis. Each month, a psychological assessment was performed through the PDA software about anxiety (STAI-6; Spielberger's State Trait Anxiety Inventory, depression (PHQ-9; Patient Health Questionnaire) 18 and perceived well being (PGWBI; Perception of General Well-Being Inventory)." Vuorinen 2014: "Patients regularly reported their most important health parameters to the nurse using a mobile phone app. At the beginning of the study, the patients were given a homecare package including a weight scale, a blood pressure meter, a mobile phone, and self care instructions. The patients were advised to carry out and report the measurements together with the assessment of symptoms once a week." Woodend 2008: Daily transmission of weight and periodic transmission of ECG and BP. Weekly video conferences by tele-home care nurse. Video conferences more frequent in first few weeks and tapered over the 3 months. (n=13192) Intervention 3: Usual care - Usual care (standard post discharge care without intensified attendance at cardiology or HF disease management clinic, or home visiting). . 'Usual care' consisted of standard post-discharge care without intensified attendance at cardiology clinics or clinic-based heart failure disease management programme, or home visiting as described above.. Duration 3-24 months. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Studies report various sources of funding. Funnel plots constructed by the authors of this review demonstrated a strong publication bias in the included studies.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STRUCTURED TELEPHONE SUPPORT (MONITORING OR SELF-CARE MANAGEMENT USING SIMPLE TELEPHONE TECHNOLOGY) versus USUAL CARE (STANDARD POST DISCHARGE CARE WITHOUT INTENSIFIED ATTENDANCE AT CARDIOLOGY OR HF DISEASE MANAGEMENT CLINIC, OR HOME VISITING).

Protocol outcome 1: All-cause mortality
All-cause mortality during study at 3-24 month

Recent admission

Angermann 2012 (INH) - STS: 32/352; UC: 52/363

Risk of bias: All domain –High, Random sequence generation - Low, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - High, Selective reporting - Low; Indirectness of outcome: No indirectness

Barth 2001 - STS: 0/17; UC: 0/17

Risk of bias: All domain –Very high, Random sequence generation - Unclear, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data - Unclear, Selective reporting - Low; Indirectness of outcome: No indirectness

Capomolla 2004 - STS: 5/67; UC: 7/66

Risk of bias: All domain –Very high, Random sequence generation - Unclear, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data - Unclear, Selective reporting - Low; Indirectness of outcome: No indirectness

Chaudhry 2010 (Tele-HF) - STS: 92/826; UC: 94/827

Risk of bias: All domain –High, Random sequence generation - Low, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - Low, Selective reporting - High; Indirectness of outcome: No indirectness

Cleland 2005 (Struct-tele) (TENS-HMS) - STS: 27/173; UC: 20/85

Risk of bias: All domain –High, Random sequence generation - Low, Allocation concealment – Low, Blinding of outcome assessment - Unclear, Incomplete outcome data - High, Selective reporting – Low; Indirectness of outcome: No indirectness

DeBusk 2004 - STS: 21/228; UC: 29/234

Risk of bias: All domain –High, Random sequence generation - Low, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - High, Selective reporting – Low; Indirectness of outcome: No indirectness

Domingues 2011 - STS: 8/57; UC: 13/63

Risk of bias: All domain –Very high, Random sequence generation - Unclear, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data - High, Selective reporting – Low; Indirectness of outcome: No indirectness

Laramee 2003 - STS: 13/141; UC: 15/146

Risk of bias: All domain –Very high, Random sequence generation - Unclear, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data - High, Selective reporting – Low; Indirectness of outcome: No indirectness

Rainville 1999 - STS: 1/19; UC: 4/19

Risk of bias: All domain –High, Random sequence generation - Unclear, Allocation concealment – Low, Blinding of outcome assessment - Unclear, Incomplete outcome data - Low, Selective reporting - Low Indirectness of outcome: No indirectness

Riegel 2002 - STS: 16/130; UC: 32/228

Risk of bias: All domain –High, Random sequence generation - Unclear, Allocation concealment – Low, Blinding of outcome assessment - Unclear, Incomplete outcome data - Unclear, Selective reporting – Low; Indirectness of outcome: No indirectness

Riegel 2006 - STS: 6/70; UC: 8/65

Risk of bias: All domain –Low, Random sequence generation - Unclear, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - Low, Selective reporting – Low; Indirectness of outcome: No indirectness
Sales 2014 – STS:5/70; UC:5/67
Risk of bias: All domain –High, Random sequence generation - Low, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data - Unclear, Selective reporting – Low; Indirectness of outcome: No indirectness
Tsuyuki 2004 - STS: 16/140; UC: 12/136
Risk of bias: All domain –High, Random sequence generation - Low, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data - Unclear, Selective reporting – Low; Indirectness of outcome: No indirectness
Wakefield 2008 - STS: 25/99; UC: 11/49
Risk of bias: All domain –Low, Random sequence generation - Low, Allocation concealment – Low, Blinding of outcome assessment - Unclear, Incomplete outcome data - Low, Selective reporting – Low; Indirectness of outcome: No indirectness

Community
Baker 2011 - STS: 0/303; UC: 2/302
Risk of bias: All domain –High, Random sequence generation - Low, Allocation concealment – Low, Blinding of outcome assessment - Unclear, Incomplete outcome data - High, Selective reporting - Low; Indirectness of outcome: No indirectness
Bento 2009 - STS: 0/20; UC: 1/20
Risk of bias: All domain –Very high, Random sequence generation - Low, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data - Unclear, Selective reporting – High; Indirectness of outcome: No indirectness
DeWalt 2006 - STS: 3/62; UC: 4/65
Risk of bias: All domain –High, Random sequence generation - Low, Allocation concealment – Unclear, Blinding of outcome assessment - High, Incomplete outcome data - Low, Selective reporting – Low; Indirectness of outcome: No indirectness
Galbreath 2004 - STS: 54/710; UC: 39/359
Risk of bias: All domain –Very high, Random sequence generation - Unclear, Allocation concealment – Low, Blinding of outcome assessment - Unclear, Incomplete outcome data - High, Selective reporting – Low; Indirectness of outcome: No indirectness
Gattis 1999 (PHARM) - STS: 3/90; UC: 5/91
Risk of bias: All domain –High, Random sequence generation - Low, Allocation concealment – Unclear, Blinding of outcome assessment - Low, Incomplete outcome data - Unclear, Selective reporting - Low Indirectness of outcome: No indirectness
GESICA 2005 (DIAL) - STS: 116/760; UC: 122/758
Risk of bias: All domain –Low, Random sequence generation - Low, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - Low, Selective reporting – Low; Indirectness of outcome: No indirectness
Krum 2013 (CHAT) - STS: 17/188; UC: 16/217

Risk of bias: All domain –Low, Random sequence generation - Low, Allocation concealment – Unclear, Blinding of outcome assessment - Low, Incomplete outcome data - Low, Selective reporting – Low; Indirectness of outcome: No indirectness
Sisk 2006 - STS: 22/203; UC: 22/203
Risk of bias: All domain – Low, Random sequence generation - Low, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - Low, Selective reporting – Low; Indirectness of outcome: No indirectness

Mixed
Mortara 2009 (Struct Tele) (HHH) - STS: 7/94; UC: 9/160
Risk of bias: All domain –High, Random sequence generation - Unclear, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - Unclear, Selective reporting – Unclear; Indirectness of outcome: No indirectness

Protocol outcome 2: Quality of life
Quality of life during study at 3-24 months;
Recent admission
Angermann 2012 (INH) SF-36 Physical health component (mean (SD)): STS: 2.8 (10); UC: 1.3 (9.9)
Risk of bias: All domain –High, Random sequence generation - Low, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - High, Selective reporting - Low; Indirectness of outcome: No indirectness
Angermann 2012 (INH) SF-36 Physical functioning component (mean (SD)): STS: 5.9 (25.8); UC: 1.8 (24.7)
Risk of bias: All domain –High, Random sequence generation - Low, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - High, Selective reporting - Low; Indirectness of outcome: No indirectness
Baker 2011 HFSS (mean (SD)): STS: 65.3 (22.4); UC: 64.1 (22.8)
Risk of bias: All domain –Very high, Random sequence generation - Unclear, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data - High, Selective reporting – Low; Indirectness of outcome: No indirectness
Riegel 2006 MLWHFQ (mean (SD)): STS: 12.1 (12.3); UC: 12.9 (10.9)
Risk of bias: All domain –Low, Random sequence generation - Unclear, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - Low, Selective reporting – Low; Indirectness of outcome: No indirectness
Riegel 2006 EQ-5D (mean (SD)): STS: 0.82 (0.2); UC: 0.78 (0.2)
Risk of bias: All domain –Low, Random sequence generation - Unclear, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - Low, Selective reporting – Low; Indirectness of outcome: No indirectness

Community
DeWalt 2006 MLWHFQ (MD (SE)): 2 (3.57)

Risk of bias: All domain –High, Random sequence generation - Low, Allocation concealment – Unclear, Blinding of outcome assessment - High, Incomplete outcome data - Low, Selective reporting – Low; Indirectness of outcome: No indirectness
GESICA 2005 (DIAL) MLWHFQ (MD (SE)): -4.4 (1.3)
Risk of bias: All domain –Low, Random sequence generation - Low, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - Low, Selective reporting – Low; Indirectness of outcome: No indirectness
Sisk 2006 MLWHFQ (MD (SE)): -7.3 (2.7)
Risk of bias: All domain – Low, Random sequence generation - Low, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - Low, Selective reporting – Low; Indirectness of outcome: No indirectness

Mixed
Ramachandran 2007 KCCQ HRQoL (mean (SD)): STS: 76.3 (17.3); UC: 63.4 (21.9)
Risk of bias: All domain –Very high, Random sequence generation - Low, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data - Unclear, Selective reporting – Low; Indirectness of outcome: No indirectness

Protocol outcome 3: All-cause hospitalisation
All-cause hospitalisation during study at 3-24 months
Recent admission
Angermann 2012 (INH) - STS: 119/352; UC: 112/363
Risk of bias: All domain –High, Random sequence generation - Low, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - High, Selective reporting - Low; Indirectness of outcome: No indirectness
Chaudhry 2010 (Tele-HF) - STS: 407/826; UC: 392/827
Risk of bias: All domain –High, Random sequence generation - Low, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - Low, Selective reporting - High; Indirectness of outcome: No indirectness
Cleland 2005 (Struct Tele) (TENS-HMS) - STS: 85/173; UC: 46/85
Risk of bias: All domain –High, Random sequence generation - Low, Allocation concealment – Low, Blinding of outcome assessment - Unclear, Incomplete outcome data - High, Selective reporting – Low; Indirectness of outcome: No indirectness
DeBusk 2004 - STS: 116/228; UC: 117/234
Risk of bias: All domain –High, Random sequence generation - Low, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - High, Selective reporting – Low; Indirectness of outcome: No indirectness
Domingues 2011 - STS: 20/57: UC: 23/63
Risk of bias: All domain –Very high, Random sequence generation - Unclear, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data - High, Selective reporting – Low; Indirectness of outcome: No indirectness

Laramee 2003 - STS: 49/141: UC: 46/146
Risk of bias: All domain –Very high, Random sequence generation - Unclear, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data - High, Selective reporting – Low; Indirectness of outcome: No indirectness
Riegel 2002 - STS: 56/130; UC: 114/228
Risk of bias: All domain –High, Random sequence generation - Unclear, Allocation concealment – Low, Blinding of outcome assessment - Unclear, Incomplete outcome data - Unclear, Selective reporting – Low; Indirectness of outcome: No indirectness
Riegel 2006 - STS: 39/70; UC: 37/65
Risk of bias: All domain –Low, Random sequence generation - Unclear, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - Low, Selective reporting – Low; Indirectness of outcome: No indirectness
Tsuyuki 2004 - STS: 59/140; UC: 51/136
Risk of bias: All domain –High, Random sequence generation - Low, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data - Unclear, Selective reporting – Low; Indirectness of outcome: No indirectness
Wakefield 2008 - STS: 41/99; UC: 29/49
Risk of bias: All domain –Low, Random sequence generation - Low, Allocation concealment – Low, Blinding of outcome assessment - Unclear, Incomplete outcome data - Low, Selective reporting – Low; Indirectness of outcome: No indirectness

Community
Bento 2009 - STS: 2/20; UC: 10/20
Risk of bias: All domain –Very high, Random sequence generation - Low, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data - Unclear, Selective reporting – High; Indirectness of outcome: No indirectness
Gattis 1999 (PHARM) - STS: 17/90; UC: 30/91
Risk of bias: All domain –High, Random sequence generation - Low, Allocation concealment – Unclear, Blinding of outcome assessment - Low, Incomplete outcome data - Unclear, Selective reporting - Low Indirectness of outcome: No indirectness
GESICA 2005 (DIAL) - STS: 261/760; UC: 296/758
Risk of bias: All domain –Low, Random sequence generation - Low, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - Low, Selective reporting – Low; Indirectness of outcome: No indirectness
Krum 2013 (CHAT) - STS: 74/188; UC: 114/217
Risk of bias: All domain –Low, Random sequence generation - Low, Allocation concealment – Unclear, Blinding of outcome assessment - Low, Incomplete outcome data - Low, Selective reporting – Low; Indirectness of outcome: No indirectness
Sisk 2006 - STS: 62/203; UC: 74/203
Risk of bias: All domain – Low, Random sequence generation - Low, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - Low, Selective reporting – Low; Indirectness of outcome: No indirectness

Mixed
Mortara 2009 (Struct Tele) (HHH) - STS: 34/94; UC: 48/160
Risk of bias: All domain –High, Random sequence generation - Unclear, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - Unclear, Selective reporting – Unclear; Indirectness of outcome: No indirectness

Protocol outcome 4: Adherence to intervention
Adherence to intervention at 3-24 months;
Recent admission
Laramee 2003 (STS)
Weigh self daily (MD (SE)): 1.5 (0.45)
Check ankles and feet for swelling (MD (SE)): 0.4 (0.13)
Follow fluid recommendation (MD (SE)): 0.4 (0.14)
Follow low-salt diet (MD (SE)): 0.3 (0.09)
Take medications (MD (SE)): 0.1 (0.07)
Risk of bias: All domain –Very high, Random sequence generation - Unclear, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data - High, Selective reporting – Low; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TELEMONITORING (DIGITAL/BROADBAND/SATELLITE/WIRELESS OR BLUETOOTH TRANSMISSION OF PHYSIOLOGICAL OR OTHER NON-INVAISIVE DATA) versus USUAL CARE (STANDARD POST DISCHARGE CARE WITHOUT INTENSIFIED ATTENDANCE AT CARDIOLOGY OR HF DISEASE MANAGEMENT CLINIC, OR HOME VISITING).

Protocol outcome 1: All-cause mortality
All-cause mortality during study at 3-24 months
Recent admission
Antonicelli 2008 - TM: 3/28; UC: 5/29
Risk of bias: All domain –High, Random sequence generation - Unclear, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data - Low, Selective reporting – Low; Indirectness of outcome: No indirectness
Biannic 2012 (SEDIC) - TM: 8/45; UC: 14/45
Risk of bias: All domain –Very high, Random sequence generation - Unclear, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data - High, Selective reporting – Low; Indirectness of outcome: No indirectness
Cleland 2005 (Telemon) (TENS-HMS) - TM: 28/168; UC: 20/85

Risk of bias: All domain –High, Random sequence generation - Low, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data - High, Selective reporting – Low; Indirectness of outcome: No indirectness
Dendale 2012 (TEMA-HF1) - TM: 4/80; UC: 14/80
Risk of bias: All domain –Low, Random sequence generation - Low, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - Low, Selective reporting – Low; Indirectness of outcome: No indirectness
Goldberg 2003 (WHARF) - TM: 11/138; UC: 26/142
Risk of bias: All domain –Low, Random sequence generation - Unclear, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - Low, Selective reporting – Low; Indirectness of outcome: No indirectness
Lynga 2012 (WISH) - TM: 5/166; UC: 8/153
Risk of bias: All domain –High, Random sequence generation - Unclear, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data - Low, Selective reporting – Low; Indirectness of outcome: No indirectness
Scherr 2009 (MOBITEL) - TM: 0/66; UC: 1/54
Risk of bias: All domain –High, Random sequence generation - Unclear, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data - Low, Selective reporting – Low; Indirectness of outcome: No indirectness
Villani 2014 (ICAROS) - TM: 5/40; UC: 9/40
Risk of bias: All domain –Low, Random sequence generation - Low, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data - Low, Selective reporting – Low; Indirectness of outcome: No indirectness
Woodend 2008 - TM: 5/62; UC: 4/59
Risk of bias: All domain –Very high, Random sequence generation - Unclear, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data - Unclear, Selective reporting – High; Indirectness of outcome: No indirectness

Community
De Lusignan 2001 - TM: 2/10; UC: 3/10
Risk of bias: All domain –High, Random sequence generation - Low, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data - Unclear, Selective reporting – Low; Indirectness of outcome: No indirectness

Mixed
Balk 2008 - TM: 9/101; UC: 8/113
Risk of bias: All domain –Low, Random sequence generation - Low, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data – Low, Selective reporting – Low; Indirectness of outcome: No indirectness
Blum 2014 (MCCD) - TM: 49/104; UC: 45/102
Risk of bias: All domain –Very high, Random sequence generation - Unclear, Allocation concealment – Unclear, Blinding of outcome assessment -

Unclear, Incomplete outcome data - High, Selective reporting – Low; Indirectness of outcome: No indirectness
Giordano 2009 - TM: 21/230; UC: 32/230
Risk of bias: All domain –Very high, Random sequence generation - Unclear, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data - High, Selective reporting – Low; Indirectness of outcome: No indirectness
Koehler 2011 (TIM-HF) - TM: 54/354; UC: 55/356
Risk of bias: All domain –Low, Random sequence generation - Low, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - Low, Selective reporting – Low; Indirectness of outcome: No indirectness
Mortara 2009 (Telemon) (HHH) - TM: 8/101; UC: 9/160
Risk of bias: All domain –High, Random sequence generation - Unclear, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - Unclear, Selective reporting – Unclear; Indirectness of outcome: No indirectness
Seto 2012 - TM: 3/50; UC: 0/50
Risk of bias: All domain –High, Random sequence generation - Low, Allocation concealment – Low, Blinding of outcome assessment - High, Incomplete outcome data - High, Selective reporting – Low; Indirectness of outcome: No indirectness
Soran 2008 - TM: 11/160; UC: 17/155
Risk of bias: All domain –High, Random sequence generation - Unclear, Allocation concealment – Unclear, Blinding of outcome assessment - Low, Incomplete outcome data - Low, Selective reporting – Low; Indirectness of outcome: No indirectness
Vuorinen 2014 - TM: 0/47; UC: 0/47
Risk of bias: All domain –High, Random sequence generation - High, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data - High, Selective reporting – Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Quality of life
Quality of life during study at 3-24 months
Recent admission
Antonicelli 2008 SF-36 Physical component summary (mean (SD)): TM: 39 (11); UC: 39 (11)
Risk of bias: All domain –Very high, Random sequence generation - Unclear, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data - High, Selective reporting – Low; Indirectness of outcome: No indirectness
Antonicelli 2008 SF-36 Mental component summary (mean (SD)): TM: 53 (12); UC: 48 (9)
Risk of bias: All domain –High, Random sequence generation - Unclear, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data - Low, Selective reporting – Low; Indirectness of outcome: No indirectness
Goldberg 2003 (WHARF) MLWHFQ total score (mean (SD)): TM: 27.8 (23.8); UC: 23.3 (26.9)
Risk of bias: All domain –Low, Random sequence generation - Unclear, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - Low, Selective reporting – Low; Indirectness of outcome: No indirectness

Goldberg 2003 (WHARF) SF-12 Physical (mean (SD)): TM: 6.7 (10.4); UC: 4.3 (11.4)
Risk of bias: All domain –Low, Random sequence generation - Unclear, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - Low, Selective reporting – Low; Indirectness of outcome: No indirectness
Goldberg 2003 (WHARF) SF-12 Mental (mean (SD)): TM: 5.9 (10.6) UC: 5.2 (13.2)
Risk of bias: All domain –Low, Random sequence generation - Unclear, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - Low, Selective reporting – Low; Indirectness of outcome: No indirectness
Goldberg 2003 (WHARF) Health distress score (mean (SD)): TM: 4.8 (8.3) UC: 5.5 (8.8)
Risk of bias: All domain –Low, Random sequence generation - Unclear, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - Low, Selective reporting – Low; Indirectness of outcome: No indirectness
Biannic 2012 (SEDIC) MLWHFQ (MD (SE)): 1.9 (2.61)
Risk of bias: All domain –Very high, Random sequence generation - Unclear, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data - High, Selective reporting – Low; Indirectness of outcome: No indirectness

Mixed
Blum 2014 (MCCD) SF-36 Physical component summary (mean (SD)): TM: 38 (10); UC: 38 (11)
Risk of bias: All domain –Very high, Random sequence generation - Unclear, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data - High, Selective reporting – Low; Indirectness of outcome: No indirectness
Blum 2014 (MCCD) SF-36 Mental component summary (mean (SD)): TM: 52 (11); UC: 55 (9)
Risk of bias: All domain –Very high, Random sequence generation - Unclear, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data - High, Selective reporting – Low; Indirectness of outcome: No indirectness
Blum 2014 (MCCD) MLWHFQ (mean (SD)): TM: 24 (24); UC: 18 (21)
Risk of bias: All domain –Very high, Random sequence generation - Unclear, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data - High, Selective reporting – Low; Indirectness of outcome: No indirectness
Seto 2012 MLWHFQ (mean (SD)): TM: 41.4 (26.7); UC: 47.3 (23.4)
Risk of bias: All domain –High, Random sequence generation - Low, Allocation concealment – Low, Blinding of outcome assessment - High, Incomplete outcome data - High, Selective reporting – Low; Indirectness of outcome: No indirectness
Koehler 2011 (TIM-HF) SF-36 Physical functioning component (mean (SD)): TM: 53.8 (1.4); UC: 51.7 (1.4)
Risk of bias: All domain –Very high, Random sequence generation - Unclear, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data - High, Selective reporting – Low; Indirectness of outcome: No indirectness

Protocol outcome 3: All-cause hospitalisation
All-cause hospitalisation during study at 3-24 months;

Recent admission

Antonicelli 2008 - TM: 9/28; UC: 26/29
Risk of bias: All domain –High, Random sequence generation - Unclear, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data - Low, Selective reporting – Low; Indirectness of outcome: No indirectness
Biannic 2012 (SEDIC) - TM: 19/45; UC: 35/45
Risk of bias: All domain –Very high, Random sequence generation - Unclear, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data - High, Selective reporting – Low; Indirectness of outcome: No indirectness
Cleland 2005 (Telemon) (TENS-HMS) - TM: 80/168; UC: 46/85
Risk of bias: All domain –High, Random sequence generation - Low, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data - High, Selective reporting – Low; Indirectness of outcome: No indirectness
Dendale 2012 (TEMA-HF1) - TM: 64/80; UC: 66/80
Risk of bias: All domain –Low, Random sequence generation - Low, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - Low, Selective reporting – Low; Indirectness of outcome: No indirectness
Goldberg 2003 (WHARF) - TM: 65/138; UC: 67/142
Risk of bias: All domain –Low, Random sequence generation - Unclear, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - Low, Selective reporting – Low; Indirectness of outcome: No indirectness
Lynga 2012 (WISH) - TM: 79/166; UC: 84/153
Risk of bias: All domain –High, Random sequence generation - Unclear, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data - Low, Selective reporting – Low; Indirectness of outcome: No indirectness
Scherr 2009 (MOBITEL) - TM: 11/66; UC: 17/54
Risk of bias: All domain –High, Random sequence generation - Unclear, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data - Low, Selective reporting – Low; Indirectness of outcome: No indirectness
Woodend 2008 - TM: 60/62; UC: 54/59
Risk of bias: All domain –Very high, Random sequence generation - Unclear, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data - Unclear, Selective reporting – High; Indirectness of outcome: No indirectness

Mixed

Blum 2014 (MCCD) - TM: 80/104; UC: 74/102
Risk of bias: All domain –Very high, Random sequence generation - Unclear, Allocation concealment – Unclear, Blinding of outcome assessment - Unclear, Incomplete outcome data - High, Selective reporting – Low; Indirectness of outcome: No indirectness
Giordano 2009 - TM: 67/230; UC: 96/230
Risk of bias: All domain –Very high, Random sequence generation - Unclear, Allocation concealment – Unclear, Blinding of outcome assessment -

Unclear, Incomplete outcome data - High, Selective reporting – Low; Indirectness of outcome: No indirectness Koehler 2011 (TIM-HF) - TM: 192/354; UC: 179/356 Risk of bias: All domain –Low, Random sequence generation - Low, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - Low, Selective reporting – Low; Indirectness of outcome: No indirectness Mortara 2009 (Telemon) (HHH) - TM: 35/101; 48/160 Risk of bias: All domain –High, Random sequence generation - Unclear, Allocation concealment – Low, Blinding of outcome assessment - Low, Incomplete outcome data - Unclear, Selective reporting – Unclear; Indirectness of outcome: No indirectness Seto 2012 - TM: 14/50; UC: 10/50 Risk of bias: All domain –High, Random sequence generation - Low, Allocation concealment – Low, Blinding of outcome assessment - High, Incomplete outcome data - High, Selective reporting – Low; Indirectness of outcome: No indirectness Soran 2008 - TM: 75/160; UC: 66/155 Risk of bias: All domain –High, Random sequence generation - Unclear, Allocation concealment – Unclear, Blinding of outcome assessment - Low, Incomplete outcome data - Low, Selective reporting – Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Not applicable

Study	**BEAT-HF trial: Ong 2016[1085]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=Intervention: 715; Usual care: 722)
Countries and setting	Conducted in USA; Setting: Patients home or usual care (hospital)
Line of therapy	Not applicable
Duration of study	Intervention time: 180 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis

Stratum	Recent admission
Subgroup analysis within study	Not applicable
Inclusion criteria	Individuals admitted as hospital inpatients or on observation status were eligible if they were 50 years or older, were receiving active treatment for decompensated HF (defined as HF with the initiation of or an increase in diuretic treatment), were expected to be discharged to their home, and were capable of providing written informed consent in English, Spanish, Farsi, or Russian
Exclusion criteria	Patients who did not have the cognitive or physical ability (eg, dementia or weight >204kg) or access to resources (eg, working telephone or usual source of care) required to fully participate in the BEAT-HF intervention. Patients already in a system of care providing more health professional contacts than the planned intervention (eg, living in a skilled nursing facility, receiving chronic heamodialysis, or awaiting or having received an organ transplant). Patients whose HF was due to a cardiovascular condition that was expected to improve because of medical intervention (eg, percutaneous coronary intervention or interventional valve procedure during hospitalization).
Age, gender and ethnicity	Age - Median (IQR): Intervention: 73 (62-84); Usual care: 74 (63-82). Gender (M:F): Intervention (% female): 46.6 (42.9-50.2); Usual care (% female): 47.1 (42.8-51.4). Ethnicity: Intervention %: African American - 21.5 (18.5-24.5); Hispanic/Latino - 12.0 (9.6 - 14.3); White - 54.7 (51.0-58.4); Asian/Pacific Islander or other - 11.8 (9.4-14.2) Usual Care %: African American - 22.7 (19.6-25.8); Hispanic/Latino - 10.9 (8.6-13.1); White - 54.3 (50.7-58.0); Asian/Pacific Islander or other - 12.1 (9.7-14.5)
Further population details	Not reported
Indirectness of population	No indirectness
Interventions	(n=715) Intervention 1: Structured telephone support - Structured telephone support (monitoring or self-care management using simple telephone technology). STS + TM The intervention consisted of 3 components conducted by registered nurses: pre discharge HF education, regularly scheduled telephone coaching, and home telemonitoring of weight, blood pressure, heart rate and

	symptoms. Pre discharge HF education was conducted by a trained nurse who guided patients through a booklet developed for patients with low health literacy that covered an explanation of HF, medication adherence, salt avoidance, fluid monitoring, exercising with HF, and daily check-up of weight and edema, as well as when to call the HF treatment team. The pre education also included a demonstration of how to use the remote home telemonitoring equipment and an explanation of why monitoring physiological variables is important for patients. The electronic equipment consisted of a wireless transmission pod, a weigh scale, and a blood pressure and heart rate monitor integrated with a device that could display text questions and send simple text responses. Devices automatically transmitted data back to central servers for telemonitoring review by telephone call center study nurses based at the primary study site. Intervention patients were scheduled to receive 9 telephone coaching calls over a 6-month period, who had access to patients medical histories and medication records. The nurse first contacted each enrolled patient 2 or 3 days after discharge from the hospital to reinforce the pre discharge health coaching topics. Subsequent telephone nurse coaching then occurred on a weekly basis during the first month after discharge. After the first month, nurse coaching telephone calls were made monthly until the end of the 6-month study period. All telephone calls covered content reinforcing the pre discharge education materials. Patients were asked to use the telemonitoring equipment daily to transmit their weight, blood pressure, heart rate and responses to 3 symptom questions, which were sent via cellular bandwidth to a secure server and were accessed daily by the telephone call centre nurses. Readings that exceeded predetermined threshold variables generated a trigger for the nurse to telephone the patient to investigate potential causes. . Duration 180 days. Concurrent medication/care: The intervention did not substitute for usual care surveillance. Patients were not precluded from exposure to other readmission reduction or chronic disease management programs implemented by hospitals, physician groups, or health plans, such as education about HF, pharmacist consultation, and post discharge telephone calls. Indirectness: No indirectness (n=722) Intervention 2: Usual care - Usual care (standard post discharge care without intensified attendance at cardiology or HF disease management clinic, or home visiting). . Usual care included robust pre discharge education and often a post discharge follow-up telephone call. No additional surveillance was provided to control patients beyond whatever may have been requested as part of routine clinical practice.. Duration 180 days. Concurrent medication/care: Not reported. Indirectness: No indirectness

Funding	Academic or government funding (Agency for Healthcare Research and Quality, the National Heart, Lung, and Blood Institute, National Centre for Advancing Translational Science of the University of California, Robert Wood Johnson Foundation, Sierra Health Foundation, and the University of California Centre for Health Quality and Innovation)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STRUCTURED TELEPHONE SUPPORT (MONITORING OR SELF-CARE MANAGEMENT USING SIMPLE TELEPHONE TECHNOLOGY) versus USUAL CARE (STANDARD POST DISCHARGE CARE WITHOUT INTENSIFIED ATTENDANCE AT CARDIOLOGY OR HF DISEASE MANAGEMENT CLINIC, OR HOME VISITING). Protocol outcome 1: All-cause mortality - Actual outcome for Recent admission: 180-day mortality at 180 days; Group 1: 100/715, Group 2: 114/722 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Quality of life - Actual outcome for Recent admission: QoL measured by MLHFQ at 180 days; Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: All-cause hospitalization - Actual outcome for Recent admission: 180-day all-cause readmission at 180 days; Group 1: 363/715, Group 2: 355/722 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Adherence to intervention

Study	**Sales 2014[1238]**

Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=137)
Countries and setting	Conducted in USA; Setting: New York Methodist Hospital
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 30 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Recent admission
Subgroup analysis within study	Not applicable
Inclusion criteria	Clinical signs and symptoms of CHF.
Exclusion criteria	Dementia or other severe psychiatric illness, and patients transferred to another hospital before discharge.
Recruitment/selection of patients	A team of trained volunteer staff and cardiologists worked together to recruit the patients for this study; volunteers initially screened for potential candidates by: 1) daily review of all admissions through the emergency room for shortness of breath; 2) daily review of all telemetry and coronary care unit admissions for shortness of breath; and 3) daily review of all pro-B type natriuretic peptide levels (>1,000 pg/mL) in the hospital via the electronic medical record system. Patients found with any of these 3 criteria were presented to a cardiologist who reviewed the hospital chart and visited the patient. Once the cardiologist confirmed that the patient presented with clinical signs and symptoms of CHF, and established CHF as the primary diagnosis, the patient was approached to be enrolled in the study.
Age, gender and ethnicity	Age - Mean (SD): 72.6 (14.1). Gender (M:F): 58/79. Ethnicity: Not reported

Further population details	Not reported
Indirectness of population	No indirectness
Interventions	(n=70) Intervention 1: Structured telephone support - (monitoring or self-care management using simple telephone technology). Before being discharged from the hospital, the patients received a visit from one of the volunteer staff to receive additional education regarding their CHF conditions and a treatment and management plan. The education addressed the following: 1) information regarding their main diagnosis; 2) review of all discharge medications, including their names, dosages and frequencies of administration; 3) primary care physicians name (PCP), telephone number and date and time of their follow up visit; 4) advice on following a low salt diet; 5) advice to restrict oral fluid intake to 1.5L/d; and 6) instructions to monitor weight daily and to call PCP if there was >2-3 lb weight gain in 1 week. Within 24-48 hours of their discharge, patients received their first follow-up phone call from one of the volunteer staff. Subsequently, patietns continued to receive a weekly phone call for 1 month to reinforce the discharge instructions. The volunteer staff educated and coached patients to call their PCP if they were not feeling well or have expressed discomfort, or to call 911 if they were feeling an acute episode. Progress and results were documented and shred with cardiologists. Duration 30 days. Concurrent medication/care: Not reported. Indirectness: No indirectness (n=67) Intervention 2: Usual care - (standard post discharge care without intensified attendance at cardiology or HF disease management clinic, or home visiting). . Patients received standard hospital care in accordance with the current clinical guidelines for patients with CHF. The standard of care in the hospital included a standardized discharge instruction sheet and a nurse led review of medications and patient education about medication, diet, and their diagnosis, with a total conversation time of 10-15 minutes. Before discharge all patients received their schedule appointments with their PCP as arranged by the hospital physicians and unit clerks. In case the patients did not have the exact follow-up date in mind, they were given clear instructions and written information of their PCP's name and telephone number.. Duration 30 days. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STRUCTURED TELEPHONE SUPPORT (MONITORING OR SELF-CARE MANAGEMENT USING SIMPLE TELEPHONE TECHNOLOGY) versus USUAL CARE (STANDARD POST DISCHARGE CARE WITHOUT INTENSIFIED ATTENDANCE AT CARDIOLOGY OR HF DISEASE MANAGEMENT CLINIC, OR HOME VISITING). Protocol outcome 1: All-cause mortality - Actual outcome for Recent admission: All-cause mortality at 30 days; Group 1: 5/70, Group 2: 5/67 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: All-cause hospitalisation - Actual outcome for Recent admission: Readmission for HF at 30 days; Group 1: 5/70, Group 2: 13/67 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life; Adherence to intervention

Study	**Stavrianopoulos 2016**[1323]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in Greece; Setting: People in the prefecture of Ilia in Greece.
Line of therapy	Not applicable
Duration of study	Intervention + follow up: 16 weeks

Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Mixed
Subgroup analysis within study	Not applicable
Inclusion criteria	People aged 18 years and over and those who could be contacted by telephone were eligible for the study.
Exclusion criteria	People unable to be reached by phone, or under 18 years of age were excluded
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Other: 50-60 years: 11; >60 years: 39. Gender (M:F): 34/16. Ethnicity: Not reported
Further population details	Not reported
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Structured telephone support - (monitoring or self-care management using simple telephone technology). Telephone intervention was performed on a weekly basis for 16 weeks. Each phone intervention lasted up to 20 minutes depending on the severity of symptoms and the type of HF. Participants received recommendations for the prevention of risk factors. Specifically the recommendations focused on understanding the importance of refraining from smoking, of good control of blood pressure in hypertensive patients and blood sugar in diabetics, of maintaining normal body weight, and of changing dietary habits including avoidance of salt. Moreover, avoiding increased intake of fluids, limiting alcohol consumption and preventing malnutrition were also recommended. The importance of introducing mild daily exercise was also underlined. Strict consistency in their medication regime, close observation of their symptoms (especially breathlessness and fatigue) and the control of edema were also stressed. Patients were encouraged to communicate with the nurses if they had any further questions.. Duration 16 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness

	(n=25) Intervention 2: Usual care - (standard post discharge care without intensified attendance at cardiology or HF disease management clinic, or home visiting). . Not fully described. Patients seem to have received routine care. Duration 16 weeks. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: STRUCTURED TELEPHONE SUPPORT (MONITORING OR SELF-CARE MANAGEMENT USING SIMPLE TELEPHONE TECHNOLOGY) versus USUAL CARE (STANDARD POST DISCHARGE CARE WITHOUT INTENSIFIED ATTENDANCE AT CARDIOLOGY OR HF DISEASE MANAGEMENT CLINIC, OR HOME VISITING). Protocol outcome 1: Quality of life - Actual outcome for Mixed: Minnesota Living with Heart Failure Questionnaire at 16 weeks; Group 1: mean -19.36 (SD 7.251); n=25, Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	All-cause mortality; All-cause hospitalisation; Adherence to intervention

F.12 Multi-Disciplinary Teams

Study	Agvall 2013[27]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=160)

Countries and setting	Conducted in Sweden; Setting: Five primary care health centres in south-east Sweden
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: Intervention 6-12 months, follow-up at 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: According to ESC guidelines (echo repeated prior to randomisation)
Stratum	Community: Population risk: Low, Intervention type: Nurse-led clinic, Length:Long
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with NYHA class I-IV HF with reduced EF <50%
Exclusion criteria	Preserved ejection fraction, unstable pts on the waiting list for surgery, recent MI (3 months), creatinine >250umol/l, liver enzyme >3x normal, on steroids or oxygen for pulmonary complaint, expected survival of <1y, unable to give informed consent due to cognitive function, participation in other studies
Recruitment/selection of patients	301 suspected HF, 141 excluded after echo
Age, gender and ethnicity	Age - Mean (SD): int 75(8.6) usual 75(7.1). Gender (M:F): 110:50. Ethnicity: Not stated
Further population details	
Extra comments	Stratification by age (80y+/-) and daily dose of furosemide (80mg+/-) in blocks of 12 to maintain 1:1 randomisation. Baseline characteristics (int/usual)-- NYHA class I 4/7%, II 65/56%, III 32/40%, IV 0/0% EF <30 13/23%, NT-proBNP 1091/588 IHD 81/85%, DM 22/32% RAS-blockade 78/83%, beta blocker 68/75%

Indirectness of population	No indirectness
Interventions	(n=79) Intervention 1: Multidisciplinary team - Nurse. Intervention involved heart-failure nurse working primary care with the aim of optimising renin-angiotensin-system (RAS) blockade and beta blockade, with the support of GP. It involved GP assessment and GP-led medication changes, with oral and written information about HF delivered by the nurse, backed up with computer-based information programme. There were planned HF nurse visits after enrolment and two months later, with further telephone calls after 1 month and 6 months, although extra contacts could be made if clinical need. Participants could contact the heart failure nurse via the primary care centre for advice. Duration 12 months. Concurrent medication/care: All planned healthcare was given in primary care, with hospital care reserved for unexpected events (n=81) Intervention 2: Usual care - Primary care. GP reviewed participant after enrollment, and adjusted medication if needed; then provided care as per their usual practice. No contact with HF nurse. Duration 12 months. Concurrent medication/care: Review is usually carried out once a year according to local guidelines
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NURSE versus PRIMARY CARE

Protocol outcome 1: Mortality
- Actual outcome for Community: Died at 12 months; Group 1: 4/79, Group 2: 5/81
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - BNP higher in intervention group.; Indirectness of outcome: No indirectness; Baseline details: Well-matched at baseline, except BNP much higher in intervention group (1091 v 588) despite other measures of severity trending in opposite direction.; Group 1 Number missing: 1, Reason: Withdrawn; Group 2 Number missing: 3, Reason: Withdrawn

Protocol outcome 2: Unplanned hospitalisation (all-cause)
- Actual outcome for Community: Number of admissions at 12 months; rate ratio: 36:51 or 0.72);
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - BNP higher in intervention group.; Indirectness of outcome: No

indirectness ; Baseline details: Well-matched at baseline, except BNP much higher in intervention group (1091 v 588) despite other measures of severity trending in opposite direction.; Group 1 Number missing: 1, Reason: Withdrawn; Group 2 Number missing: 3, Reason: Withdrawn

Protocol outcome 3: Medicine optimisation/adherance at 12 months
- Actual outcome for Community: RAS blockade (ACEi/ARB) prescribed at 12 months; Group 1: 79/79, Group 2: 68/81; Comments: Using last-observation-taken-forwards
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - BNP higher in intervention group.; Indirectness of outcome: No indirectness ; Baseline details: Well-matched at baseline, except BNP much higher in intervention group (1091 v 588) despite other measures of severity trending in opposite direction.; Group 1 Number missing: 5, Reason: Withdrawn or died; Group 2 Number missing: 8, Reason: Withdrawn or died
- Actual outcome for Community: Beta blockers prescribed at 12 months; Group 1: 58/79, Group 2: 63/81
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - BNP higher in intervention group.; Indirectness of outcome: No indirectness ; Baseline details: Well-matched at baseline, except BNP much higher in intervention group (1091 v 588) despite other measures of severity trending in opposite direction.; Group 1 Number missing: 5, Reason: Withdrawn or died; Group 2 Number missing: 8, Reason: Withdrawn or died

Protocol outcome 4: Adverse events - renal function at 12 months
- Actual outcome for Community: Serum creatinine at 12 months; Group 1: mean 109.5 umol/L (SD 32.6); n=79, Group 2: mean 111.4 umol/L (SD 31.8); n=81
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - BNP higher in intervention group. No baseline average creatinine.; Indirectness of outcome: No indirectness ; Baseline details: Well-matched at baseline, except BNP much higher in intervention group (1091 v 588) despite other measures of severity trending in opposite direction. No mean creatinine given for baseline.; Group 1 Number missing: 5, Reason: Withdrawn or died; Group 2 Number missing: 8, Reason: Withdrawn or died

Protocol outcomes not reported by the study	Quality of life at 12 months ; Dying in preferred place at 12 months; Adverse events - hyperkalaemia at 12 months; Patient and carer experience at 12 months; Adverse events - hypotension at 12 months

Study (subsidiary papers)	Aukland-HF trial: Doughty 2002[401] (Walsh 2000[1460])
Study type	RCT (Cluster randomised; Parallel)
Number of studies (number of participants)	1 (n=197)
Countries and setting	Conducted in New Zealand; Setting: Recruited at Auckland Hospital. Single centre trial, with cluster randomisation of 132 GPs (all who were approached)
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 1 year intervention and follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Based on typical signs/symptoms and test results (CXR/ECG/echo as available)
Stratum	Recent admission: Population risk: High (recent decompensation, severe during exacerbation); Intervention type: MDT clinic; Length: Long
Subgroup analysis within study	Not applicable
Inclusion criteria	Admitted to general wards with primary diagnosis of heart failure, and confirmed to have so by study team
Exclusion criteria	(i) surgically remedial cause HF (ii) consideration of heart transplant (iii) unable to provide consent (iv) terminal cancer (v) participation in any other study
Recruitment/selection of patients	Initial aim was to recruit 180 patients to each arm, but subsequent analysis showed higher event rates, therefore study recruitment stopped early. Unclear dates or how many met eligibility.
Age, gender and ethnicity	Age - Mean (SD): int/control 72.5(11.6) / 73.5(10). Range 34-92. Gender (M:F): Int/Control % 36/43. Ethnicity: Int/Control: NZ european 77/79, Maori 8/7, Pacific Island 14/9, Other 1/2

Further population details	
Extra comments	Baseline characteristics: NYHA IV on adm 76%, Aetiology ischaemic 52%, >1 prev adm 30%, prev MI 45%, DM 28%, AF 32%, LVEF 32%
Indirectness of population	No indirectness
Interventions	(n=100) Intervention 1: Multidisciplinary team - MDT. Team involved clinic with cardiologist and specialist nurse in explicit partnership with GP, as well as patient and their family. Intervention started within two weeks of hospital discharge with a clinic visit to review clinical status and remediable exacerbating factors. Pharmacological treatment was titrated according to guidelines. Nurse-delivered education in measuring daily weights, and given educational material, record of medication and a diary for daily weights. This was later reinforced by two group education sessions (6wk and 6m after dc). Detailed letter followed each clinic appointment faxed to GP and given to patient, and was follow-up by phonecall to GP if there were any changes in management. Following initial appointment, further appointments were made at 6wk intervals alternating GP and clinic. The MDT clinic took phonecalls from GPs and patients during working hours. During exacerbations, pt encouraged to see GP in first instance, and GP could arrange earlier clinic appt or admission if required.. Duration 1 year. Concurrent medication/care: Inpatient care some for both groups, optimising condition and medication. Other conditions would be managed as usual.; Indirectness comment: Ave number visits to clinic = 4, Ave number visits to GP = 14, 60% attended first group, 40% attended second. Comments: NZ has a fee-for-consultation model, and these costs were not borne by the trial. (n=97) Intervention 2: Usual care - Primary care. Usual care under GP with any additional follow-up measures organised by the in-patient team. Duration 1 year. Concurrent medication/care: Inpatient care same for both groups, optimising condition and medication. Other conditions would be managed as usual. Comments: NZ has a fee-for-consultation model, and these costs were not borne by the trial.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MDT versus PRIMARY CARE

Protocol outcome 1: Mortality
- Actual outcome for Recent admission: Died at 1y; Group 1: 19/100, Group 2: 24/97
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Analysed ITT. Less than 40% completed full protocol. Effect of protocol likely under-estimated. Recruitment stopped early due to results, but unlikely to cause bias (overall rate of events, so could have adequate power with less people).; Indirectness of outcome: No indirectness ; Baseline details: Age 72/73, female 36/43, severest 76/73. prev adm>1 34/27. DM 32/25, LVEF 31/33, creat 49/49; Group 1 Number missing: 1, Reason: 1 person lost to follow up. Less than 40% appear to have completed full protocol; Group 2 Number missing: 0

Protocol outcome 2: Quality of life at 12 months
- Actual outcome for Recent admission: Minnesota Living with Heart Failure Questionnaire (overall scale) at 1y; Group 1: mean -19.5 (SD 27); n=81, Group 2: mean -12.5 (SD 2.5); n=73; MLWHFQ 0-105 Top=High is poor outcome; Comments: Overall scores
Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Analysed ITT. Less than 40% completed full protocol. Effect of protocol likely under-estimated. Recruitment stopped early due to results, but unlikely to cause bias (overall rate of events, so could have adequate power with less people). Unblinded; Indirectness of outcome: No indirectness ; Baseline details: Age 72/73, female 36/43, severest 76/73. prev adm>1 34/27. DM 32/25, LVEF 31/33, creat 49/49; Group 1 Number missing: 1, Reason: 1 person lost to follow up. Less than 40% appear to have completed full protocol; Group 2 Number missing: 0

Protocol outcome 3: Unplanned hospitalisation (all-cause)
- Actual outcome for Recent admission: Number of all-cause admissions at 1y; rate ratio: 0.74 (0.6-0.96) admissions);
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Analysed ITT. Less than 40% completed full protocol. Effect of protocol likely under-estimated. Recruitment stopped early due to results, but unlikely to cause bias (overall rate of events, so could have adequate power with less people).; Indirectness of outcome: No indirectness ; Baseline details: Age 72/73, female 36/43, severest 76/73. prev adm>1 34/27. DM 32/25, LVEF 31/33, creat 49/49; Group 1 Number missing: 1, Reason: 1 person lost to follow up. Less than 40% appear to have completed full protocol; Group 2 Number missing: 0

Protocol outcome 4: Medicine optimisation/adherance at 12 months
- Actual outcome for Recent admission: receiving ACE inhibitor at 1y; Group 1: 67/81, Group 2: 53/73

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Analysed ITT. Less than 40% completed full protocol. Effect of protocol likely under-estimated. Recruitment stopped early due to results, but unlikely to cause bias (overall rate of events, so could have adequate power with less people).; Indirectness of outcome: No indirectness ; Baseline details: Age 72/73, female 36/43, severest 76/73. prev adm>1 34/27. DM 32/25, LVEF 31/33, creat 49/49; Group 1 Number missing: 1, Reason: 1 person lost to follow up. Less than 40% appear to have completed full protocol; Group 2 Number missing: 0 - Actual outcome for Recent admission: average dose ACE inhibitor (Enalopril eq.) at 1y; Group 1: mean 15.4 mg per day (SD 43.2); n=81, Group 2: mean 12.4 mg per day (SD 41.8); n=73 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Analysed ITT. Less than 40% completed full protocol. Effect of protocol likely under-estimated. Recruitment stopped early due to results, but unlikely to cause bias (overall rate of events, so could have adequate power with less people).; Indirectness of outcome: No indirectness ; Baseline details: Age 72/73, female 36/43, severest 76/73. prev adm>1 34/27. DM 32/25, LVEF 31/33, creat 49/49; Group 1 Number missing: 1, Reason: 1 person lost to follow up. Less than 40% appear to have completed full protocol; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Dying in preferred place at 12 months; Adverse events - hyperkalaemia at 12 months; Adverse events - renal function at 12 months ; Patient and carer experience at 12 months; Adverse events - hypotension at 12 months

Study (subsidiary papers)	Berger 2010[157] (Adlbrecht 2011[18])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=186 in our comparison)
Countries and setting	Conducted in Austria; Setting: Eight Viennese hospitals
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 12months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: By signs and symptoms during admission
Stratum	Recent admission: Population risk: High (recent hospitalisation and deterioration to NYHA III-IV), Intervention type: Case management, Length: Long
Subgroup analysis within study	Not applicable
Inclusion criteria	1) clinical signs and symptoms of cardiac decompensation during the present hospitalisation, 2) NYHA functional class III or IV on admission, 3) cardiothoracic ratio >0.5 or LVEF <40% on echo. NT pro-BNP also needed to be taken from all, as they could be randomised to management guided by BNP levels.
Exclusion criteria	None stated
Recruitment/selection of patients	July 2003-Sept 2004. 441 pts eligible, 278 randomised (reason not stated, it was stated that those included were younger)
Age, gender and ethnicity	Age - Mean (SD): Int 71 (13), Control 73 (11). Gender (M:F): Int 30:66, Control 31:59. Ethnicity: Not stated
Further population details	

Extra comments	NT pro-BNP levels in intervention and control 2469 and 2359 pg/ml. % in int/control Severity (baseline) NYHA IV 39/47; Cause of heart failure: CAD 67/76, HTN 26/23, valvular 5/2; Comorbidities: pastMI 51/51, HTN 72/64, AF 34/34, DM 49/37 reduced renal funct 18/19; LV function: preserved 9/9, mild reduction 19/34, severe reduction 76/69.
Indirectness of population	No indirectness
Interventions	(n=96) Intervention 1: Multidisciplinary team - Nurse. Multidisciplinary care delivered by a doctor and CHF specialised nurse. It starts with a full assessment 10 days after discharge, following which a tailored recommendation was made for the optimisation of medical therapy, including titration of necessary medication, adjustment of diuretics and stopping inappropriate medication. Blood tests were scheduled to follow up medication changes, and another visit after two months. Nurse was responsible for implementing plan and checking results by phone and four home visits. At home visits, would monitor, and also deliver individualised patient and caregiver education, including enhancement of self-management. The nurse was able to ask for medical review if deterioration noted or otherwise appropriate. Minimum 6 face-to-face meetings, plus telephone contact.. Duration 12 months fixed programme. Concurrent medication/care: Would continue to be under primary care physician. Indirectness: No indirectness (n=90) Intervention 2: Usual care - Primary care. Usual care in primary care. A management plan was sent from hospital to the primary care physician, who was asked to implement it. If there was a need, the patient would also be referred to the cardiology clinic, but would not have contact with the CHF specialists in the trial. Blood would be taken at 1, 3, 6 and 12 months for the trial (implication is that results would not be acted upon).. Duration 12 months. Concurrent medication/care: Primary care physician would be responsible for treatment, evaluation and management of decompensation. Indirectness: No indirectness (n=90) Intervention 3: Multidisciplinary team - MDT. NP guided arm not extracted for this analysis. Duration x. Concurrent medication/care: x. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CASE MANAGEMENT versus PRIMARY CARE

Protocol outcome 1: Mortality
- Actual outcome for Recent admission: Death rate at 18 months; Group 1: 21/96, Group 2: 35/90; Comments: Calculated from percentages, 22% v 39%
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Some imbalance in baseline (under-estimate). ITT reported with per-protocol available.; Indirectness of outcome: No indirectness ; Baseline details: There is a trend for more and more diabetes and severe illness in the intervention group in NYHA and LVEF, although not NT pro-BNP.; Blinding details: Note, that since were three arms, those in our intervention arms would be aware not in maximum intervention group.; Group 1 Number missing: , Reason: 63% followed for full 18 months, remaining followed 12-18 months. Implied none lost.; Group 2 Number missing: , Reason: 63% followed for full 18 months, remaining followed 12-18 months. Implied none lost.

Protocol outcome 2: Unplanned hospitalisation (all-cause)
- Actual outcome for Recent admission: Rehospitalised for any cause at 18 months; Group 1: 64/85, Group 2: 39/47
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Some imbalance in baseline (under-estimate). Per protocol analysis loses 48% of control group.; Indirectness of outcome: No indirectness, Comments: Protocol requests for count rate, this is dichotomous. Lower numbers due to "per-protocol" analysis in economics paper; Baseline details: There is a trend for more and more diabetes and severe illness in the intervention group in NYHA and LVEF, although not NT pro-BNP.; Blinding details: Note, that since were three arms, those in our intervention arms would be aware not in maximum intervention group.; Group 1 Number missing: 11, Reason: not per protocol; Group 2 Number missing: 43, Reason: not per protocol

Protocol outcome 3: Medicine optimisation/adherance at 12 months
- Actual outcome for Recent admission: Prescribed ACE-I or ARB at 18 months; Group 1: 88/90, Group 2: 87/90
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Some imbalance in baseline (under-estimate).; Indirectness of outcome: No indirectness; Baseline details: There is a trend for more and more diabetes and severe illness in the intervention group in NYHA and LVEF, although not NT pro-BNP.; Blinding details: Note, that since were three arms, those in our intervention arms would be aware not in maximum intervention group.; Group 1 Number missing: , Reason: 63% followed for full 18 months, remaining followed 12-18 months. Implied none lost.; Group 2 Number missing: , Reason: 63% followed for full 18 months, remaining followed 12-18 months. Implied none lost.
- Actual outcome for Recent admission: Prescribed Beta-blocker at 18 months; Group 1: 92/96, Group 2: 76/90
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Some imbalance in baseline (under-estimate).; Indirectness of outcome:

No indirectness, Comments: It is noted that the usual care group is prescribed lower dose (ave 38% target dose vs 58%); Baseline details: There is a trend for more and more diabetes and severe illness in the intervention group in NYHA and LVEF, although not NT pro-BNP.; Blinding details: Note, that since were three arms, those in our intervention arms would be aware not in maximum intervention group.; Group 1 Number missing: , Reason: 63% followed for full 18 months, remaining followed 12-18 months. Implied none lost.; Group 2 Number missing: , Reason: 63% followed for full 18 months, remaining followed 12-18 months. Implied none lost.	
Protocol outcomes not reported by the study	Quality of life at 12 months ; Dying in preferred place at 12 months; Adverse events - hyperkalaemia at 12 months; Adverse events - renal function at 12 months ; Patient and carer experience at 12 months; Adverse events - hypotension at 12 months

Study	Capomolla 2002[235]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=234)
Countries and setting	Conducted in Italy; Setting: Heart failure unit: Joint venture between Montescano Medical Centre and Heart Transplantation Program of Policlinico S. Mattei, Pavia
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 12 months (+/- 3 months)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Diagnosis of CHF supported by history, physical signs and symptoms, and by echocardiographic findings (LVEF<40%)
Stratum	Recent admission: Population risk: High (recent decompensation); Intervention type: MDT clinic; Length: Long
Subgroup analysis within study	Not applicable
Inclusion criteria	To be discharged from specialist heart failure inpatient unit with LV ejection fraction <40% (HFrEF), NYHA grade I-IV
Exclusion criteria	Nil stated
Recruitment/selection of patients	Recruited from the ward Jan 1999 to Jan 2000
Age, gender and ethnicity	Age - Mean (SD): 56(9). Gender (M:F): 196/38 (int 102/20). Ethnicity: Not stated
Further population details	

Extra comments	Extensive pre-randomisation testing: including functional state, cardiopulmonary exercise test, echo-Doppler, right haemodynamic measurements.. Baseline attributes, int/usual: NYHA IIIorIV % 35/34E; Aetiology ischaemic % 41/41, mean LVEF % 31/29, AF % 19/13, loop diuretics % 81/85, ACEi % 96/98, beta-blocker % 39/40.
Indirectness of population	No indirectness
Interventions	(n=112) Intervention 1: Multidisciplinary team - MDT. Day-hospital based management, consisting of an individualised management programme for HF. Staff included cardiologist, four experienced nurses, two physiotherapists, and access to a dietician, psychologist and social assistant. The team members in collaboration with the patient create a care plan, and the process of care is structured around this. Tailored interventions that can be delivered depending on the plan include cardiovascular risk stratification, physical training, correction of risk factors, health care education, counselling aimed at promoting change through self-management. There is a multi-disciplinary meeting each morning to discuss individual patients, and efforts made to provide continuity with community care. Pts have open-access to the day hospital, and can receive review and medication for any decompensation as an outpatient where possible (including IV therapy). Duration 12 months. Concurrent medication/care: After inpatient investigations, prescribed individually tailored therapies according to HF guidelines and EBM (medications optimised). Indirectness: No indirectness Comments: Patients seen at day hospital average 5.5 (sd. 3.9) times over one year (n=122) Intervention 2: Usual care - Clinic. Pts referred to their primary care physician and a cardiologist on discharge.. Duration 12 months. Concurrent medication/care: After inpatient investigations, prescribed individually tailored therapies according to HF guidelines and EBM (medications optimised).. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MDT versus CLINIC	

Protocol outcome 1: Mortality - Actual outcome for Recent admission: Cardiac death at 12 months; Group 1: 3/112, Group 2: 21/122 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - No detail on randomisation or allocation concealment, although baseline variables well balanced.; Indirectness of outcome: Serious indirectness, Comments: Cardiac death only (unclear if any deaths from other causes); Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Quality of life at 12 months - Actual outcome for Recent admission: Utility by time trade-off (TTO) at 12 months; Group 1: mean 0.72 (SD 0.17); n=109, Group 2: mean 0.63 (SD 0.22); n=101; utility 0.0-1.0 Top=High is good outcome Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - No detail on randomisation or allocation concealment, although baseline variables well balanced. No loss to follow-up reported.; Indirectness of outcome: Serious indirectness, Comments: Indirect measure of quality of life; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Unplanned hospitalisation (all-cause) - Actual outcome for Recent admission: Hospital admissions required (count) at 12 months; Rate ratio: 11:63 or 0.18 admissions, Comments: In total, 91 hospitalisations for 56 patients); Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - No detail on randomisation or allocation concealment, although baseline variables well balanced. No loss to follow-up reported.; Indirectness of outcome: No indirectness; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 4: Medicine optimisation/adherance at 12 months - Actual outcome for Recent admission: ACEi dose prescribed (long-acting) at 12 months; Group 1: mean 20 mg/day (SD 8); n=109, Group 2: mean 12 mg/day (SD 10); n=101; Comments: At baseline: Int 14(7), usual 15(9)mg/day Short-term ACEi - baseline: Int 101(31), usual 100(40) Short-term ACEi - 12mo: Int 139(26), usual 103(39) Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - No detail on randomisation or allocation concealment, although baseline variables well balanced. No loss to follow-up reported, but would be expected in this population.; Indirectness of outcome: No indirectness, Comments: Not directly measure of appropriateness of nor adherence to prescription; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Recent admission: Beta blocker dose prescribed at 12 months; Group 1: mean 34 mg/day (SD 23); n=109, Group 2: mean 13 mg/day

(SD 29); n=101; Comments: Baseline: Int 10(19), usual 13(12) Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - No detail on randomisation or allocation concealment, although baseline variables well balanced. No loss to follow-up reported, but would be expected in this population.; Indirectness of outcome: No indirectness, Comments: Not directly measure of appropriateness of nor adherence to prescription; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Dying in preferred place at 12 months; Adverse events - hyperkalaemia at 12 months; Adverse events - renal function at 12 months ; Patient and carer experience at 12 months; Adverse events - hypotension at 12 months

Study (subsidiary papers)	COACH - Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure trial: Jaarsma 2008[680] (Jaarsma 2008[679], Postmus 2011[1168], Jaarsma 2004[678], Jaarsma 2002[681])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 study, 3 arms (n=1023)
Countries and setting	Conducted in Netherlands; Setting: 17 experienced HF centres
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 18 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Typical signs/symptoms
Stratum	Recent admission: Population risk: High (recent decompensation); Intervention type: Nurse-led clinic; Length: Long
Subgroup analysis within study	Not applicable:
Inclusion criteria	Admitted to hospital with signs and symptoms of heart failure requiring IV medication, aged 18 and over with structural underlying heart dx on cardiovascular imaging, HFrEF or HFpEF. Need to have been stabilised on medication prior to entry in study
Exclusion criteria	Inclusion in another study or HF clinic, inability to complete the questionnaires, invasive procedure or cardiac surgery intervention performed in last 6m or such procedure planned in next 3 months, ongoing evaluation for heart transplantation, terminal illness precluding participation, and inability or unwillingness to give informed consent
Recruitment/selection of patients	October 2002 - Feb 2005, 2957 eligible pts, 1117 did not meet inclusion criteria, 282 refused, 509 excluded for mainly logistical reasons

Age, gender and ethnicity	Age - Mean (SD): 71(11). Gender (M:F): 62:38. Ethnicity: Not stated
Further population details	
Extra comments	HF variables: NYHA class II 50%, III 46%, IV 4%; LVEF 34(14)%; prev HF admissions 32%, index hospital stay 10(7-16), NT pro-BNP 2528(4291). Comorbidities: HTN 43%, AF 36%, DM 28%, prev MI 43%, eGFR 55(21) Medications: ACE or ARB 83%, BB 66%
Indirectness of population	No indirectness
Interventions	(n=339) Intervention 1: Usual care - Clinic. Cardiology and primary care only. Duration 18 months. Concurrent medication/care: Cardiology clinic less than two months after admission and every six months after. Indirectness: No indirectness (n=340) Intervention 2: Multidisciplinary team - Nurse. MDT consisted of nurse and cardiologist. Visited by an HF nurse during admission and at the outpatient clinic, where pt educated using protocol and behavioural strategies to improve adherence and improve self-efficacy. Pts were instructed to contact the nurse if there was any change in their condition. Pts received an extra 20h contact time compared with control clinic.. Duration 18 months. Concurrent medication/care: Cardiology clinic less than two months after admission and every six months after.. Indirectness: No indirectness (n=344) Intervention 3: Multidisciplinary team - MDT. Intensive support was led by a nurse, given by an MDT including cardiologist, physiotherapist, dietician and social worker. Visited in hospital. In the first month after hospital discharge, weekly telephone contacts were made and the patient was visited at home by the HF nurse. Telephone and/or home visits were made by physiotherapist, dietician, and social worker to give advice. Materials used in the intervention included a patient diary, brochures on HF and its management, and samples of sodium-restricted food seasonings. Patients were instructed to seek help if symptoms increased or if they gained weight. The extra contact amounted to 40h clinical time over the control clinic. Duration 18 months. Concurrent medication/care: Cardiology clinic less than two months after admission and every six months after. Indirectness: No indirectness

Funding	Study funded by industry (Netherlands Heart Foundation, Biosate France SAS (BNP), Roche Diagnostics (NT pro-BNP) and Novartis)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NURSE (BASIC) versus CONTROL CLINIC

Protocol outcome 1: Mortality
- Actual outcome for Recent admission: Death all causes at 18m; Group 1: n=340 ; Group 2: n=339; HR 0.88; Lower CI 0.66 to Upper CI 1.18; Test statistic: unadjusted cox regression p=0.39; Actuarial or Kaplan Meier curves reported? yes
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Randomisation procedures not explained; Indirectness of outcome: No indirectness ; Baseline details: Age: 72/71/70, Female 40/34/39, NYHA class IV 4/3/4, AF 36/36/35, prev MI 44/42/42, on digoxin 30/32/29, NT pro-BNP 2677/2404/2505; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Unplanned hospitalisation (all-cause)
- Actual outcome for Recent admission: No of hospitalisations at 18m; Rate ratio: 1.01);
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Randomisation procedures not explained; Indirectness of outcome: No indirectness ; Baseline details: Age: 72/71/70, Female 40/34/39, NYHA class IV 4/3/4, AF 36/36/35, prev MI 44/42/42, on digoxin 30/32/29, NT pro-BNP 2677/2404/2505; Group 1 Number missing: ; Group 2 Number missing:

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MDT (INTENSIVE) versus CONTROL CLINIC

Protocol outcome 1: Mortality
- Actual outcome for Recent admission: Death all causes at 18m; Group 1: n=344 ; Group 2: n=339; HR 0.81; Lower CI 0.6 to Upper CI 1.08; Test statistic: unadjusted cox regression model p=0.15; Actuarial or Kaplan Meier curves reported? yes
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Randomisation procedures not explained; Indirectness of outcome: No indirectness ; Baseline details: Age: 72/71/70, Female 40/34/39, NYHA class IV 4/3/4, AF 36/36/35, prev MI 44/42/42, on digoxin 30/32/29, NT pro-BNP 2677/2404/2505; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Unplanned hospitalisation (all-cause)

- Actual outcome for Recent admission: No of hospitalisations at 18m; Rate ratio : 1.10); Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Randomisation procedures not explained; Indirectness of outcome: No indirectness ; Baseline details: Age: 72/71/70, Female 40/34/39, NYHA class IV 4/3/4, AF 36/36/35, prev MI 44/42/42, on digoxin 30/32/29, NT pro-BNP 2677/2404/2505; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at 12 months ; Dying in preferred place at 12 months; Medicine optimisation/adherance at 12 months; Adverse events - hyperkalaemia at 12 months; Adverse events - renal function at 12 months ; Patient and carer experience at 12 months; Adverse events - hypotension at 12 months

Study	DEAL-HF trial: De la porte 2007[356]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=240)
Countries and setting	Conducted in Netherlands; Setting: Recruited from two hospitals, both inpatients and outpatients. Cardiologists in this area are known for their interest in heart failure (according to paper)
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: According to the ESC criteria 2001
Stratum	Mixed: Population risk: High (all NYHA III-IV), Intervention type: MDT clinic, Length: Long
Subgroup analysis within study	Not applicable
Inclusion criteria	Inpatients and outpatients with NYHA class III or IV heart failure (HFrEF and HFpEF)
Exclusion criteria	Dementia or psychiatric dx (22), living in nursing home, having any disease other than HF (103), expected survival <1 year (37), participating in other studies (15), planned hospitalisations (22), receiving renal replacement therapy.
Recruitment/selection of patients	797 pts with HF screened, 473 eligible, 240 consented. 39% recruited while hospitalised and 69% in community
Age, gender and ethnicity	Age - Mean (SD): int 70(10) usual 71(10). Gender (M:F): 174:66. Ethnicity: Not stated
Further population details	

Extra comments	Baseline values: Living alone (int) 20% (usual) 17%, LVEF (both) 31%, NYHA IV (int) 2% (usual) 5%, prior MI (int) 53% (usual) 56%, DM (int) 31% (usual) 28%, NT-proBNP (int) 262 (usual) 244, Creatinine (int) 123 (usual) 130, Diuretics (int) 97% (usual) 96%, ACE/BB prescribed (int) 84/60% (usual) 88/69%
Indirectness of population	No indirectness
Interventions	(n=118) Intervention 1: Multidisciplinary team - MDT. Follow-up in heart failure outpatient clinic led by specialist physician and nurse. The first two visits involved physical and social assessment, followed by comprehensive education package about heart failure and its treatment. A treatment plan was collaboratively devised, usually involving a meeting with a dietician regarding an individualised diet. Seven further appointments (one with physician) provided review, counselling and reinforcement of education, with the aim to optimise medication. Easy access to the clinic was also provided in case of questions. Clinic programme fixed at 12 months.. Duration 12 months. Concurrent medication/care: Primary care as usual. Indirectness: No indirectness (n=122) Intervention 2: Usual care - Clinic. Cardiologist follow-up. It was felt that they would be offered routine care in accordance with the ESC 2001 guidelines, including medication optimisation. Duration 12 months. Concurrent medication/care: Primary care as usual. Indirectness: No indirectness Comments: No information given on actual care received
Funding	Study funded by industry (Supportive grant from Novartis, AstraZeneca, Bristol-Myers Squibb. Roche diagnostics provided BNP assay.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MDT versus CLINIC

Protocol outcome 1: Mortality
- Actual outcome for Mixed: Death (all-cause) at 12 months; Group 1: 12/118, Group 2: 23/122; Comments: Cardiovascular deaths: (int) 10 (usual) 25
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Quality of life at 12 months - Actual outcome for Mixed: Minnisota Living with Heart Failure questionnaire reported incompletely at not extracted; Mean; (p Value: 0.038) pt); Risk of bias: All domain - ; Indirectness of outcome: No indirectness Protocol outcome 3: Unplanned hospitalisation (all-cause) - Actual outcome for Mixed: Days in hospital at 12 months; rate ratio: 0.56 (0.49-0.64) days in hospital); Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: Serious indirectness, Comments: Not count of admissions, but days admitted; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Medicine optimisation/adherance at 12 months - Actual outcome for Mixed: Prescription data presented incoherently at not extracted; Proportion; (Dose of ACEi prescribed 14.3mg (int), 14.2mg (control): "non-significant p value")); Risk of bias: All domain - Unclear, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Very high, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Table not possible to interpret (percentages over 100); Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: Adverse events - renal function at 12 months - Actual outcome for Mixed: Creatinine levels (umol/l) at 12 months; Mean; (int) 121 (usual) 138 (p Value stat significance difference between groups: 0.002) umol/l); Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Spread not reported at baseline or follow-up; Indirectness of outcome: No indirectness, Comments: No sd given; Baseline details: Int 123, Control 130 (no spread given); Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Dying in preferred place at 12 months; Adverse events - hyperkalaemia at 12 months; Patient and carer experience at 12 months; Adverse events - hypotension at 12 months

Study (subsidiary papers)	Del sindaco 2007[368] (Pulignano 2010[1176], Del sindaco 2012[367])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=173)
Countries and setting	Conducted in Italy; Setting: Two hospital heart failure clinics in Rome, Italy
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: Pro-active intervention appears to be 6 months, last outcome at 2 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Determined by ESC guidelines and rated on NYHA scale
Stratum	Recent admission: Population risk: V.High (recent decompensation, >50% severe disease, age 70y or over); Intervention type: MDT clinic (with cardiologist as case manager); Length: Long
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 70 years or more and discharged home after a hospitalisation due to heart failure, defined as NYHA III-IV of at least 24h hours requiring specific intravenous therapy (not restricted to IV diuretics)
Exclusion criteria	(i) valvular disease requiring planned surgical intervention (ii) active disease likely to limit compliance (substance abuse, confined to bed, dementia and other psychiatric disorder) (iii) coexisting non-cardiac illness likely to reduce life-expectancy (iv) need for long-term inotropic support (v) not consenting (vi) living in nursing home or outside the area
Recruitment/selection of patients	January 2001 til December 2002. 236 eligible, 52 had exclusion criteria (22 living outside area, 11 refused to co-operate, the remainder clinical factors). 11 subsequently lost to follow-up (6 from intervention, 5 from control).

Age, gender and ethnicity	Age - Mean (SD): int 77.4 (5.9), control 77.5 (5.7). Gender (M:F): 45:55. Ethnicity: Not stated
Further population details	
Extra comments	There are subgroup analyses of the trial by frailty (using frailty rating) and cognitive impairment. Not reported here. % participantsl: Aetiology ischaemia 54, HTN 12; Comorbid HTN 65, DM 32, prev MI 52; NYHA II 38, III 54, IV 6; prescribed ACE 81, BBs 47, digoxin 60. Ave LVEF 33% (11), creatinine clearance 41 ml/min (15)
Indirectness of population	No indirectness
Interventions	(n=86) Intervention 1: Multidisciplinary team - MDT. Management by two teams, each consisting of cardiologist with experience in geriatrics, supported by specialised nurses and the patient's primary care physician. Intervention consisted of discharge planning, continuing education, therapy optimisation, improved communication between healthcare providers, early attention to signs and symptoms of deterioration, and a flexible diuretic regimen. Pt was given a list of recommendations, an educational booklet, a weight chart, and a contact number available 6h a day. They were seen in the HF clinic at 7d, 14d, 1month, 3months and 6months. Nurses played a key role in education and co-ordinating care. They made phone-calls to patients and followed up if they did not attend appointments. The primary care physician was asked to assess adherence, evaluate possible drug reactions, treat worsening conditions at home, as well as managing comorbidities and were asked to consider dietary factors. Pts continued to be seen every six months until 2 years.. Duration 2 years. Concurrent medication/care: As usual. Felt to have medication optimised in hospital.. Indirectness: No indirectness; Indirectness comment: Classified variously as MDT clinic, case management, and disease management programme. It appears to best fir MDT clinic. Comments: 36% discontinued before 2y (n=87) Intervention 2: Usual care - Primary care. Received baseline clinical evaluation and therapeutic plan. After discharge, all treatment would be decided by their primary care physician (and/or personal cardiologist if they had one). Duration 2 years. Concurrent medication/care: 6-monthly phone calls for outcome measures. Felt to have medication optimised in hospital.. Indirectness: No indirectness; Indirectness comment: Not known how many people seen by cardiologist. Unclear if primary care physician had access to therapeutic plan made in hospital.

Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MDT versus PRIMARY CARE

Protocol outcome 1: Mortality
- Actual outcome for Recent admission: All-cause death at 2y; Group 1: 27/86, Group 2: 32/87
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - No details on randomisation process. Reported ITT; Indirectness of outcome: No indirectness ; Baseline details: Severity: II 37/39, III 51/56, IV 11/6, frus dose 61(78)/67(17), LVEF 139(11)/138(4), MLWHF 40(18)/35(20)
Demographics: Age 77(6)/78(6), male 51/53, edu<5y 52/54
Comorbid: Charlson score 2.3(1.6)/2.3(1.5), prev MI 51/55, DM 33/31; Blinding details: Those allocated to control were not told what intervention would involve - therefore partly blinded; Group 1 Number missing: 6, Reason: 6 lost to f/u, 31 dropped out of intervention but provided follow-up in intervention group; Group 2 Number missing: 5, Reason: 5 lost to fu

Protocol outcome 2: Quality of life at 12 months
- Actual outcome for Recent admission: QoL results not reported at 2y;
Risk of bias: All domain - ; Indirectness of outcome: No indirectness, Comments: Minnisota Living with Heart Failure Questionnaire used, but results for control group not given. EQ-5D also used, although can't find full results.

Protocol outcome 3: Unplanned hospitalisation (all-cause)
- Actual outcome for Recent admission: All-cause admission at 2y; Group 1: 48/86, Group 2: 65/87
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - No details on randomisation process. Reported ITT; Indirectness of outcome: No indirectness, Comments: Nb not protcol preferred admission rates; Baseline details: Severity: II 37/39, III 51/56, IV 11/6, frus dose 61(78)/67(17), LVEF 139(11)/138(4), MLWHF 40(18)/35(20)
Demographics: Age 77(6)/78(6), male 51/53, edu<5y 52/54
Comorbid: Charlson score 2.3(1.6)/2.3(1.5), prev MI 51/55, DM 33/31; Blinding details: Those allocated to control were not told what intervention would involve - therefore partly blinded; Group 1 Number missing: 6, Reason: 6 lost to f/u, 31 dropped out of intervention but provided follow-up in intervention group; Group 2 Number missing: 5, Reason: 5 lost to fu

Protocol outcomes not reported by the study	Dying in preferred place at 12 months; Medicine optimisation/adherance at 12 months; Adverse events - hyperkalaemia at 12 months; Adverse events - renal function at 12 months ; Patient and carer experience at 12 months; Adverse events - hypotension at 12 months

Study	Driscoll 2014[407]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=25)
Countries and setting	Conducted in Australia; Setting: Specialist outpatient clinic operating a secondary and tertiary long-term management for complex heart failure patients
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 3 to 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Attending heart failure clinic and recent scan showing poor LV function
Stratum	Population risk: high (community); Intervention type: Nurse-led; Length: Mid
Subgroup analysis within study	Not applicable
Inclusion criteria	"Stable" patients with confirmed HFrEF not on beta blockers, or at less than half optimal doses (HFrEF not defined)
Exclusion criteria	Previously failed trial of beta blockers, or assessed as being inappropriate for beta blockers or uptitration in nurse-led clinic (due to need for more frequent cardiology review). Unable to read and speak English
Recruitment/selection of patients	306 consecutive patients screened, 68 eligible, 28 agreed to participate, 25 randomised
Age, gender and ethnicity	Age - Mean (SD): int 65(14.2) usual 68(18.7). Gender (M:F): 18:7. Ethnicity: 17 of 25 Caucasian
Further population details	

Extra comments	Optimal doses of beta-blocker defined as carvedilol 50mg, metoprolol XL 190mg and bisoprolol 10mg. Baseline characteristics given by group nurse/usual: living alone 4/4, DM 3/4, chronic renal impairment 2/3, AF 1/5, NYHA classI 1/7, II 7/4, III 3/2, IV 1/0, LVEF 34/31%, ACE 11/10. Beta blocker prescription at baseline not given.
Indirectness of population	No indirectness: HFrEF on sub-optimal treatment
Interventions	(n=12) Intervention 1: Multidisciplinary team - Nurse. Clinic for beta blocker up-titration led by heart failure nurse. Seen by nurse repeatedly until they reached optimal beta-blocker doses (or had spent six months in clinic). Each visit included clinical examination, education and a discussion about medication. The participant was provided with a list of the current medication regimen. A consultant cardiologist oversaw, wrote prescriptions and was available to see patients. The nurse could also undertake any tests needed, or refer onwards. Duration 3 to 6 months depending on need. Concurrent medication/care: Seen by cardiologist at three and six months. Indirectness: No indirectness (n=13) Intervention 2: Usual care - Clinic. Heart failure clinic. Seen by consultant cardiologist for treatment recommendations, which were given to the patient and their primary care physician. . Duration 6 months. Concurrent medication/care: Seen again after three and six months.. Indirectness: No indirectness
Funding	Other (Support acknowledged from the Nurses Board of Victoria in Australia, and the National Health and Medical Research Council of Australia (not stated that this was entire funding))

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NURSE versus CLINIC

Protocol outcome 1: Mortality
- Actual outcome for Community: Died at 6 months; Group 1: 1/12, Group 2: 0/13; Comments: paper reports death was due to septicaemia following toe amputation
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Severity differed at baseline, more severe in nurse-led group. 1 death and 1 withdrawal in the same arm. Under-estimate effect.; Indirectness of outcome: No indirectness ; Baseline details: Severity differed at

baseline, more severe in nurse-led group; Group 1 Number missing: 1, Reason: 1 withdrew; Group 2 Number missing: 0 Protocol outcome 2: Quality of life at 12 months - Actual outcome for Community: Minnesota Living with Heart Failure questionnaire at 6 months; Group 1: mean 6.7 (SD 16.2); n=11, Group 2: mean 9.5 (SD 10.8); n=13; MLWHF overall 0-105 Top=High is poor outcome; Comments: paper reports p=0.6 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Severity differed at baseline, more severe in nurse-led group; Indirectness of outcome: No indirectness ; Baseline details: Severity differed at baseline, more severe in nurse-led group; Group 1 Number missing: 1, Reason: 1 withdrew; Group 2 Number missing: 0 Protocol outcome 3: Unplanned hospitalisation (all-cause) - Actual outcome for Community: Hospitalisation / emergency department visits at 6 months; Rate ratio: 0.67 hospital admissions, Comments: Two further hospital admissions were planned (prostectomy and electrophysiological study)); Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Severity differed at baseline, more severe in nurse-led group.; Indirectness of outcome: No indirectness ; Baseline details: Severity differed at baseline, more severe in nurse-led group; Group 1 Number missing: 1, Reason: 1 withdrew; Group 2 Number missing: 0 Protocol outcome 4: Medicine optimisation/adherance at 12 months - Actual outcome for Community: Optimal dose of beta blocker prescribed at 6 months; Group 1: 9/11, Group 2: 5/13; Comments: In nurse group two further on suboptimal doses. In clinic group, seven further on suboptimal doses and one not on beta blockers. Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Numbers on beta blocker at start are missing. Severity differed at baseline, more severe in nurse-led group; Indirectness of outcome: No indirectness ; Baseline details: Numbers on beta blocker at start are missing. Severity differed at baseline, more severe in nurse-led group; Group 1 Number missing: 1, Reason: 1 withrew; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Dying in preferred place at 12 months; Adverse events - hyperkalaemia at 12 months; Adverse events - renal function at 12 months ; Patient and carer experience at 12 months; Adverse events - hypotension at 12 months

Study	Ducharme 2005[412]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=230)
Countries and setting	Conducted in Canada; Setting: Montreal Heart Institute
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 6 months intervention and follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Presence of signs and symptoms of "congestive" heart failure
Stratum	Recent admission: Population risk: High (recent decompensation, >50% requiring medicine titration); Intervention type: MDT clinic; Length: Mid
Subgroup analysis within study	Not applicable:
Inclusion criteria	At least one of: tachycardia, gallop rhythm, increased JVP >10cm or pulmonary crackles. At least one of: dyspnoea at rest, PND or orthopnea. Either radiological or echocardiographical evidence of congestion/reduced EF (<45%)
Exclusion criteria	Primary diagnosis MI, discharge to chronic care facility, scheduled cardiac surgery, unwillingness, participating in another trial, living outside area
Recruitment/selection of patients	January 1998 - January 2000. 1203 eligible, 789 refused, 115 scheduled for cardiac surgery, 69 lived outside area
Age, gender and ethnicity	Age - Mean (SD): 70(10) int, 68(10) control. Gender (M:F): 82:18. Ethnicity: Not stated

Further population details	
Extra comments	. HF variables: NYHA II 14/8, NYHA III 63/68, NYHA IV 38/39, EF% 35(15)/34(14), months with HF 45(47)/48(51), ischaemic cause 69/63 Comorbidities: prior MI 50/49, HTN 55/51, DM 28/32 Medication: ACEi 76/84, BBs 34/52 QoL emotional 7.5(6.2)/7.5(7.1), physical 22.0(11.0)/22.9(11.6)
Indirectness of population	No indirectness
Interventions	(n=115) Intervention 1: Multidisciplinary team - MDT. MDT consisted of cardiologists, clinician nurses, dieticians and pharmacists, with access to social workers and other medical specialists as required. Intervention started with a nurse telephone call within 72h. Within two weeks of discharge an evaluation with special attention paid to potentially remediable exacerbating factors, a dietary assessment, and analysis by a pharmacist leading to an individualised treatment plan, including titrating ACEi, BBs and MRA as appropriate, as well as eliminating unnecessary medication to simplify the regimen. Pt and family were educated about HF, symptoms indicative of HF, medications, exercise and diet. They were encouraged to weigh themselves daily, given a diary, clinical notes and medication record. They could phone the clinic during working hours. They had appointments at the clinic once a month, and phone calls in-between, with extra appointments arranged as needed. If there was deterioration, they could be assessed in the clinic, and receive IV diuretics if appropriate. Duration 6 months. Concurrent medication/care: Noncardiac medical problems were managed by primary care physicians outside the specialised clinic. Indirectness: No indirectness Comments: Total of 694 visits to clinic (average 6 per patients, range 0-15), 52 visits to cardiologist outside the intervention, 214 visits to family physician and 35 visits to other physician (n=115) Intervention 2: Usual care - Primary care. Same in-hospital care, with follow-up according to the standards of the inpatient cardiologist. Duration 6 months. Concurrent medication/care: "the control group also had excellent access to medical, including specialist, care". Indirectness: No indirectness Comments: There were 595 cardiology visits, 306 primary care visits, 42 other physician visits

Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MDT versus PRIMARY CARE Protocol outcome 1: Mortality - Actual outcome for Recent admission: Death at 6 months; Group 1: 12/115, Group 2: 19/115 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Pts randomised to intervention arm were more likely to already be on ACEi and BBs; Indirectness of outcome: No indirectness ; Baseline details: Pts randomised to intervention arm were not likely to already be on ACEi and BBs, otherwise ok: NYHA II 14/8, NYHA III 63/68, NYHA IV 38/39, EF% 35(15)/34(14), months with HF 45(47)/48(51), Comorbidities: prior MI 50/49, HTN 55/51, DM 28/32, Medication: ACEi 76/84, BBs 34/52; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Quality of life at 12 months - Actual outcome for Recent admission: QoL not properly reported at not extracted; ; Risk of bias: All domain - ; Indirectness of outcome: No indirectness Protocol outcome 3: Unplanned hospitalisation (all-cause) - Actual outcome for Recent admission: Number of hospital admissions at 6 months; rate ratio: 0.68); Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Pts randomised to intervention arm were more likely to already be on ACEi and BBs; Indirectness of outcome: No indirectness ; Baseline details: Pts randomised to intervention arm were more likely to already be on ACEi and BBs, otherwise ok: NYHA II 14/8, NYHA III 63/68, NYHA IV 38/39, EF% 35(15)/34(14), months with HF 45(47)/48(51), Comorbidities: prior MI 50/49, HTN 55/51, DM 28/32, Medication: ACEi 76/84, BBs 34/52; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Dying in preferred place at 12 months; Medicine optimisation/adherance at 12 months; Adverse events - hyperkalaemia at 12 months; Adverse events - renal function at 12 months ; Patient and carer experience at 12 months; Adverse events - hypotension at 12 months

Study (subsidiary papers)	Ekman 1998[431] (Ekman 2003[432])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=158)
Countries and setting	Conducted in Sweden; Setting: Recruited by screening the admissions to the medical wards for eligible patients
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: By history, examination and review of previous tests by specialist nurse
Stratum	Recent admission: Population risk: High (Most recent decompensation, all >65y), Intervention type: Nurse-led clinic, Length: Mid
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged over 65, Boston criteria score 8, NYHA class III or IV at the last hospitalisation and living in catchment area
Exclusion criteria	Large MI in the last 8 weeks, need of specialist treatment, serum creatinine >300umol/l, need of permanent nursing home, serious or life-threatening other disease or communication problems
Recruitment/selection of patients	1731 patients had chronic heart failure or cardiomyopathy recorded, of which 1541 were over 65. 1058 were screened for inclusion, 158 were eligible and consented
Age, gender and ethnicity	Age - Mean (SD): 80.3 (6.8). Gender (M:F): 101:67. Ethnicity: Not stated

Further population details	
Extra comments	. Baseline characteristics int/usual: living alone 61/57%, DM 30/25%, prev MI 44/46%, ischaemic etiology 65/71%, LVEF 0.38/0.43, AF 33/49%, on ACEi 35/39%, on beta blocker 35/25, on furosemide 92/96%
Indirectness of population	No indirectness
Interventions	(n=79) Intervention 1: Multidisciplinary team - Nurse. Nurse-monitored outpatient clinic with goal of delivering a care package that would make participants to recognise symptoms of deterioration and be knowledgeable about the medications prescribed. An attending doctor was responsible for medical decision and saw the participants at least at 3 and 6 months. The nurse met with the participant and a relative or care-giver to plan an individual programme of visits and set goals for self care/monitoring. The nurse could also contact patients by phone to follow-up any issues raised in clinic visits - or as an alternative to clinic visits in patients unable to attend. The nurse would also communicate with the primary care provider and any home care provider to better co-ordinate care. Participants could also call the nurse if there was a deterioration or they had any questions - if necessary, could be see or even admitted without visiting the emergency department. Duration 6 months. Concurrent medication/care: Ongoing care in primary care. Indirectness: No indirectness Comments: Numbers attending at least one face to face meeting (1-14 visits) = 56pts: 1-5 visits = 31pts, >5 visits = 25. Numbers with at least one phone contact (1-14 pc) = 77, 1-5 pc = 54pts, >5 pc = 23pts (n=79) Intervention 2: Usual care - Primary care. Managed in accordance with current clinical practice. In general this meant that the patient was treated in a general practitioner and visited the emergency department if symptoms worsened. Duration 6 months. Concurrent medication/care: At discretion of treating doctors. Indirectness: No indirectness
Funding	Other (Mixed public and industry - Swedish Medical Research Council, HLR, Swedish Foundation or Health Care Sciences and Allergy Research, and Merck, Sharp & Dohme.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NURSE versus PRIMARY CARE

Protocol outcome 1: Mortality
- Actual outcome for Recent admission: Death at 6 months; Group 1: 21/79, Group 2: 17/79; Comments: If using care received rather than ITT, 9 vs 29
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Some minor disequilibrium at baseline.; Indirectness of outcome: No indirectness, Comments: Note large difference between ITT and care-received analysis; Baseline details: Well-matched except for LVEF (higher int), AF (higher usual), beta blockers (higher int) - likely cancel out; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Quality of life at 12 months
- Actual outcome for Recent admission: Change in NYHA at 6 months; Group 1: mean -0.2 (SD 0.9); n=79, Group 2: mean -0.3 (SD 0.7); n=79; New York Heart Association class I,II,III,IV Top=High is poor outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Some minor disequilibrium at baseline. Reports as continuous variable (is nominal).; Indirectness of outcome: Serious indirectness, Comments: Defined in protocol as alternative to QoL; Baseline details: Well-matched except for LVEF (higher int), AF (higher usual), beta blockers (higher int) - likely cancel out; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Unplanned hospitalisation (all-cause)
- Actual outcome for Recent admission: Readmissions (any cause) count at 6 months; rate ratio: 87:95 or 0.92 hospital admissions, Comments: Calculated from mean admissions per participant. Number of pts admitted due to HF (nurse) 36 (usual) 38);
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Some minor disequilibrium at baseline.; Indirectness of outcome: No indirectness ; Baseline details: Well-matched except for LVEF (higher int), AF (higher usual), beta blockers (higher int) - likely cancel out; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Medicine optimisation/adherance at 12 months
- Actual outcome for Recent admission: Achieved target ACEi dose at 6 months; Group 1: 18/70, Group 2: 8/75; Comments: Total on ACEi at end of study: (nurse) 49 (usual) 47
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Some minor disequilibrium at baseline. Pts excluded from measure due to contraindication to med (not true missing data).; Indirectness of outcome: No indirectness; Baseline details: Well-matched except for LVEF (higher int), AF (higher usual), beta blockers (higher int) - likely cancel out; Group 1 Number missing: 9, Reason: ACEi contraindicated; Group 2 Number missing: 4,

Reason: ACEi contraindicated - Actual outcome for Recent admission: Prescribed ACE-I at 6 months; Group 1: 49/70, Group 2: 47/75 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Some minor disequilibrium at baseline.; Indirectness of outcome: No indirectness; Baseline details: Well-matched except for LVEF (higher int), AF (higher usual), beta blockers (higher int) - likely cancel out; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Dying in preferred place at 12 months; Adverse events - hyperkalaemia at 12 months; Adverse events - renal function at 12 months ; Patient and carer experience at 12 months; Adverse events - hypotension at 12 months

Study	Gonzalez-guerrero 2014[543]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=117)
Countries and setting	Conducted in Spain; Setting: Geriatric department of Spanish hospital
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 6m intervention, 12m f/u
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical diagnosis of acute decompensation of chronic heart failure
Stratum	Recent admission: Population risk: High (recent decompensation, geriatric setting); Intervention type: MDT clinic; Length: Mid
Subgroup analysis within study	Not applicable
Inclusion criteria	Pts due to be discharged after hospital stay of 2 days or greater to geriatric dept of hospital with acute HF, diagnosed according to ESC guidelines
Exclusion criteria	Terminal disease with expected survival <6m, bedridden patients, dementia patients with GFS<5 or other psychiatric disorder that would make follow-up difficult, living in care-home with independent medical service, and pts not giving consent
Recruitment/selection of patients	March 2007-09, 203 pts identified, 83 met exclusion criteria, 120 pts randomised, 3 (1 int, 2 control) went to live outside area and were excluded
Age, gender and ethnicity	Age - Mean (SD): Int 85 (6.4), Control 85 (6.3). Gender (M:F): 42:85. Ethnicity: Not stated

Further population details	
Extra comments	Medication: ACE-IorARB 92/93%, BB 39/29%. Comorbidities: Charlson CM Index 2.9(1.6)/3(1.8), HTN 92/83%, DM 44/33%, hx MI 27/17%, AF 41/52%, depression 34/26% HF factors: Prior dx 58/61%, NYHA class ave 2.5(0.7)/2.3(0.8), LVEF% ave 60(15)/57(16), MLWHFQ ave 44(15)/38(15)
Indirectness of population	No indirectness
Interventions	(n=59) Intervention 1: Multidisciplinary team - MDT. Intervention consisted of a disease management programme delivered by a geriatrician, nurse and social worker. They met participants before discharge to give education, and nurse contacted again 48h after discharge. Clinic visits were at 10 days, 1 month and 6 months - and at three months they received a phone-call from the geriatrician. At each contact, the pt was evaluated for possible decompensation, self-management recommendations were made, and the treatment compliance / pt ability to fulfil recommendations was assessed. Comorbidities were considered, with special attention paid to changes in functional, cognitive, affective and social capacities of the pt, with changes to the global therapeutic regime made if appropriate. Any unscheduled medical consultations were followed up with contact from the clinic, and a geriatrician was available every morning to answer queries.. Duration 6 months. Concurrent medication/care: As usual. Indirectness: No indirectness (n=58) Intervention 2: Usual care - Primary care. Given booklet on HF, but no education. Treatment was expected to be delivered by primary care physician, and if referral to geriatric or other services needed, this was provided by clinicians outside the study.. Duration 6 months. Concurrent medication/care: As usual. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MDT versus PRIMARY CARE

Protocol outcome 1: Mortality

- Actual outcome for Recent admission: Deaths at 12m; Group 1: 13/59, Group 2: 22/58 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Imbalances at baseline; Indirectness of outcome: No indirectness ; Baseline details: Multiple assymetries in comorbidities (eg AF 41/52), QoL (MLWHFQ 44/39) and tx (BB 39/29) - may cancel each other out; Group 1 Number missing: 3, Reason: 3 did not start study protocol, 3 left study protcol (6 overall); Group 2 Number missing: 3 Protocol outcome 2: Unplanned hospitalisation (all-cause) - Actual outcome for Recent admission: Readmissions at 12m; Rate ratio: 0.92); Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Imbalances at baseline; Indirectness of outcome: No indirectness ; Baseline details: Multiple assymetries in comorbidities (eg AF 41/52), QoL (MLWHFQ 44/39) and tx (BB 39/29) - may cancel each other out; Group 1 Number missing: 3, Reason: 3 did not start study protocol, 3 left study protcol (6 overall); Group 2 Number missing: 3	
Protocol outcomes not reported by the study	Quality of life at 12 months ; Dying in preferred place at 12 months; Medicine optimisation/adherance at 12 months; Adverse events - hyperkalaemia at 12 months; Adverse events - renal function at 12 months ; Patient and carer experience at 12 months; Adverse events - hypotension at 12 months

Study (subsidiary papers)	HICMan trial: Peters-klimm 2010[1131] (Peters-klimm 2007[1132])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=199)
Countries and setting	Conducted in Germany; Setting: GPs with a practice that accept all German insurance, ensuring that patients of different social levels are able to access the surgery (around 200 GPs in the area). GPs also had to have a physicians assistant / practice nurse prepared to be upskilled. 31 GPs from 29 practices took part, of which 19 had taken part in a previous trial regarding improving the implementation of guidelines for CHF.
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Confirmed with echo
Stratum	Community: Population risk: Low; Intervention type: Case management; Length: Long
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged >40 with chronic HF confirmed on echo, and EF ≤45%, currently no dyspnoea, but with hx of hospitalisation due to HF class II-IV in the past 2 years.
Exclusion criteria	Lacked capacity to give consent, participation in another trial, resident in nursing home, valvular disease or HOCM/RCM, pre or post-transplant, short life expectancy <2y due to other disease, drug addiction with ongoing abuse.
Recruitment/selection of patients	Case finding in the 31 practices was by "brainstorming", opportunistic and through searching electronic medical records. 10653 pts initially identified, of which only 256 met criteria: 51 refused to participate/did not attend/lived too far away; 6 had died/were in hospital/were too unfit

Age, gender and ethnicity	Age - Mean (SD): int 70.4(10.0) usual 68.9(9.7). Gender (M:F): 143:56. Ethnicity: Not stated
Further population details	
Extra comments	Baseline characteristics given by group - int/control %: lower social class 32/30, NYHA I 1/5, NYHA II 65/67, NYHA III 34/27, NYHA IV 0/1, ischaemic aetiology 47/47, AF 26/29, DM 32/35, GFR<60 44/43, px ACE/ARB 94/95, px BB 72/84, px loop diuretic 62/59, PCI 30/36, ICD implant 11/21 (control group, trend towards more intervention). mean(sd): LVEF 36(8)/38(7)% duration CHF 6(5)/7(6)y. Details of the practices given - 10 single-handed, 10 urban, 12 had list >15,000pts. Details of doctor's assistants given - mean age 33(sd10), female 100%, mean work experience 11years(sd9)
Indirectness of population	No indirectness
Interventions	(n=99) Intervention 1: Multidisciplinary team - Nurse. Case management by practice nurse / doctors assistant specifically trained in case management for heart failure in the community (1.5 days' instruction). Case management, including 5-A counselling, which involved: (1) introduction, information about HF and self-monitoring; (2) three home visits spread over the year, with a formalised assessment of cardiac/physical functioning and screening, which will be fed back to the participant, and clinician if action suggested; (3) telephone monitoring between the visits, frequency between 3 and 6 weekly depending on severity, to check physical condition and medication adherence; (4) seven months from start, GP will receive information on drug prescription for participant, based on percentage of target dose, and around the same time a GP appointment will be made for specific encounter as part of 5-A counselling; (5) reminders given for doctors appointments and prescription collection. Duration 12 months. Concurrent medication/care: Physicians all received a guideline for the management of heart failure and an introduction to a structured counselling for heart failure (5-A). Indirectness: No indirectness Comments: The title "practice nurse" is used throughout protocol paper, but "doctors assistant" is used in results paper (n=100) Intervention 2: Usual care - Primary care. Care as usual from GP practice. Duration 12 months. Concurrent medication/care: Physicians all received a guideline for the management of heart failure and an introduction to a structured counselling for heart failure (5-A). Indirectness: No indirectness

Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NURSE versus PRIMARY CARE

Protocol outcome 1: Mortality
- Actual outcome for Community: Died at 12 months; Group 1: 5/92, Group 2: 5/98; Comments: Denominator excludes all who withdrew at whatever stage. Cardiac deaths 2 (nurse) 3 (PC).
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Imbalance in intervention / hospitalisation at baseline.; Indirectness of outcome: No indirectness ; Baseline details: Severity measures similar, but intervention and healthcare use rates higher in control group; Group 1 Number missing: 2, Reason: 2 withdrew prior to intervention; Group 2 Number missing: 0

Protocol outcome 2: Quality of life at 12 months
- Actual outcome for Community: SF-36 physical score at 12 months; Group 1: mean 38 (SD 8.6); n=61, Group 2: mean 38.3 (SD 8.6); n=70; SF-36 overall 0-100 Top=High is good outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Higher healthcare use / interventions for control group at baseline. Large numbers missing without explanation; Indirectness of outcome: No indirectness ; Baseline details: SF-36 similar at baseline. Higher healthcare use / interventions for control group at baseline; Group 1 Number missing: 38, Reason: 5 died, 2 withdrew prior to intervention, 5 discontinued before follow-up + 16 unknown; Group 2 Number missing: 30, Reason: 5 died, 2 withdrew before follow-up + 23 unknown
- Actual outcome for Community: KCCQ summary overall score at 12 months; Group 1: mean 68 (SD 16.9); n=87, Group 2: mean 66.3 (SD 17.2); n=93; Kansas City Cardiomyopathy Questionnaire 0-100 Top=High is good outcome; Comments: change scores (nurse) 2.6 improvement, (usual) 1.6 improvement
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Higher healthcare use / interventions for control group at baseline; Indirectness of outcome: No indirectness ; Baseline details: KCCQ similar at baseline. Higher healthcare use / interventions for control group at baseline; Group 1 Number missing: 12, Reason: 5 died, 2 withdrew prior to intervention, 5 discontinued before follow-up; Group 2 Number missing: 8, Reason: 5 died, 2 withdrew before follow-up + 1 unknown
- Actual outcome for Community: SF-36 mental score at 12 months; Group 1: mean 46.5 (SD 9.9); n=61, Group 2: mean 46.6 (SD 9.9); n=70; SF-36 mental composite score 0-100 Top=High is good outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low,

<table>
<tr><td colspan="2">Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Higher healthcare use / interventions for control group at baseline. Large numbers missing without explanation; Indirectness of outcome: No indirectness ; Baseline details: SF-36 similar at baseline. Higher healthcare use / interventions for control group at baseline; Group 1 Number missing: 38, Reason: 5 died, 2 withdrew prior to intervention, 5 discontinued before follow-up + 16 unknown; Group 2 Number missing: 30, Reason: 5 died, 2 withdrew before follow-up + 23 unknown

Protocol outcome 3: Unplanned hospitalisation (all-cause)
- Actual outcome for Community: Hospital admissions, any cause (count) at 12 months; Rate ratio: 46:37 or 1.23 admissions);
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Rate ratio 1.3 at baseline (+0.17 more admissions per person in control group); Indirectness of outcome: No indirectness ; Baseline details: In 12 months prior to intervention, admission rates were 56 in 97people (nurse) and 74 in 100people (usual) - although numbers due to HF are the same; Group 1 Number missing: 12, Reason: 5 died, 2 withdrew prior to intervention, 5 discontinued before follow-up; Group 2 Number missing: 9, Reason: 5 died, 2 withdrew before follow-up + 2 unknown

Protocol outcome 4: Medicine optimisation/adherance at 12 months
- Actual outcome for Community: Prescribed ACE/ARB and beta-blocker at 12 months; Group 1: 63/87, Group 2: 67/93; Comments: change: nurse +4%, usual -7%
Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - 12% difference in baseline value, likely to under-estimate effect.; Indirectness of outcome: No indirectness ; Baseline details: px ACE/ARB and BB: 68/80% (due to rates of BB px being higher); Group 1 Number missing: 12, Reason: 5 died, 2 withdrew prior to intervention, 5 discontinued before follow-up; Group 2 Number missing: 7, Reason: 5 died, 2 withdrew before follow-up</td></tr>
<tr><td>Protocol outcomes not reported by the study</td><td>Dying in preferred place at 12 months; Adverse events - hyperkalaemia at 12 months; Adverse events - renal function at 12 months ; Patient and carer experience at 12 months; Adverse events - hypotension at 12 months</td></tr>
</table>

Study (subsidiary papers)	J-HOMECARE trial: Tsuchihashi-makaya 2013[1408] (Tsuchihashi-makaya 2011[1409])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=161)
Countries and setting	Conducted in Japan; Setting: 3 cardiology hospitals in Hokkaido, Japan chosen for their organisational capacity and enthusiasm for the study
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 6 months (int) + 6 months fu
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical diagnosis meeting NYHA II-IV criteria
Stratum	Recent admission: Population risk: High (recent decompensation), Intervention type: Case management, Length: Mid
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 18 years or older; had a hospital admission for HF with symptoms and signs of HF and a pre-existing history of chronic HF (NYHA class II-IV)
Exclusion criteria	End-stage HF defined as requiring mechanical support or continuous intravenous inotropic support; a serious life-threatening illness with a life-expectancy of <6 months; stroke within the last 3 months; cognitive dysfunction; substance abuse or psychotic disorder; patients whose physician or nurses refused access.
Recruitment/selection of patients	December 2007 to March 2010 screened 384 pts, 154 did not meet inclusion, 58 met exclusion, 4 declined

Age, gender and ethnicity	Age - Mean (SD): Int 77(10), Control 76(12). Gender (M:F): 70:91. Ethnicity: Not stated
Further population details	
Extra comments	HF factors: LVEF% mean 47, BNP mean 310, creatinine mean 1.4 mg/dl. Medication%: ACE-I or ARB 75, BBlocker 46, MRA 47. Etiol HF%: Isch 28, HTN 35, valve 27, cardiomyopathy 25. Comorbid%: HTN 52, DM 25, AF 7. HF factors%: Prev adm 27, NYHA I 14, II 80, III 6, LVEF<40 36
Indirectness of population	No indirectness
Interventions	(n=84) Intervention 1: Multidisciplinary team - MDT. A home-based disease management program consisted of home visit by nurses to provide symptom monitoring, education, and counselling, and telephone follow-up by nurses in addition to routine follow-up by cardiologists. A home visit was made within 14 days after discharge from hospital. Nurses visited each patient's home to assess how the patient was coping in the home environment, HF status, general health status, adherence to medication, lifestyle modification, daily activity, and social support needs. Home visits were made once every 2 weeks until 2 months after discharge. At the conclusion of home visiting, nurses then conducted monthly telephone follow-up until six months after discharge, monitoring general health status and need for other healthcare and social support. Regular multi-disciplinary meetings were held with a cardiology, dietician, pharmacist and social worker . Duration 6 months. Concurrent medication/care: All enrolled patients received comprehensive discharge education by cardiologist, nurse, dietitian, and pharmacist using a booklet that provided information on pathophysiology, medical treatment, diet, physical activity, lifestyle modification, self measurement of body weight, self-monitoring of worsening HF, and emergency contact methods. Follow-up assessments were performed 2, 6, and 12 months after discharge. Indirectness: No indirectness Comments: 94% participants completed programme (n=84) Intervention 2: Usual care - Clinic. After hospital discharge, patients assigned to the usual-care group continued to receive routine management by the cardiologist. No extra follow-up by a HF nurse or multidisciplinary team was provided

	. Duration 6 months. Concurrent medication/care: All enrolled patients received comprehensive discharge education by cardiologist, nurse, dietitian, and pharmacist using a booklet that provided information on pathophysiology, medical treatment, diet, physical activity, lifestyle modification, self measurement of body weight, self-monitoring of worsening HF, and emergency contact methods. Follow-up assessments were performed 2, 6, and 12 months after discharge. . Indirectness: No indirectness Comments: 97% completed protocol
Funding	Other (Grants from the Japanese Ministry of Health, Labour and Welfare, the Japan Heart Foundation, and Pfizer Health Research Foundation)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MDT versus CLINIC

Protocol outcome 1: Mortality
- Actual outcome for Recent admission: Death at 12 months;
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Randomisation not clear, slight imbalance at baseline; Indirectness of outcome: No indirectness ; Baseline details: More AF in usual care AF 43v62, otherwise ok. Age 77v76, Female 37v33, etiol isch 22v22, prior adm 22v21, DM 21v16, LVEF 47v47, NYHA III 5v6, ACE-I 73v79, BB 47v45, ICD 1v2; Group 1 Number missing: 3, Reason: 1 LFU, 2 discontinued due to cognitive impairment; Group 2 Number missing: 2, Reason: 1 LFU, 1 did not receive protcol

Protocol outcome 2: Quality of life at 12 months
- Actual outcome for Recent admission: QOL physical health at 12 months; Group 1: mean 44 (SD 9); n=70, Group 2: mean 42 (SD 10); n=68; SF-8 (related to SF-36) 0-100 Top=High is good outcome
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Randomisation not clear, slight imbalance at baseline,

unblind, read from graph. Acceptable validated measure; Indirectness of outcome: No indirectness ; Baseline details: QOL same. More AF in usual care AF 43v62, otherwise ok. Age 77v76, Female 37v33, etiol isch 22v22, prior adm 22v21, DM 21v16, LVEF 47v47, NYHA III 5v6, ACE-I 73v79, BB 47v45, ICD 1v2; Group 1 Number missing: 9; Group 2 Number missing: 14 - Actual outcome for Recent admission: QOL mental health at 12 months; Group 1: mean 49 (SD 8); n=70, Group 2: mean 47 (SD 8); n=68; SF-8 (related to SF-36) 0-100 Top=High is good outcome Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Randomisation not clear, slight imbalance at baseline, unblind, read from graph. Acceptable validated measure; Indirectness of outcome: No indirectness ; Baseline details: QOL same. More AF in usual care AF 43v62, otherwise ok. Age 77v76, Female 37v33, etiol isch 22v22, prior adm 22v21, DM 21v16, LVEF 47v47, NYHA III 5v6, ACE-I 73v79, BB 47v45, ICD 1v2; Group 1 Number missing: 9; Group 2 Number missing: 14 Protocol outcome 3: Unplanned hospitalisation (all-cause) - Actual outcome for Recent admission: HF hospitalisation at 12 months; Group 1: Observed events 16 n=84 ; Group 2: Observed events 34 n=84; HR 0.52; Lower CI 0.27 to Upper CI 0.96; Test statistic: cox proportional hazards p=0.037 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: Serious indirectness, Comments: Protocol outcome is all-cause admissions; Baseline details: Difference of AF 43v62, otherwise ok; Group 1 Number missing: 3, Reason: 1 LFU, 2 cog imp; Group 2 Number missing: 2, Reason: 1 LFU, 1 wrong intervention	
Protocol outcomes not reported by the study	Dying in preferred place at 12 months; Medicine optimisation/adherance at 12 months; Adverse events - hyperkalaemia at 12 months; Adverse events - renal function at 12 months ; Patient and carer experience at 12 months; Adverse events - hypotension at 12 months

Study (subsidiary papers)	Ledwidge 2003[843] (Mcdonald 2001[969], Mcdonald 2002[970])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=98)
Countries and setting	Conducted in Irish Republic; Setting: Cardiology service of hospital
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 3m
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Cardiologist confirmed diagnosis based on hx, exam, CXR, echo and response to initial therapy
Stratum	Recent admission: Population risk: High (recent admission), Intervention type: MDT clinic, Length: Short
Subgroup analysis within study	Not applicable
Inclusion criteria	Admitted with a confirmed diagnosis of HF
Exclusion criteria	Presentation in context of MI, other illness that compromise survival over the course of the trial, cognitive impairment, no consent
Recruitment/selection of patients	Nov 1998 - April 2000, 337 pts thought to have HF, 214 confirmed that primary reason for admission was HF, 116 were excluded or refused, 98 included
Age, gender and ethnicity	Age - Mean (SD): 70.8(10.5). Gender (M:F): 65:33. Ethnicity: Not stated
Further population details	
Extra comments	HF factors: systolic dysfunction 71%, prev HF 53%, prev adm 45%, LVEF 37(13)%, EF<50% 52%. Etiology

	Ischaemia 52%
Indirectness of population	No indirectness
Interventions	(n=51) Intervention 1: Multidisciplinary team - MDT. In addition to optimisation, pts received inpatient specialist nurse and dietician consultations on at least three occasions, and were educated about daily weight monitoring, disease and medication understanding, and salt restriction - carers and family were also educated as appropriate. On discharge, they received a phone call from the same nurse specialist to assess clinical status and any educational issues necessary – phone calls were then made weekly for 12 weeks. Pt and any carers were seen in clinic at 2 weeks and 6 weeks after discharge for review. The clinic also monitored urea and electrolytes. Pt was encouraged to contact if any deterioration or weight gain when tiered medical response would be triggered - oral diuretic, clinical review, IV diuretic, inpatient admission - depending on severity and response. Duration 3 months. Concurrent medication/care: Both arms were optimised in hospital, including titration of an ACE-I if impaired LV systolic function. Required to fulfil stability criteria before discharge: symptomatically improved, off IV therapy for 2 days, stable oral therapy with no change for two days, stable dry weight (no change > 1kg) for 2 days. Indirectness: No indirectness (n=47) Intervention 2: Usual care - Primary care. After inpatient optimisation (did not receive education from nurse and dietician), referred back to primary care physician, who was free to manage as saw fit, including referral to cardiology if needed. Duration 3 months. Concurrent medication/care: Both arms were optimised in hospital, including titration of an ACE-I if impaired LV systolic function. Required to fulfil stability criteria before discharge: symptomatically improved, off IV therapy for 2 days, stable oral therapy with no change for two days, stable dry weight (no change > 1kg) for 2 days. Indirectness: No indirectness
Funding	Other (Irish heart foundation and Servier Laboratories Ltd.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MDT versus PRIMARY CARE Protocol outcome 1: Mortality - Actual outcome for Recent admission: Deaths at 3 months; Group 1: 3/51, Group 2: 3/47	

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Randomisation procedure not explained; Indirectness of outcome: No indirectness ; Baseline details: Age: 51(10)/71(11), HFREF: 39/32, Prev HF 29/24, prev adm: 23/22; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Unplanned hospitalisation (all-cause) - Actual outcome for Recent admission: HF readmissions at 3 months; Rate ratio: 0.15); Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Randomisation procedure not explained; Indirectness of outcome: Serious indirectness, Comments: Protocol outcome is all-cause hospitalisation; Baseline details: Age: 51(10)/71(11), HFREF: 39/32, Prev HF 29/24, prev adm: 23/22; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at 12 months ; Dying in preferred place at 12 months; Medicine optimisation/adherence at 12 months; Adverse events - hyperkalaemia at 12 months; Adverse events - renal function at 12 months ; Patient and carer experience at 12 months; Adverse events - hypotension at 12 months

Study	Martensson 2005[945]
Study type	RCT (Cluster randomised; Parallel)
Number of studies (number of participants)	1 (n=153)
Countries and setting	Conducted in Sweden; Setting: Eight primary care centres
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Based on a record of diagnosis of heart failure from echo, CXR, or typical signs and symptoms (74% had echo)
Stratum	Population risk: Low (community), Intervention type: Case management, Length: Long
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults with documented diagnosis of HF, NYHA class II-IV, resident in catchment area
Exclusion criteria	Serious psychiatric disease, suffering from life-threatening disease, being seen in heart failure clinic, cannot speak Swedish
Recruitment/selection of patients	Disease register searched and 837 HF pts found, but most had a tentative diagnosis or fulfilled one of exclusion criteria. Of 225 eligible pts, 153 agreed to participate
Age, gender and ethnicity	Age - Mean (SD): 79(7). Gender (M:F): 83:70. Ethnicity: Not stated
Further population details	
Extra comments	. Baseline: Married 54%, prior MI 40%, DM 22%, diuretics 92%, NYHA class II 41%, III 53%, IV 6%

Indirectness of population	No indirectness
Interventions	(n=78) Intervention 1: Multidisciplinary team - Nurse. Case-management by primary care nurses. In the "intervention" centres, primary care nurses and physicians were educated by a heart failure nurse and cardiologists for up to 9h. Nurses were up-skilled so that they could deliver a programme of education and counselling to heart failure patients in their care. One face to face session was provided in the home of the participant, including their family if they wished. Literature was provided, and a multimedia program on CD-ROM. Further coaching sessions were carried out by phone monthly, or more if needed due to new or worsening symptoms. Sessions aimed at enhancing the patients understanding of heart failure and improving self-management - eg by fluid and salt restriction, weight monitoring, noting early symptoms of decompensation, and flexible diuretic regimen. Participants could vary their own Frusemide dose. Duration 12 months. Concurrent medication/care: Primary care, and onward referral to hospitals and other institutions as needed. Comments: There were an average of 9.6 contacts. (n=75) Intervention 2: Usual care - Primary care. In the "control" practices, care was delivered as usual by the primary care team, which may include contact with the nurse (not upskilled) or home visits, not according to a protocol. Duration 12 months. Concurrent medication/care: Primary care, and onward referral to hospitals and other institutions as needed.
Funding	Other (Financial support received from Research Council of Southeastern Sweden, the Swedish Heart and Lung Foundation, the County Research Council of Jonkoping and the Health Care Section of Jonkoping County Council.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NURSE versus PRIMARY CARE

Protocol outcome 1: Mortality
- Actual outcome for Community: Died at 12 months; Group 1: 10/76, Group 2: 3/73
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Cluster randomised, some difference in pt baseline data (likely

to underestimate). Possible background tx differed, as from different health providers (4 in intervention and 4 in usual arms).; Indirectness of outcome: No indirectness ; Baseline details: Trend towards more severe in intervention group (more MYHA IV, more impaired on SF-36). Intervention arm had 8pts with NYHA IV, six of whom died. Control arm had only one.; Group 1 Number missing: 2, Reason: withdrew consent; Group 2 Number missing: 2, Reason: withdrew consent

Protocol outcome 2: Quality of life at 12 months
- Actual outcome for Community: Quality of life outcomes incompletely reported at not extracted;
Risk of bias: All domain - ; Indirectness of outcome: No indirectness

Protocol outcome 3: Medicine optimisation/adherance at 12 months
- Actual outcome for Community: Prescribed an ACEi at target dose at 12 months; Group 1: 30/62, Group 2: 39/68; Comments: Calculated from percentages (49% vs 58%)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Cluster randomised, some difference in pt baseline data. Possible background tx differed, as from different health providers (4 in intervention and 4 in usual arms). Pt attrition differential (16 vs 7).; Indirectness of outcome: No indirectness, Comments: nb Improving medication regimen was not an aim of the trial; Baseline details: Trend towards more severe in intervention group (more MYHA IV, more impaired on SF-36). Reported as no difference in px at baseline.; Group 1 Number missing: 16, Reason: 2 withdrew consent, 10 died, 4 lost to follow-up (as too unwell); Group 2 Number missing: 7, Reason: 2 withdrew consent, 3 died, 2 lost to follow-up (as too unwell)
- Actual outcome for Community: Prescribed an beta blocker at target dose at 12 months; Group 1: 14/62, Group 2: 16/68; Comments: Calculated from percentage (23% v 23%)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Cluster randomised, some difference in pt baseline data. Possible background tx differed, as from different health providers (4 in intervention and 4 in usual arms). Pt attrition differential (16 vs 7).; Indirectness of outcome: No indirectness, Comments: nb Improving medication regimen was not an aim of the trial; Baseline details: Trend towards more severe in intervention group (more MYHA IV, more impaired on SF-36). Reported as no difference in px at baseline.; Group 1 Number missing: 16, Reason: 2 withdrew consent, 10 died, 4 lost to follow-up (as too unwell); Group 2 Number missing: 7, Reason: 2 withdrew consent, 3 died, 2 lost to follow-up (as too unwell)

Protocol outcomes not reported by the study	Unplanned hospitalisation (all-cause) at during study; Dying in preferred place at 12 months; Adverse events - hyperkalaemia at 12 months; Adverse events - renal function at 12 months ; Patient and carer experience

	at 12 months; Adverse events - hypotension at 12 months

Study (subsidiary papers)	NorthStar trial: Schou 2013[1258] (Schou 2014[1257])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=921)
Countries and setting	Conducted in Denmark; Setting: 40 heart failure clinics
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: Mean 24 months (range 1-6 years)
Method of assessment of guideline condition	Method of assessment /diagnosis not stated: Established patients in heart failure clinic with reduced EF
Stratum	Community: Population risk: Low; Intervention type: MDT clinic; Length: Long
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults who have attended at least two appointments at heart failure clinic. Stable on last two visits (no fluid overload, NYHA class stable, no changes in diuretic dose). LVEF≤45% prior to interventions at HF clinic. On optimal therapy, including ACEi/ARB unless contraindicated, betablocker and MRA unless contraindicated, ICD and/or CRT if indicated
Exclusion criteria	Creatinine >200umol/L, waiting transplant or other heart surgery (including percutaneous), reversible cause o cardiomyopathy, malignancy with life expectancy <5y and dementia
Recruitment/selection of patients	1640 met inclusion criteria: 54 met exclusion, 210 declined, 256 could not be stratified, 199 were in a different study
Age, gender and ethnicity	Age - Other: Median (int) 69, (usual) 69, 95%CI (int) 47-86, (usual) 43-86. Gender (M:F): 692:228 (male 75%). Ethnicity: Not stated

Further population details	
Extra comments	Baseline stats extensive. Selection: NYHA<3 89%, EF 0.31, AF 33%, Adm in last 12mo 43%, Ischaemic etiology 58%, previous MI 50%, NT pro-BNP 798, ACE/ARB 87%, betaB 84%, loop diuretic 57%, ICD 8%. Included pts had been in HF clinic an average of 9 months (95% centiles 2 and 62 months). Study aimed to recruit equal numbers of pts with NT-proBNP above median and NT-proBNP below previously documented median of 1000pg/ml, but identified an excess of 256 people with <1000pg/ml who could not be enrolled in study
Indirectness of population	No indirectness: Distinct population to other studies
Interventions	(n=460) Intervention 1: Multidisciplinary team - MDT. Extended follow-up in heart failure clinic. Seen at 1-3 month intervals as needed, medical treatment reviewed and adherence promoted. Signs and symptoms reviewed to see if escalation of treatment required. Comorbidity also managed in the clinic. Participants were able to phone the clinic for a nurse consultation on weekdays.. Duration Mean 4 years (range 1-6 years). Concurrent medication/care: Data were captured in an electronic Case Report Form used in all of the heart failure clinics.. Indirectness: No indirectness (n=460) Intervention 2: Usual care - Primary care. Discharged from clinic to care of GP, where they could arrange an individual follow-up. Follow-up data shows that 62% saw GP regularly (at least every three months) and 12% saw a cardiologist during follow-up.. Duration Average 4 years (range 1-6y). Concurrent medication/care: Data were captured in an electronic Case Report Form used in the heart failure clinics.. Indirectness: No indirectness
Funding	Study funded by industry (Funded by unrestricted grant from Roche Diagnostics. Also supported by Merck, Sharp and Dohme; and the Copenhagen Hospital Corporation.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MDT versus PRIMARY CARE

Protocol outcome 1: Mortality
- Actual outcome for Community: Death at During follow-up (ave 4y); HR; 1.05 (95%CI 0.74 to 1.5);

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: "Balanced and simple randomization with strata", stratified by severity based on BNP levels; Blinding details: Extracted by separate investigator, did not know group.; Group 1 Number missing: 1, Reason: 1 - withdrew consent; Group 2 Number missing: 0

Protocol outcome 2: Quality of life at 12 months
- Actual outcome for Community: Minnesota Living with Heart Failure Questionnaire at At follow-up (ave 4y); Minnesota Living with Heart Failure 0-100 Top=High is poor outcome; Median starting values were int 25 (95centiles 0-75) usual 22 (0-73);
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - No blinding. Seems unlikely had full return of questionnaire. Reports only change score and IQR of change score.; Indirectness of outcome: No indirectness ; Baseline details: Similar score at baseline: 25 (0-75), 22 (0-73); Group 1 Number missing: 1, Reason: 1 - withdrew consent; Group 2 Number missing: 0

Protocol outcome 3: Unplanned hospitalisation (all-cause)
- Actual outcome for Community: Number of admissions, total at During follow-up (ave 4y); Rate ratio: 655:694 or 0.94, Comments: Patients admitted (int) 255, (usual) 236, Hazard ratio 10.3 (0.74-1.44));
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - From registry.; Indirectness of outcome: No indirectness ; Baseline details: "Balanced and simple randomization with strata", stratified by severity based on BNP levels; Blinding details: Extracted by separate investigator, did not know group.; Group 1 Number missing: 1, Reason: 1 - withdrew consent; Group 2 Number missing: 0

Protocol outcome 4: Medicine optimisation/adherance at 12 months
- Actual outcome for Community: Change in ACE/ARB therapy at During follow-up (ave 4y); change in proportion prescribed: (int) +3.1% (usual) 0.0%);
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - High rates of missing data (int 19.3%, usual 23.4%); Indirectness of outcome: No indirectness, Comments: Presume prescription rate, no indication if appropriate or compliance; Baseline details: "Balanced and simple randomization with strata", stratified by severity based on BNP levels; Blinding details: Extracted by separate investigator, did not know group.; Group 1 Number missing: 89, Reason: Not stated; Group 2 Number missing: 108, Reason: Not stated
- Actual outcome for Community: Change in beta blocker therapy at During follow-up (ave 4y); change in proportion prescribed: (int) +4.0% (usual) +3.4%);
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - High rates of missing data (int 19.3%, usual 23.4%); Indirectness of

	outcome: No indirectness, Comments: Presume prescription rate, no indication if appropriate or compliance; Baseline details: "Balanced and simple randomization with strata", stratified by severity based on BNP levels; Blinding details: Extracted by separate investigator, did not know group.; Group 1 Number missing: 89, Reason: Not stated; Group 2 Number missing: 108, Reason: Not stated Protocol outcome 5: Adverse events - hypotension at 12 months - Actual outcome for Community: systolic blood pressure <90mmHg at At follow-up (ave 4y); Group 1: 3/372, Group 2: 2/351 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - High rates of missing data (int 19%, usual 24%); Indirectness of outcome: No indirectness, Comments: Possible indirectness. Reported as hypotension "at follow-up", rather than during follow-up, so likely asymptomatic rather than intermittent symptomatic cases, or those that have been treated.; Baseline details: "Balanced and simple randomization with strata", stratified by severity based on BNP levels; Blinding details: Extracted by separate investigator, did not know group.; Group 1 Number missing: 88, Reason: Not stated; Group 2 Number missing: 109, Reason: Not stated Protocol outcome 6: Adverse events - hyperkalaemia at 12 months - Actual outcome for Community: p-potassium > 5.0mmol/l at At follow-up (ave 4y); Group 1: 13/372, Group 2: 22/351 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - High rates of missing data (int 19%, usual 24%); Indirectness of outcome: No indirectness, Comments: Possible indirectness. Reported as hyperkalaemia "at follow-up", rather than during follow-up, so may not include cases that have occurred and been treated (or fatal).; Baseline details: "Balanced and simple randomization with strata", stratified by severity based on BNP levels; Blinding details: Extracted by separate investigator, did not know group.; Group 1 Number missing: 88, Reason: Not stated; Group 2 Number missing: 109, Reason: Not stated Protocol outcome 7: Adverse events - renal function at 12 months - Actual outcome for Community: >50% increase in p-creatinine at At follow-up (ave 4y); Group 1: 13/372, Group 2: 13/351 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - High rates of missing data (int 19%, usual 24%); Indirectness of outcome: No indirectness; Baseline details: "Balanced and simple randomization with strata", stratified by severity based on BNP levels; Blinding details: Extracted by separate investigator, did not know group.; Group 1 Number missing: 88, Reason: Not stated; Group 2 Number missing: 109, Reason: Not stated
Protocol outcomes not reported by the study	Dying in preferred place at 12 months; Patient and carer experience at 12 months

Study	Nucifora 2006[1059]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=200)
Countries and setting	Conducted in Italy; Setting: Italian university hospital dept internal medicine
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Signs and symptoms as per Framingham criteria for congestive heart failure
Stratum	Recent admission: Population risk: High (most recent decompensation, most req titration), Intervention type: MDT clinic; Length: Mid
Subgroup analysis within study	Not applicable
Inclusion criteria	Inpatients aged 85 and under screening positive for congestive heart failure
Exclusion criteria	Chronic cor pulmonale, terminal illness in addition to HF, severe dementia or other severe psychiatric illness, indication for surgery in the next six months, or unwilling
Recruitment/selection of patients	March 1999 - January 2001. 200 consecutive eligible pts were randomised.
Age, gender and ethnicity	Age - Mean (SD): 73(9). Gender (M:F): 62:38. Ethnicity: Not stated
Further population details	
Extra comments	Medication at baseline: ACE-I 80/80, beta-blockers 14/11. Severity: NYHA I 0/2, II 33/37, III 64/61, IV 3/1,

	LVEF<45% 58/60, AF 27/48, 4+ prev adm 22/21. Comorbidities: IHD 46/46, renal insufficiency 33/27, digoxin 50/71
Indirectness of population	No indirectness
Interventions	(n=99) Intervention 1: Multidisciplinary team - Nurse. Experienced cardiovascular research nurse delivered inpatient education, using a bespoke booklet regarding symptoms of HF, remediable lifestyle factors, signs of deterioration, fluid and weight control. Three days after discharge nurse phone-called to assess, encourage self-management and reinforce education and assess compliance with aspects of the treatment plan. Pts were encouraged to contact the nurse if there were any signs of deterioration, and the nurse could recommend extra diuretics and contact the doctor for instructions. Review with the doctor was scheduled for 15 days, 1 and 6 months after discharge at the outpt, where pt would be assessed, and Dr would consider medication changes. The nurse would also visit any pts who were re-admitted during the intervention to reinforce educational messages and assess compliance. Duration 6 months. Concurrent medication/care: As usual. Indirectness: No indirectness (n=101) Intervention 2: Usual care - Primary care. Pre-existing standard of discharge and post-discharge care - no structured education, fu phonecall or medical visits. Cared for by primary care physician.. Duration 6 months. Concurrent medication/care: As usual. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NURSE versus PRIMARY CARE

Protocol outcome 1: Mortality
- Actual outcome for Recent admission: Deaths at 6 months; Group 1: 14/99, Group 2: 8/101; Comments: Time from admission to death 70(36) days in intervention and 64(50) days in control
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Unclear randomisation procedure; Indirectness of outcome: No indirectness ; Baseline details: Study notes difference in AF (27/48%), other main ok; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Quality of life at 12 months
- Actual outcome for Recent admission: Minnesota LWHFQ at 6 months; Group 1: mean 14 pts (SD 20); n=74, Group 2: mean 10 pts (SD 16); n=75; Minnesotal Living with Heart Failure Questionnaire 0-105 Top=High is poor outcome; Comments: Component physical scores: 7(10)/5(7), emotional score: 3(5),2(4)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Unclear randomisation procedure, unblinded; Indirectness of outcome: No indirectness ; Baseline details: Study notes difference in AF (27/48%). Baseline, slight difference in MLWHFQ (36 vs 34), benefitting usual care ; Group 1 Number missing: 25, Reason: not clear; Group 2 Number missing: 24, Reason: not clear

Protocol outcome 3: Unplanned hospitalisation (all-cause)
- Actual outcome for Recent admission: Admissions at 6 months; Mean; Int 0.8 (SD 1.2), Control: 0.8 (SD 1.2) (Rate ratio: 1));
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Unclear randomisation procedure; Indirectness of outcome: No indirectness ; Baseline details: Study notes difference in AF (27/48%), other main ok; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Medicine optimisation/adherance at 12 months
- Actual outcome for Recent admission: Taking prescribed medication at 6 months; Group 1: 74/85, Group 2: 78/93
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Unclear randomisation procedure, unclear how measured; Indirectness of outcome: No indirectness ; Baseline details: Study notes difference in AF (27/48%), other main ok; Group 1 Number missing: 14, Reason: unclear; Group 2 Number missing: 8, Reason: unclear
- Actual outcome for Recent admission: Prescribed ACE-I at 6 months; Group 1: 68/85, Group 2: 75/93
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Unclear randomisation procedure; Indirectness of outcome: No indirectness ; Baseline details: Study notes difference in AF (27/48%), other main ok; Group 1 Number missing: 14, Reason: unclear; Group 2 Number missing: 8, Reason: unclear
- Actual outcome for Recent admission: Prescribed beta-blocker at 6 months; Group 1: 12/85, Group 2: 18/93
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Unclear randomisation procedure; Indirectness of outcome: No indirectness ; Baseline details: Study notes difference in AF (27/48%), other main ok; Group 1 Number missing: 14, Reason: unclear; Group 2 Number missing: 8, Reason: unclear

Protocol outcomes not reported by the study	Dying in preferred place at 12 months; Adverse events - hyperkalaemia at 12 months; Adverse events - renal function at 12 months ; Patient and carer experience at 12 months; Adverse events - hypotension at 12 months

Study	OPTIMAL (optimising congestive heart failure outpatient clinic project) trial: Mejhert 2004[983]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=208)
Countries and setting	Conducted in Sweden; Setting: Danderyd University Hospital, Stockholm (catchment 300,000 - characterised as older and healthier than average Sweden)
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: Intervention length 6-18 months; follow-up at 12 months and average of 37 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: NYHA class II-IV + LVSD on echo (not clear who ascertained, and whether clinical diagnosis or for purpose of study)
Stratum	Recent admission: Population risk: High, Intervention type: nurse-led clinic; Length: Long
Subgroup analysis within study	Not applicable
Inclusion criteria	Hospitalised with heart failure, aged over 60, HF class II-IV NYHA, left ventricular systolic dysfunction on echocardiography
Exclusion criteria	Acute myocardial infarction, unstable angina or stroke in last three months (n=6), valvular stenosis (n=5), dementia/confusion (n=5), severe concomitant disease (n=6), no LVSD (n=23), or did not wish to participate (n=32)
Recruitment/selection of patients	285 elderly patients with HF screened from acute wards.
Age, gender and ethnicity	Age - Mean (SD): over 60 years, 75.8 (7.1). Gender (M:F): 120:88. Ethnicity: Not stated

Further population details	
Extra comments	Women older than men (78 v 74y). Baseline characteristics: NYHA% - I=0, II=129, III=77, IV=2 (int 0/60/43/0, usual 0/69/34/2) Ejection fraction mean - 0.34 sd0.11 (int 0.34, usual 0.35) Previously known HF % - 57 (int 57, usual 57) Ischaemic HD % - 67 (int 63, usual 70) Arrythmia % - 53 (int 52, usual 54) Diabetes M % - 22 (int 25, usual 19)
Indirectness of population	No indirectness
Interventions	(n=103) Intervention 1: Multidisciplinary team - Nurse. Nurse-monitored management programme at hospital outpatient clinic. Senior cardiologist supervises programme. Nurse is allowed to institute ACE inhibitors, ARBs, beta-blockers, potassium supplements and diuretics and titrate them according to a standardised protocol. Pt encouraged to weigh regularly. Given information about early signs of decompensation, and encouraged to call clinic and/or change diuretic dose. Dietary advice given. Booklets and computerised educational resources about HF and management introduced.. Duration flexible 6-18 months (up to ten clinic visits). Concurrent medication/care: There is a well-established health care plan agreed and discussed with general practitioners for implementation in primary care, which would be expected to be followed after discharge from the clinic. To facilitate this, written information given in a structured format to the general practitioner at discharge. Comments: Participants made between 0 and 10 visits to the clinic, median 1, mean 2.2, sd 2.3 (n=105) Intervention 2: Usual care - Primary care. There is a well-established health care plan agreed and discussed with general practitioners for implementation in primary care, which would be expected to be followed after discharge from hospital. To facilitate this, written information given in a structured format to the general practitioner at discharge.. Duration 18 months. Concurrent medication/care: Health care programme (ie what GP is asked to implement in primary care) includes: pt education according to checklist, ACE inhibitor in EF<40%, spironolactone and beta blocker where indicated, referral to surgeon if indicated, and appropriate monitoring.

Funding	Other (Support listed from Vardal Foundation (public funding), Swedish Heart and Lung Foundation, Swedish Society of Medicine, and Karolinska Institutet (a medical school) - but no indication this covers all funding.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: NURSE versus PRIMARY CARE

Protocol outcome 1: Mortality
- Actual outcome for Recent admission: All cause mortality at mean 37 months; Group 1: 40/103, Group 2: 34/105; Comments: 49 pts died in first 18 months (group not given)
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Unclear randomisation and allocation blinding. Unclear how many lost to follow-up, but followed through records, so probably accurate.; Indirectness of outcome: No indirectness ; Baseline details: Out of 20 paramaters, only one >5% different was use of digitalis (54v48); Group 1 Number missing: , Reason: NR; Group 2 Number missing: , Reason: NR

Protocol outcome 2: Quality of life at 12 months
- Actual outcome for Recent admission: Nottingham Health Profile Part 1 Total (QoL) at 12 months; Group 1: mean 136 (SD 107); n=103, Group 2: mean 127 (SD 15); n=105; Nottingham Health Profile, Total score 0-600 Top=High is poor outcome; Comments: Component scores: Emotional reaction 14/15, Sleep 23/27. Energy 46/38, Pain 15/12, Physical mobility 27/23, Social isolation 11/12
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Unclear randomisation and allocation blinding. Unclear how many lost to follow-up.; Indirectness of outcome: No indirectness; Baseline details: Out of 20 paramaters, only one >5% different was use of digitalis (54v48); Group 1 Number missing: , Reason: NR; Group 2 Number missing: , Reason: NR

Protocol outcome 3: Unplanned hospitalisation (all-cause)
- Actual outcome for Recent admission: Readmissions per participant at mean 37 months; Rate ratio: 44:49 or 0.90 Readmissions/patient, Comments: 85 out of 103 patients had admission in nurse group. 86 out of 105 patients had admission in usual group.);
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Unclear randomisation and allocation blinding. Unclear how many lost to follow-up, but followed through records, so probably accurate.; Indirectness of outcome: No indirectness, Comments: From readmissions per patient during follow-up; Baseline details: Out of 20 paramaters, only one >5% different was use of digitalis (54v48); Group 1 Number missing: , Reason: NR; Group 2 Number missing: , Reason: NR

Protocol outcome 4: Medicine optimisation/adherance at 12 months - Actual outcome for Recent admission: Taking ACE inhibitor at 12 months; Group 1: 68/103, Group 2: 77/105 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Unclear randomisation and allocation blinding. Unclear how many lost to follow-up. Appears that medication history taken at follow-up visit.; Indirectness of outcome: No indirectness; Baseline details: Out of 20 parameters, only one >5% different was use of digitalis (54v48); Group 1 Number missing: 26, Reason: NR; Group 2 Number missing: 37, Reason: NR - Actual outcome for Recent admission: Taking beta-adrenoblockers at 12 months; Group 1: 57/103, Group 2: 65/105; Comments: Calculated from percentage (55%vs.62%) Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Unclear randomisation and allocation blinding. Unclear how many lost to follow-up. Appears that medication history taken at follow-up visit.; Indirectness of outcome: No indirectness, Comments: Presume this is proportion prescribed. No indication of appropriateness or compliance.; Baseline details: Out of 20 paramaters, only one >5% different was use of digitalis (54v48); Group 1 Number missing: , Reason: NR; Group 2 Number missing: , Reason: NR	
Protocol outcomes not reported by the study	Dying in preferred place at 12 months; Adverse events - hyperkalaemia at 12 months; Adverse events - renal function at 12 months ; Patient and carer experience at 12 months; Adverse events - hypotension at 12 months

Study (subsidiary papers)	**PREFER trial: Brannstrom 2014[203] (Markgren 2016[944], Brannstrom 2013[202], Sahlen 2016[1235])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=72)
Countries and setting	Conducted in Sweden; Setting: Recruited from primary care centres that fed into the Dept geriatric medicine
Line of therapy	Adjunctive to current care
Duration of study	Intervention time: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: According to criteria of ESC
Stratum	Population risk: V.high (severity, elderly, comorbidity / recent decompensation); Intervention type: MDT (in the community); Length: Mid
Subgroup analysis within study	Not applicable
Inclusion criteria	NYHA class III or IV heart failure and at least one of markers of severity (i) hospitalisation requiring IV diuretics, despite being on "optimal" medication (ii) needing frequent IV support (iii) chronic poor quality of life (<50 on visual analogue scale) (iv) cachexia (v) life expectancy <1y
Exclusion criteria	Declined (30), severe communication problems, or disorders such as dementia severe enough that HF treatment not a priority (81), short life expectancy due to non-cardiac disorder, lives too far (85) or part of another trial
Recruitment/selection of patients	517 HF patients screened, 304 met inclusion, 232 met exclusion
Age, gender and ethnicity	Age - Mean (SD): int 81.9 (7.2) usual 76.6 (10.2). Gender (M:F): 21:51. Ethnicity: Not stated

Further population details	
Extra comments	Although no minimum age given, likely to have recruited mainly 'geriatric' patients due to setting. Extensive baseline information.Sample: int/usual -- single 39/39%, IHD 36/36%, AF 64/61%, DM 19/17%, depression 17/33%, GFR<60 69/61%, NYHA IV 22/31%, severe dyspnoea 11/17%, EF<30 19/8%, RAS blockade 86/92%, loop diuretics 89/83%, median number of non-cardiac drugs 5/6
Indirectness of population	No indirectness
Interventions	(n=36) Intervention 1: Multidisciplinary team - MDT. Multidisciplinary approach involving collaboration between specialists in palliative care and heart failure care, including heart failure nurse, palliative care nurse, cardiologist, palliative care physician, physiotherapist and occupational therapist. Offered person-centred care at home, which involves the patients and their family/carers, professional caregivers and the PREFER team planning a partnership according to a mutual care plan, which includes goals and strategies for implementation and follow-up. This included identification of co-morbidities and assessment of physiological, social and spiritual needs. The team itself had regular meetings to discuss patients, and information was shared through documentation in medical records and phone calls. The team took responsibility for "total care" i.e. including co-morbidities. IV and SC diuretics could be given at home, as well as blood tests and ECGs performed.. Duration 6 months. Concurrent medication/care: After six months, patients were discharged to original care providers with an established individualised care plan. (n=36) Intervention 2: Usual care - Primary care. Usual care was provided mainly by general practitioners and/or the nurse-led HF clinic at the dept geriatric medicine . Duration 6 months. Concurrent medication/care: Continued with usual healthcare provider; Indirectness comment: Results show that the 26 participants in usual care saw a hospital physician 133 times with 86 phonecalls (median 3 each), hospital nurse 60 times (median 2), primary care physician 54 times with 145 phonecalls (median 2 visits, 1 phonecall)
Funding	Other (Supported by Swedish Association of Local Authorities and Regions, the Swedish Heart and Lung Association, the Ronnbaret Foundation Skelleftea Municipality and FOU-Vasterbotten)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MDT versus PRIMARY CARE Protocol outcome 1: Mortality - Actual outcome for Mixed: Mortality at 6 months; Group 1: 8/36, Group 2: 4/36 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Intervention group slightly older, otherwise well matched (82v77); Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Quality of life at 12 months - Actual outcome for Mixed: Euro Qol-5D at 6 months; Group 1: mean 60.4 (SD 20.6); n=36, Group 2: mean 52.3 (SD 23.2); n=36; EQ-5D range unstated Top=High is good outcome; Comments: Paper reports that no significant difference on any of five dimensions Risk of bias: All domain - Very high, Selection - Low, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - ITT last values taken forward (numbers missing not reported, possibly up to a third); Indirectness of outcome: No indirectness ; Baseline details: Intervention group slightly older, otherwise well matched (82v77); Group 1 Number missing: 12, Reason: According to the KCCQ-12, done only in experimental arm, 12 missing at six months, and 3 missing at all f/u points; Group 2 Number missing: 3 Protocol outcome 3: Unplanned hospitalisation (all-cause) - Actual outcome for Mixed: Hospitalisation (count) at 6 months; rate ratio : 0.28 (0.16-0.50) admissions); Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Intervention group slightly older, otherwise well matched (82v77); Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Dying in preferred place at 12 months; Medicine optimisation/adherance at 12 months; Adverse events - hyperkalaemia at 12 months; Adverse events - renal function at 12 months ; Patient and carer experience at 12 months; Adverse events - hypotension at 12 months

Study (subsidiary papers)	PRICE (Prevención de Reingresos por Insuficiencia Cardíaca en España) trial: Atienza 2004[98] (Ojeda 2005[1077])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=388 (153 in follow up paper))
Countries and setting	Conducted in Spain; Setting: Three tertiary referral University Hospitals in Spain
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: Ave 16 month (range 12-25) intervention, with subset followed up 12 months after (ave 18)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Presence of symptoms and signs of heart failure in conjunction with objective evidence of major cardiac dysfunction at rest
Stratum	Recent admission: Population risk: High (recent decompensation, most NYHA III-IV), Intervention type: (MDT clinic), Length: Long
Subgroup analysis within study	Stratified then randomised: The follow-up paper is in subgroup (one out of three centres), which was one of stratification variables
Inclusion criteria	Discharged with the primary diagnosis of congestive heart failure from the cardiology wards, confirmed by researcher to have HF
Exclusion criteria	Expected survival of less than 3 months, discharge to a nursing home or long-term care facility, home distance from the hospital >30 km, impossibility to contact by telephone, dementia or psychiatric illness, and inclusion on to a waiting list for invasive cardiology or heart surgery at discharge
Recruitment/selection of patients	From January through June 1999, a total of 572 patients planned to be discharged with the primary diagnosis of congestive heart failure were screened for inclusion in the study. Among them, 234 (41%) met

	at least one exclusion criteria. Inclusion on to waiting list for cardiac surgery or other invasive procedure (43%), followed by patient or responsible physician refusal (19%) and participation in other clinical trial (15%) were the most common causes for exclusion
Age, gender and ethnicity	Age - Median (IQR): Int 69 (61-74), Control 67 (58-74). Gender (M:F): 60:40. Ethnicity: Not stated
Further population details	
Extra comments	Medication at discharge (Int/Control%): ACE-I 67/68, BBlocker 19/12, Digoxin 51/48. NYHA class I/II/III/IV: 10/40/40/10. Comorbidities%: DM 35, HTN 54, IHD 32, AF 44. LVEF median 36%.
Indirectness of population	No indirectness
Interventions	(n=164) Intervention 1: Multidisciplinary team - MDT. Intervention involved specialist cardiac nurse, cardiologist and primary care physician. In the first phase, prior to discharge, the nurse had an in-depth interview with the patient and caregivers. Specifically, the nurse assessed the patient knowledge of the disease, the ability to identify signs and symptoms of heart failure worsening, and the most common responses to the situations of deterioration. Individualized strategies were used to improve treatment adherence and to empower patients to manage health problems (i.e. diuretic self-adjustment). All this process was supported by using a teaching brochure developed by the study investigators. In the second phase, a visit with the primary care physician was scheduled within 2 weeks of discharge. The aims of this visit were to monitor patients' clinical progress, identify incipient physical signs of decompensation, and reinforce the educational knowledge, modify the discharge treatment or refer the patient to the hospital for reassessment. During the third phase, regular follow-up visits at the outpatient Heart Failure Clinic were scheduled every 3 months where, for clinical assessment, correcting strategies to improve treatment adherence and response, reinforce pts ability to manage health problems. The heart failure specialist coordinated visits to other specialists, diagnostic tests and treatments prescribed by other instances. Provided a 24-h mobile phone contact number and the clinic team was also available for consultation during working hours. Patients were instructed to contact the team in case of doubts or signs of worsening.. Duration Ave 16 months (range 12-25m). Concurrent medication/care: On admission, all patients with heart failure considered for inclusion were managed by the responsible cardiologist according to guidelines published at the time of designing the study. The patient was discharged home by the responsible

	cardiologist who prescribed treatment without knowledge of the assignment group Comments: In follow-up group n=78 (n=174) Intervention 2: Usual care - Primary care. Control group patients received discharge planning according to the routine protocol of the study hospitals. To avoid contamination of the control group management, additional follow-up was performed by primary care physicians and cardiologists not participating in the study. Duration Ave 16 months (range 12-25m). Concurrent medication/care: On admission, all patients with heart failure considered for inclusion were managed by the responsible cardiologist according to guidelines published at the time of designing the study. The patient was discharged home by the responsible cardiologist who prescribed treatment without knowledge of the assignment group. Indirectness: No indirectness Comments: In 12m follow-up group n=77
Funding	Other (Dr. Atienza was funded by the Spanish Society of Cardiology, Madrid, Spain. Prof. Martinez-Alzamora was funded by a Research Incentive Program from the Polytechnic University of Valencia, Spain. Merck, Sharp & Dohme contributed financially to the edition and printing of the brochure for heart failure patients used in the study)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MDT versus PRIMARY CARE

Protocol outcome 1: Mortality
- Actual outcome for Recent admission: Deaths at 16m; Group 1: 51/164, Group 2: 30/174
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:
- Actual outcome for Recent admission: Deaths at 16m+12m; Group 1: 19/76, Group 2: 30/77
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Some concern over severity NYHA IV (int v control) 35 v 23%, otherwise ok; Group 1 Number missing: , Reason: Smaller numbers due to subgroup analysis; Group 2 Number missing:

Protocol outcome 2: Quality of life at 12 months
- Actual outcome for Recent admission: MLWHFQ at 16m; Group 1: mean 28.9 (SD 6.1); n=110, Group 2: mean 35.5 (SD 7.9); n=110; MLWHFQ 0-105 Top=High is poor outcome
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: MLWHFQ 51.9 v 51.6; Group 1 Number missing: 20, Reason: Missing through death + 37 not reported; Group 2 Number missing: 17, Reason: Missing through death + 37 not reported

Protocol outcome 3: Unplanned hospitalisation (all-cause)
- Actual outcome for Recent admission: Admissions at 16m; Rate ratio: 0.67);
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 4: Medicine optimisation/adherance at 12 months
- Actual outcome for Recent admission: ACE-I prescribed at 16m+12m; Group 1: 44/66, Group 2: 36/56
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Some concern over severity NYHA IV (int v control) 35 v 23%, otherwise ok - but does not report medication use at baseline; Group 1 Number missing: , Reason: Smaller numbers due to subgroup analysis; Group 2 Number missing:
- Actual outcome for Recent admission: Beta-blocker prescribed at 16m+12m; Group 1: 31/66, Group 2: 23/56
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Some concern over severity NYHA IV (int v control) 35 v 23%, otherwise ok - but does not report medication use at baseline. Marginal difference between beta blocker rates in larger study (19 v 12%); Indirectness of outcome: No indirectness ; Baseline details: Some concern over severity NYHA IV (int v control) 35 v 23%, otherwise ok - but does not report medication use at baseline. Marginal difference between beta blocker rates in larger study (19 v 12%); Group 1 Number missing: 10, Reason: Smaller numbers due to subgroup analysis. Drop due to death; Group 2 Number missing: 21
- Actual outcome for Recent admission: ACE-I prescribed at 16m; Group 1: 51/76, Group 2: 53/77
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - ; Indirectness of outcome: No indirectness ; Baseline details: Some concern over severity NYHA IV (int v control) 35 v 23%, otherwise ok - but does not report medication use at baseline; Group 1 Number missing: , Reason:

Smaller numbers due to subgroup analysis; Group 2 Number missing: - Actual outcome for Recent admission: Beta-blocker prescribed at 16m; Group 1: 48/76, Group 2: 30/77 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Some concern over severity NYHA IV (int v control) 35 v 23%, otherwise ok - but does not report medication use at baseline. Marginal difference between beta blocker rates in larger study (19 v 12%); Indirectness of outcome: No indirectness ; Baseline details: Some concern over severity NYHA IV (int v control) 35 v 23%, otherwise ok - but does not report medication use at baseline. Marginal difference between beta blocker rates in larger study (19 v 12%); Group 1 Number missing: , Reason: Smaller numbers due to subgroup analysis; Group 2 Number missing:	
Protocol outcomes not reported by the study	Dying in preferred place at 12 months; Adverse events - hyperkalaemia at 12 months; Adverse events - renal function at 12 months ; Patient and carer experience at 12 months; Adverse events - hypotension at 12 months

Study	Rao 2007[1186]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=112)
Countries and setting	Conducted in United Kingdom; Setting: One-stop HF clinic in the community, or equivalent outpatient clinic.
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: At least 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Symptoms of HF plus confirmed left ventricular systolic dysfunction
Stratum	Community: Population risk: High (all new diagnosis), Intervention type: MDT clinic, Length: Short
Subgroup analysis within study	Not applicable
Inclusion criteria	New diagnosis with LVSD, NYHA I-IV
Exclusion criteria	Nil specified
Recruitment/selection of patients	Pts referred for open-access echocardiography due to suspected HF and found to have LVSD (newly diagnosed heart failure) sequentially
Age, gender and ethnicity	Age - Mean (SD): 72(12). Gender (M:F): 66/46. Ethnicity: Not stated
Further population details	
Extra comments	NYHA int: class I 3%, class II 54%, class III 36%, class IV 7% NYHA usual: class I 4%, class II 49%, class III 38%, class IV 9%. Baseline characteristics: Prev MI 22%,

	hypertension 62%, DM 10%, smoker 56%. Comparison is made with those referred who were not found to have LVSD. Non-LVSD: same age, more likely female, fewer previous MI and hypertension, but similar DM.
Indirectness of population	No indirectness
Interventions	(n=59) Intervention 1: Multidisciplinary team - MDT. Heart failure clinic staffed by registrar cardiologist and heart failure nurse, either in community or outpatient clinic. Titrated medication up to maximum tolerated level. Educated about HF, role of medication, health behaviour, and signs of early decompensation. Encouraged to keep symptom diary. Given contact number.. Duration 3-12 months. Concurrent medication/care: Routine primary care. Reviewed at three months and 12 months after start of study.. Indirectness: No indirectness (n=53) Intervention 2: Usual care - Primary care. Patients and GP were informed of result of Echo, and GP provided all follow-up.. Duration 3-12 months. Concurrent medication/care: Routine care. Reviewed at three months and 12 months after start of study.. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MDT versus PRIMARY CARE

Protocol outcome 1: Mortality
- Actual outcome for Community: Death at During follow-up (3-12 months); Group 1: 1/59, Group 2: 2/53
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Little info on randomisation and allocation concealment.; Indirectness of outcome: No indirectness, Comments: Total days' observation not given, impairing analysis of result; Baseline details: Stratified for age and gender. Equal on most measures, but MDT group more likely to have shortness of breath or fluid retention (but MYHA class fairly well balanced, hence rated low RoB).; Blinding details: Separate clinical investigator extracted information for follow-up data; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Unplanned hospitalisation (all-cause)
- Actual outcome for Community: All cause admissions (count) at During follow-up (3-12 months); Rate ratio: 1.59 admissions, Comments: Admissions

due to HF: Int 1, Usual 3.); Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Little info on randomisation and allocation concealment.; Indirectness of outcome: No indirectness, Comments: Total days' observation not given, impairing analysis of result; Baseline details: Stratified for age and gender. Equal on most measures, but MDT group more likely to have shortness of breath or fluid retention (but MYHA class fairly well balanced, hence rated low RoB).; Blinding details: Separate clinical investigator extracted information for follow-up data; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Medicine optimisation/adherance at 12 months - Actual outcome for Community: ACEi prescribed at 3 months; Group 1: 50/59, Group 2: 34/53 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Little info on randomisation and allocation concealment.; Indirectness of outcome: No indirectness ; Baseline details: Stratified for age and gender. Equal on most measures, but MDT group more likely to have shortness of breath or fluid retention - this may affect the prescription of ACEi; Blinding details: Separate clinical investigator extracted information for follow-up data; Group 1 Number missing: ; Group 2 Number missing: - Actual outcome for Community: Beta blockers prescribed at 3 months; Group 1: 30/59, Group 2: 1/53 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Little info on randomisation and allocation concealment.; Indirectness of outcome: No indirectness; Baseline details: Stratified for age and gender. Equal on most measures, but MDT group more likely to have shortness of breath or fluid retention - this may affect prescription of beta blocker.; Blinding details: Separate clinical investigator extracted information for follow-up data; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life at 12 months ; Dying in preferred place at 12 months; Adverse events - hyperkalaemia at 12 months; Adverse events - renal function at 12 months ; Patient and carer experience at 12 months; Adverse events - hypotension at 12 months

Study	Varma 1999[1434]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=83)
Countries and setting	Conducted in United Kingdom; Setting: Outpatient clinics and inpatient wards of three hospitals used to recruit.
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: CHF confirmed by consultant physician for purposes of the study
Stratum	Mixed: Population risk: Low (elderly only); Intervention type: Pharmacist-led; Length: Long
Subgroup analysis within study	Not applicable
Inclusion criteria	Over 65 years, CHF NYHA grade I-IV, usual physician in agreement with participation.
Exclusion criteria	Cognitive score according to Clifton Assessments Procedures for the Elderly (CAPE) 6 or below, significant pulmonary disease, severe mobility problems (not caused by HF)
Recruitment/selection of patients	"Most" recruited from outpatient clinics and the rest from hospital wards
Age, gender and ethnicity	Age - Mean (SD): int: 75.5 (6.4), usual: 76.4 (7.1). Gender (M:F): 34/49 (int 19/23, usual 15/26). Ethnicity:
Further population details	
Extra comments	Minimisation balancing HF grade, renal function, concomitant illness and cognitive status.. Mean (SD): NYHA

	class 2.1 (0.9), CAPE score 10 (1.7)
Indirectness of population	No indirectness
Interventions	(n=42) Intervention 1: Multidisciplinary team - Pharmacist. Pharmaceutical intervention within outpatient clinic: Research pharmacist discussed medication regimen with patient and then their physician. Pharmacist educated pt about CHF, prescribed medication and management of CHF symptoms. Pts were instructed in self-management, and encouraged to be involved in their own care. They were given monitoring cards, including daily weighing, and asked to use these cards when visiting physicians and community pharmacists (whom research pharmacist had briefed). They were instructed in how to vary their dose of diuretic according to monitoring. Further education was offered by research pharmacist at each outpatient clinic (every three months).. Duration 12 months. Concurrent medication/care: Seen in outpatient clinic every three months. Physician prescribed medication of their choice, and community pharmacist dispensed.. Indirectness: No indirectness (n=41) Intervention 2: Usual care - Clinic. Standard management, excluding contact with research pharmacist and self-monitoring.. Duration 12 months. Concurrent medication/care: Outpatient appointment every 3 months. Physician prescribed according to their choice, and community pharmacist dispensed.. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PHARMACIST versus CLINIC Protocol outcome 1: Mortality - Actual outcome for Mixed: Patient died at 12 months; Group 1: 7/42, Group 2: 7/41 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Allocation concealment not described, some disequalibrium for confounders at baseline, unclear whether withdrawn pts were followed up to see if death; Indirectness of outcome: No indirectness ; Baseline details: Knowledge of drug score and SF-36 physical functioning score higher for intervention at baseline. Other parameters ok.; Group 1 Number missing: ;	

Group 2 Number missing:

Protocol outcome 2: Quality of life at 12 months
- Actual outcome for Mixed: Minnesota Living with Heart Failure Questionnaire at 12 months; Group 1: mean 12.7 (SD 9.9); n=26, Group 2: mean 19.1 (SD 10.2); n=23; Minnisota Living with Heart Failure 0-105 Top=High is poor outcome; Comments: Score for Intervention and Usual mean: baseline 23.7/27.1; 3mo 13.3/15.2; 6mo 12.8/15.9; 9mo 15.6/14.6
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Allocation concealment not described, some disequalibrium for confounders at baseline, pts probably knew whether in intervention or control groups; Indirectness of outcome: No indirectness ; Baseline details: Knowledge of drug score and SF-36 physical functioning score higher for intervention at baseline. Other parameters ok.; Group 1 Number missing: 16, Reason: Died: 7, Withdrew: 9; Group 2 Number missing: 18, Reason: Died: 7, Withdrew: 11
- Actual outcome for Mixed: SF-36 at 12 months; Group 1: mean 67.9 (SD 26.6); n=26, Group 2: mean 49.2 (SD 34.2); n=23; SF-36 summary score 26-100 Top=High is good outcome; Comments: Baseline scores 51.6 (30.7) / 46.4 (28.7).
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Allocation concealment not described, some disequalibrium for confounders at baseline, pts probably knew whether in intervention or control groups; Indirectness of outcome: No indirectness; Baseline details: Knowledge of drug score and SF-36 physical functioning score higher for intervention at baseline. Other parameters ok.; Group 1 Number missing: 16, Reason: Died: 7, Withdrew: 9; Group 2 Number missing: 18, Reason: Died: 7, Withdrew: 11

Protocol outcome 3: Unplanned hospitalisation (all-cause)
- Actual outcome for Mixed: Hospital admissions (count) at 12 months; Rate ratio: 0.51);
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Allocation concealment not described, some disequalibrium for confounders at baseline, unclear how treated missing, reliant on pt recall for numbers; Indirectness of outcome: No indirectness ; Baseline details: Knowledge of drug score and SF-36 physical functioning score higher for intervention at baseline. Other parameters ok.; Blinding details: Admitting physician may have known what group in - might influence; Group 1 Number missing: 16, Reason: Rate given for whole year. Unclear whether this includes pts who died or withdrew from the study after an admission - number given is maximum; Group 2 Number missing: 18, Reason: Rate given for whole year. Unclear whether this includes pts who died or withdrew from the study after an admission

Protocol outcome 4: Medicine optimisation/adherance at 12 months
- Actual outcome for Mixed: Compliant with all medication (self-reported) at 12 months; Group 1: 26/26, Group 2: 22/23; Comments: Intervention arm reported 100% compliance throughout

Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Allocation concealment not described, some disequilibrium for confounders at baseline, reliant on pt recall & likely performance bias; Indirectness of outcome: Serious indirectness, Comments: At odds with findings from community pharmacist; Baseline details: Knowledge of drug score and SF-36 physical functioning score higher for intervention at baseline. Other parameters ok.; Blinding details: The group receiving pharmacist intervention will be likely to rate compliance higher because of desire to please; Group 1 Number missing: 16; Group 2 Number missing: 18 - Actual outcome for Mixed: Compliant with all medication (reported by community pharmacist) at 12 months; Group 1: 10/13, Group 2: 3/10; Comments: Three patients found to be undercompliant, and three overcompliant Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low, Comments - Allocation concealment not described, some disequilibrium for confounders at baseline. For 83 pt, community pharmacists provided 46, and only 23 were valid.; Indirectness of outcome: No indirectness, Comments: Poorly reported: for 83 pt, community pharmacists provided 46, and only 23 were valid.; Baseline details: Knowledge of drug score and SF-36 physical functioning score higher for intervention at baseline. Other parameters ok.; Group 1 Number missing: 29, Reason: Not able to be calculated, dead (7) or withdrawn (9); Group 2 Number missing: 31, Reason: Not able to be calculated, dead (7) or withdrawn (11)	
Protocol outcomes not reported by the study	Dying in preferred place at 12 months; Adverse events - hyperkalaemia at 12 months; Adverse events - renal function at 12 months ; Patient and carer experience at 12 months; Adverse events - hypotension at 12 months

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2 ## F.13 Transition between heart failure care settings

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Aim	Explore perceptions of the health-care professionals involved with three long-term care (LTC) homes regarding CHF care and practices. In

	particular they wanted to explore why heart failure pt in LTC were less likely to be receiving medication for chronic heart failure, despite the high burden of disease and acute care episodes. Part of programme aiming to develop care processes to manage CHF in these settings.
Population	18 health-care professionals (HCP), 16 primary care physicians and two nurse practitioners chosen as they provided care to one of three LTC.
	Characteristics: mean age (SD) doctors 56 (11), nurses 48 (2); years in practice mean (SD) doctors 24(11), nurses 20(20); number of LTCs that the professional is providing services for: mean, doctors 2.8, nurses 3.0
Setting	HCP chosen as providing services to one of three LTC in Northern Ontario, Canada. Sites were chosen to offer geographical variety, and different ownership models. They were home to 96, 150 and 251 residents respectively.
Study design	Qualitative descriptive study, nested in a mixed-methods protocol
Methods and analysis	Three semi-structured focus groups using interview guides developed in an earlier stage of the protocol, that aimed to elicit discussion related to diagnosis, monitoring and management of CHF among LTC residents - one in each home. The groups lasted 60 minutes and were facilitated by a trained moderator. A second investigator took field notes. All discussions were recorded and transcribed verbatim. Data was analysed using thematic content analysis using QSRI NVivo software. An inductive coding technique was used, with subsequent organisation in to categorised concepts. This was done independently by two researchers, who then developed one thematic framework based on consensus and presented their findings to a secondary analysis team. Finally the findings were presented back to the members of the focus groups as a form of member checking.
Findings	Issues 1a) Lack of continuity in HF care and Issue 3a) Poor communication between services - HCP felt that HF care was fragmented, which led to (a) a lack of continuity and (b) gaps in communication, with inadequate transfer of complete health information
Limitations and applicability of evidence	Not in the UK/NHS; population narrow as restricted to LTC residents; small sample of LTCs; limited participation by non-physicians (2:16) means likely findings dominated by physician opinions. Methodological limitations: The healthcare context of the three homes was not fully explained (context) and not all points were supported by quotations or further explanation (data richness), rated as moderate limitations.

Study	Gastelurrutia 2012 [508]
Aim	It was identified by a pharmacist intervention that there were a number of conditions that were undertreated in pt attending a HF clinic. This work aimed to explore experiences in the pharmacological management of common comorbid health problems in heart failure in order to help clinical pharmacists provide real and practical help to the doctors.
Population	Internal medicine specialists and cardiologists from a tertiary hospital HF clinic
	Characteristics: n=5 HCP; 1 male/ 4 female; mean age 38y; two internal medicine specialists, two cardiologists and the chief cardiologist of the clinic, all of whom had worked there in the last three years.
Setting	Single tertiary hospital HF clinic
Study design	Qualitative.
Methods and analysis	In-depth, semi-structured interviews by a single interviewer (a pharmacist in the HF clinic) using a total sample and a constant comparative approach. Asked two questions each about hyperuricemia, anti-platelet agents, anaemia and diabetes. To ensure the rigor of the study, there was attention to deviant cases and the inclusion of a wide range of verbatim data. Interviews carried out in Spanish and translated to colloquial English for publication.
	Transcriptions were analysed by independently by two people using an open coding constant comparative approach. Content analysis was assisted by N-Vivo software.
Findings	Issue 5b) Focus - Doctors felt that the HF clinic should be focused in treating CHF and not comorbidities, and often assumed that an issue was being treated elsewhere (example condition was diabetes). They felt there were a lack of formal clinical pathways to identify which service or centre to refer to for co-morbidity management (example condition was iron-deficiency anaemia).
Limitations and applicability of evidence	Rated as serious methodological limitations due to lack of information regarding context, data analysis and what reflection the role researchers played, also noted that findings not fully supported by data. There may also be translation issues, as data was translated from Spanish for publication. Main findings are quite specific, as regarding just four comorbidities, but indirect evidence about general interface issues, which is applicable to our population.

Study	Glogowska 2015 [523]
Aim	Gain an understanding of the issues facing clinicians as they care for this patient group in the light of recent developments including the introduction of specialist heart failure nurses
Population	Clinicians (doctors and nurses and rehab workers) from three defined locations were sampled from Primary care, Community and Specialist HF care. Staff based in primary settings were all GPs, those in the community were all nurses, and those in specialty care were cardiologists (3), HF nurses (5), rehab workers (2), a geriatrician and a liaison psychiatrist
	Characteristics: n=24 ; male/female not given; mean age not given; years in the role not given
Setting	English NHS. One location in South West where two hospitals provide HF clinics and there is a limited community HF nurse service. Second location in South Central where one hospital offers outpatient clinics and there is a community HF service for HFREF only. The third area in the Midlands has a rapid access ambulatory heart failure clinic with ongoing care in the community from specialist HF nurse.
Study design	Qualitative
Methods and analysis	Purposeful sampling to gain a range of clinicians from the three settings and care domains. In-depth interviews took place in clinicians' workplace where possible. Most were alone, with some specialist HF nurses being interviewed in pairs. Used a topic guide developed before-hand, but also allowed participants to raise their own issues, and those were carried forward to subsequent interviews.
	Analysed using the constant comparative method and systematic open coding using Nvivo. The first interview generated the coding framework, which grew and developed as analysis continued. There was discussion between the researchers and with a professional panel to ensure credibility of themes.
Findings	Issue 2b) Models to co-ordinate care - Need for clear, consistent communication among clinicians; this could be facilitated by designating a single clinician to coordinate
	Issue 3a) Poor communication between services - Transition from specialist services to primary care - Questions about where responsibility lay to ensure that medications are optimised. Discharge that happens as soon as patient is stable requires a requires a request for GP to titrate medication, and there was not confidence that this happens
Limitations and applicability of evidence	This is a UK study examining a near-current NHS experience, which has a number of clinicians from different contexts. However, assigned moderate limitations as the aims are poorly defined, method not discussed, role of the researcher not mentioned and findings not discussed adequately in the context of the study.

Study	Fuat 2005 [494]
Aim	Explore reasons for the variations in the diagnosis and management of heart failure and identify barriers to the provision of uniformly high standards of care
Population	Hospital specialists and specialist general practitioners from five acute hospital trusts involved in the direct management of heart failure across nine primary care trusts in Durham and Tess SHA. Two consultant cardiologists (one in secondary and one in tertiary care provision), four geriatricians (one with special interest in cardiology), four general physicians and two general practitioners (special interest in cardiology, involved in open-access echo-cardiology clinic)
	Characteristics: n=12 ; male/female not stated; mean age 47 (range 36-57); clinical experience mean 12 years (range 2-22)
Setting	As above
Study design	Qualitative
Methods and analysis	Purposive sample. Chief investigator interviewed and took notes, and the interviews were also tape recorded. Semi-structured based on discussion points pre-specified and formed through iteration. Saturation was reached after 12 interviews.
	Analysis follow “pragmatic variant” grounded theory and content analysis principle, with new points being taken back to subsequent interviews. There were multiple coders, and final themes decided by consensus, and a degree of constant comparison to increase coherence. Respondent validation was attempted by mailing summaries to all twelve, of whom eleven agreed or agreed strongly that it reflected their views.
Findings	Issue 2b) Models to co-ordinate care - the majority of participants felt that heart failure should be managed by conjoint working between primary and secondary care and the shared-care agreements already in use in diabetes and hypertension were signposted as possible models - with shared-care model, general practitioners to manage pt in certain categories with hospitals managing others
Limitations and applicability of evidence	Study from the UK, but only one region, and dated (12 years old). The method is appropriate and mainly rigorous, but rated as serious methodological limitations due to limited contextual information and lack of data richness in our areas of interest, leading to less convincing conclusions.

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Study	Andersson 2013 [71]
Aim	Establish whether pt' need for information, education and knowledge are met to the same extent in the HF clinic and primary care
Population	Four pt who had been treated in a HF clinic, and were now discharged to primary care Characteristics: n=4 ; 3 male/1 female; ages 60, 62, 63 (all m), 84 (f); the female patient had been living with CHF for 16 years with two years in the HF clinic and had multiple comorbidities, while the male pt had lived with CHF for 4-5 years and had spent one year in the HF clinic, one male had diabetes and AF; all NYHA II at last encounter; one male patient was educated to college level, one to high school, and the other two pt completed compulsory education.
Setting	Small town in the middle of Sweden, pt identified by using medical records from one hospital and one primary health centre. HF clinic had been running for over five years with a remit to care for pt recently admitted for HF or otherwise high risk, to optimise medical treatment and stabilise, and discharge to primary care where this was achieved.
Study design	Qualitative
Methods and analysis	Semi-structured interviews in participants' homes taking 30-60 minutes. Minimal fixed questions, but aiming to gather information about daily life with the condition, experience of information and follow-up. Informed by grounded theory. Recorded for transcription and interviewer also made notes on their impression straight after interview. Used "Burnard's method" for content analysis. Focus on identifying the message in the recordings and transcript, with meaning units processed into code words. Condensation of the code words used to generate themes, then assembled to form a framework.
Findings	Issue 1c) Discharge from HF clinic - From being called for check-ups with regularity to not being called at all, seen by some as being because they had not asked for it, but seen by others as a sign that they were not ill enough to qualify for help - Felt they were no longer part of the health system. No contact even with their primary prescriber. They wished to be called once in a while to see GP or district nurse. Issue 3c) Information after discharge from HF clinic - Experienced being well-informed about CHF while in HF clinic, but had not had any information since being in primary care, leading some to think that heart failure was no longer significant
Limitations and applicability of evidence	Not in UK/NHS system, although setting sounds similar. May be translation issues, as interviews took place in Swedish. Original aim of paper was about information, which is narrower than our aims. Methodologically rated as serious limitations due to narrow participant range compared to question, and problems with data richness and lack of clarity over researcher role.

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Study	Nordgren 2007 [1010]
Aim	Explore how middle aged people with moderate-severe CHF experience and understand formal care
Population	Pt of HF clinic aged 65 and under, with a history of moderate to severe CHF that has required at least one hospitalisation who were thought by HF specialist nurse to be able to provide a rich understanding of care, and who were as different as possible to each other
	Characteristics: n=7 ; 3 male/ 4 female; age 39-65; four had retired early due to illness, two were on sick leave and one was working; six were married and living with their partner.
Setting	Not described other than "HF clinic in Sweden"
Study design	Qualitative study from lifeworld perspective
Methods and analysis	1-2h unstructured interview by researcher in participants' houses, that were taped for transcription. Focus on eliciting lived experience of care in open and deep manner.
	Used phenomenological analysis, with conscious attempts to bridle pre-understanding to bring openness to interpretation. Text was divided into meaning units, which were translated to concrete language and used to explore patterns and meanings of the whole, and then to a general structure of the phenomenon and its constituents.
Findings	Issue 1a) Lack of continuity in HF care - Lack of continuity sometimes led to encounters appearing anonymous and meaningless
	Issue 1b) Primary Care and Issue 4c Access to urgent care - Patients valued the easy access to physicians and nurses at the HF clinic, however they also needed the care of a healthcare provider that provides individualised care with continuity, which is usually in primary care
	Issue 2a) Poor co-ordination between services - The structure of the healthcare system was viewed as unclear, and participants experienced uncertainty regarding responsibility for their health process. Where participants were unsure about who was caring for them, they lost trust and hope in the healthcare organisation, and they found it hard to focus on their own health and wellbeing
Limitations and applicability of evidence	Not in UK/NHS setting. May be translation issues as interviews in Swedish. Appraised as having minor limitations due to poor explanation of context and balance to findings. Limitations from the restricted age range, and using only pt currently in HF clinic

Study	Boyd 2004 [198]
Aim	Provide a patient-centric account of the changing and evolving needs of people with advanced heart failure, and how services address these
Population	20 pt identified by consultant cardiologist or geriatrician with NYHA grade IV CHF using purposive sampling. Pt were interviewed up to four times, an undefined number of informal carers (27 interviews plus 5 post-bereavement interviews) and an undefined number of professionals (30 interviews) were interviewed. Plus focus group of 16 participants including primary and secondary HCP, social care professionals, palliative care professionals, members of patient and carer groups and from the non-statutory sector
	Characteristics only given for pt: n=20; 11 male/9 female; mean age 70 (range 57-92); 8 lived alone; 11 had significant co-morbidity.
Setting	Not stated (appears to be secondary care-based recruitment and in Edinburgh)
Study design	Qualitative
Methods and analysis	Appears to be mainly unstructured interviews according to topic areas. 50 interviews were with pt, who were interviewed every three months until they became too ill or moved away. Interviews with professionals were by telephone or face-to-face as preferred by participant. Focus group and 'most' of the interviews were recorded and transcribed (appears to be at participant request), with field notes made after interviews. All interviews by experienced social scientist.
	Data collection and analysis were concurrent to allow emergent themes to be fed back to data collection. Used NVivo, with two researchers coding independently using a narrative analysis framework. The multidisciplinary steering group met regularly to review the data and discuss the evolving themes.
Findings	Issue 2a) Poor co-ordination and Issue 3a) Poor communication between services - Better co-ordinated services in hospital and community and improved communication between them would make a significant difference
	Issue 5a) Expectations - Pt valued HF nurse for time and psychosocial support, but GPs were ambivalent about the service that the HF nurse was providing, wanting the specialist nurse to act more as a resource for the primary care team
Limitations and applicability of evidence	Study from the UK, but only one area, and somewhat dated (13 years ago). Limiting applicability, all pt were currently in secondary care. Rated as serious methodological weaknesses due to the relative lack of reflection on methods and role of researchers, limited information on professional characteristics, and little data richness in this review's area of interest.

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Study	Lord 2015 [901]
Aim	Understand how HF services were delivered in three different trusts, and especially how primary and secondary care interact to provide continuity of care for CHF pt in a context of increasing demand and financial pressure
Population	HCP involved in the delivery of HF services from primary and secondary care. Participants were identified from a skeleton list of job titles and purposive sampling used to select and recruit consultant medical staff, HF nurses, general practitioners with a special interest in HF and managers, with snowball sampling used if further job titles were elicited during interviews
	Characteristics: n=8 nurses, 6 consultants, 2 senior managers, 3 commissioners, 4 GPs. Mainly evenly distributed over sites, but consultants and commissioners were mainly in urban trust
Setting	The three trusts were in Birmingham and the Black Country, and were designated "town trust" which had community CV nurses offering rehabilitation services, "university trust" where the HF nurses worked in community and the hospital and "urban trust" where a lead HF nurse in the hospital liaised closely with community nurses
Study design	Qualitative (service evaluation)
Methods and analysis	Semi-structured interviews with a number of interviewers with the same general approach, with all interviews recorded and transcribed
	Data collated and analysed using Framework Method, allowing a within-case and between-case analysis. Coding was undertaken by two researchers, and there were meetings to compare coding and identify themes to increase rigour and accuracy. Initial findings were fed back to the participants, asking for collaboration and partnership in finalising findings.
Findings	Issue 1b Primary Care - it was felt that GPs had a key role in the management of CHF by ensuring continuity of care, but some specialists had concerns about the management of CHF pt in primary care
	Issue 2b Models to co-ordinate care - Cross-boundary working seen as essential for appropriate diagnosis and management of CHF pt. HF nurses have a 'boundary crossing' role, and can therefore encourage close working relationships.
	Issue 3b Barriers to clear communication - Challenges to cross-boundary working included demands on clinician time and the fragmented information sharing due to the incompatibility of communication systems
	Issue 4a Access to routine care - HF nurses note the differing thresholds of GPs to refer back to HF service when pt are struggling
	Issue 5a Expectations - HF nurses found there was a mismatch between expectations of some GPs and the reality, where pt are unable to stay on the books of the HF service indefinitely and are therefore transferred back to primary care for long-term management

Study	Lord 2015 [901]
Limitations and applicability of evidence	This is a recent study in the UK/NHS setting, with aims similar to this review. It has the experiences of staff involved in secondary HF care. It is rated as moderate limitations as there is little description of the participants.

F.14 Communication needs regarding diagnosis and prognosis

Study	Aldred 2004[51]
Aim	Explore the impact of advanced heart failure on the lives of older patients and their informal carers
Population	People with heart failure who have recently been admitted to hospital with an acute deterioration in heart failure, aged ≥60 years with NYHA classification of II-IV, able to complete study materials in English and without cognitive impairment plus their partner (living with or married to) were approached by a research nurse. Patient characteristics: n=10; male/female: 7/3; mean age (range): 72 (60-77) years; 3 patients were NYHA class II, 6 were class III, and 1 was class IV; married/cohabiting: 4/1 Characteristics of carers not provided other than that they were all their partners, one was a same-sex couple.
Setting	UK NHS. People with heart failure were identified as inpatients in a 650-bed district general hospital, but were not interviewed until had been discharged for at least two weeks. Interviews were conducted in the participants own homes in 2001 – 2002.
Study design	Qualitative study, nested in a larger mixed-methods study to monitor quality of life and service use of people with heart failure
Methods and analysis	Purposive sampling (details not given). Semi-structured interviews in person’s own home, with patient and carer interviewed together, taped and transcribed verbatim. Interview guide adapted from previous schedule piloted with a sample of patients with heart failure. Collected and analysed concurrently until data saturation was reached. Data coded and analysed to identify common descriptive themes, grouped into clusters, by two researchers to ensure agreement of the coding frame. Ten initial themes, narrowed to four most relevant to aims.
Findings	Professional support Little understanding about their condition, inadequate discussion time with healthcare professionals, unaware of term ‘heart failure’ Not feeling adequately informed due to doctors’ lack of time
	Concerns for the future Concerns about limited life expectancy, unaware of poor prognosis, not feeling adequately informed by professional staff Wanting more detailed information about prognosis including time of death

Study	Aldred 2004[51]
Limitations and applicability of evidence	In the NHS/UK context, but dated (data from 2001-2). Rated as moderate methodological limitations due to lack of reflection on methods or researcher role.

Study	Barnes 2006[127]
Aim	To explore the attitudes of older people and primary care professionals towards communication of diagnosis, prognosis and symptoms in heart failure.
Population	People with heart failure were recruited for interview through 16 GP practices and had to be over 60 years of age and have a NYHA class III or IV heart failure. Characteristics: n=44 ; male/female 1/1; median age (IQR): 77 years (71-83) Healthcare professionals working in primary care and involved in heart failure management were invited for focus group discussions at the same GP practices (9 practices agreed to host the focus groups). Characteristics: total n=79 (GPs n=39, nurses n=37, others n=3) in 9 focus groups; age range: 27-58 years; time in job varied substantially between focus groups (median 1.8 to 12.0 years)
Setting	English NHS. Conducted in 2003-2004 in four geographical locations in the UK, selected for demographic variability: East Devon, West Hampshire, Bradford and Barnsley. This study is part of a larger quantitative survey aiming to explore the palliative care services for 542 heart-failure patients in the community over a 2-year period. Patients were interviewed individually in their own homes, healthcare professionals took part in focus groups.
Study design	Qualitative
Methods and analysis	People with heart failure: Purposive sampling to include a diverse group of patients, maximise coverage of age, gender, number of comorbidities and availability of an informal carer. The interviews were carried out by three different researchers, all of whom were qualified social scientists with experience of carrying out in-depth interviews. Patients were interviewed individually in their own homes (with the option of having their informal carer present) as this enabled them to discuss their own case in confidence and allowed the interviewers flexibility in following up interesting responses. Healthcare professionals: Focus groups were carried out because it generates discussion amongst the group, enabling insights to be gained into participants' shared understandings of the issues and the ways in which individuals are influenced by others in a group situation. Both interview and focus group guides had been piloted previously and subsequently adapted. Transcripts were analysed in conjunction with the observations made by a second researcher present at the focus group in order that the group dynamics and the interaction between focus group members formed part of the analysis. Data were coded and analysed to identify common descriptive themes, which were grouped into clusters. NUD*IST software was used for analysis; data collection and analysis were conducted

Study	Barnes 2006[127]
	concurrently. Two members of the research team reviewed the transcripts to ensure agreement over the coding frames.
Findings	Challenges in diagnosing heart failure Clinicians find diagnosing heart failure and giving a prognosis challenging, making it difficult to relay information back to patients. Diagnosis a gradual process. Terminology around heart failure affecting communication; language of 'heart failure' anxiety-laden, so clinicians resort to using even more complex terminology or euphemisms, leading to even poorer communication with patients, confusion for patients and lack of interest in their diagnosis as a consequence Patients want lay terms
	Understanding heart failure Lack of understanding of diagnosis of heart failure by patients, some did not want to know so it does not cause them to worry; lack of knowledge also caused panic attacks, fear of being alone, anxiety about practicalities of what to do in a crisis; lack of understanding compounded by confusion and short-term memory loss associated with heart failure Some patients find it easier to communicate with nurses; specialist environments good place to discuss patients' condition and give information Reluctance by GPs to give diagnosis meant that patients often get a shock diagnosis when admitted to secondary care
	Discussion of prognosis Reluctance to discuss prognosis with patients as it is so variable and concern that patients may get depressed Patients aware of seriousness of their condition, but report a lack of understanding of the prognosis, and in some cases did not want to know Some patients do not know that it is a terminal condition and get very frightened when informed at the end-stage
	Strategies to improve communication GPs expressed a need for education about diagnosis and prognosis of heart failure Discussions around the terminal nature of the illness lacking, lessons could be learnt from communication in cancer (clear information about prognosis) Tailor information to individual's needs (some take on board more than others) Patients with heart failure generally older and more likely to accept what doctor says and not be proactive in asking questions etc., some patients may be unwilling or unable to raise concerns about prognosis Difficulty to discuss prognosis if diagnosis is so difficult in the first place; changes in the health profession required first
Limitations and applicability of evidence	This is a UK study examining the views of both patients and health care professionals. However, moderate limitations were assigned due to limitations in context, role of the researcher not mentioned and data analysis not sufficiently rigorous.

1

Study	Browne 2014[212]
Aim	To examine patient, carer, and professional perspectives on current management of advanced heart failure and barriers and facilitators to improved care.
Population	Patients with advanced heart failure meeting the following inclusion criteria: NYHA class III or IV, symptomatic despite optimal therapy, with a history of admissions/multiple health care contacts for heart failure. Exclusion criteria included: a history of mental impairment that would suggest inability to provide informed consent, inadequate spoken English that would prevent participation. Recruitment via a heart failure liaison service, primary care, a Heart Function and Supportive Care Clinic, and local hospital admission units. Characteristics: n=30; male/female: 3/1; mean age (range): 72 (60-86); mean number of prescribed medications (range): 15 (5-27); mean number of co-morbidities (range): 5 (2-9) Carers characteristics: n=20; 11 female partners, 5 male partners, three women who were daughters or a sibling and one son Healthcare professionals included specialists in heart failure and palliative aspects of care, as well as those responsible for care in the community. Characteristics: n=65 (14 individual interviews, 6 focus groups (n=51)); general practice (GPs, practice nurses, district nurses and practice managers, n=29), accident and emergency consultant (n=1), consultants (n=5), cardiology trainees (n=14), ambulance service (n=1), specialist nurses (n=5), district nurses (n=9), pharmacists (n=2)
Setting	Scottish NHS. One health board in Scotland where patients had access to a well-developed heart failure liaison nurse service. No more information provided.
Study design	Qualitative
Methods and analysis	A purposive sampling strategy was used to identify patients with advanced heart failure. Patients could take part in up to two interviews; caregivers had a choice to be interviewed together with the patient or a one-to-one interview. Semi-structured interviews using an interview guide were conducted by an experienced health services researcher until data saturation became evident. Transcripts of interviews and focus groups were analysed using directed content, or 'framework' analysis. A coding framework that linked data categories to an explanatory model provided by Normalisation Process Theory (NPT) was developed which enabled to focus on patients' and caregivers' work of managing a terminal condition. The authors had demonstrated previously that NPT was useful in understanding treatment burden experienced by heart failure patients and the coding frame created during that study was used as a starting point for data analysis of the current study. As data was analysed iteratively, the coding frame was expanded and refined to accommodate the data in a sensible way. Patient and carer data was double coded independently by two parties, with comparison of results and discussion to ensure uniformity of coding and validity of findings. This was 'phase 1'. A purposive sampling strategy was also used to identify healthcare professionals who encounter advanced heart failure patients (specialists in heart failure and palliative aspects of care, as well as those responsible for care in the community). Healthcare professionals took part in focus groups or were interviewed individually, in which they reflected upon patient and caregiver experiences captured in phase 1 and presented in the form of clinical vignettes.

Study	Browne 2014[212]
	The healthcare professional data was mapped against the themes identified in phase 1, in order to characterise their responses in relation to the issues raised by patients and their caregivers. This was ‘phase 2’.
Findings	Knowledge and understanding deficits Patients have poor knowledge and misunderstanding of diagnosis and its implications, including treatments, their side effects and limitations Health care professionals were sympathetic to patients’ uncertainty and were aware that lack of time for communication contributed to poor understanding. They described difficulty of communicating the complex and poor prognosis. Healthcare professionals considered that patients may not want to know everything about patients’ prognosis perhaps hinting at a degree of paternalism or recognition of denial as a way of coping, the latter seemed likely for some participants interviewed.
Limitations and applicability of evidence	This is a UK study that was assigned serious limitations due to lack of reflection on researcher role in the study, limited context, reasoning for choice of methods, and richness of data.

1

Study	Doos 2015[399]
Aim	Explore experiences of multi-morbid COPD and HF patients during, and shortly after a hospital stay. Also, to focus on patient and carer information needs on transitions and any perceived gaps in relation to their multi-morbidity.
Population	Patients with HF and co-morbid COPD were approached nearer the time of discharge from hospital (admitted for a minimum of at least one night) to take part in the quantitative part of the research (survey), gaining trust in the researcher/interviewer for potential subsequent interview. Excluded were patients who were deemed by healthcare professionals to be too physically unwell to participate, those unable to give informed consent, and those with severe cognitive difficulties. Characteristics: patients n=6, male/female: 1/1; carers n=5, male/female: 1/4; patient mean age: 79 years, age range: 62-91 years; average hospital stay: 12 days, range: 1-30 days
Setting	NHS UK. Two cardiology and respiratory wards at a large regional hospital in England. Patients were interviewed in their own homes between April and June 2012.
Study design	Mixed methods study design. Survey followed by interviews.
Methods and analysis	An adapted version of the American Hospital Consumer Assessment of Healthcare providers and Systems (HCAHPS) questionnaire was used for the survey. A topic guide was produced for the interview schedule to provide additional themes for exploration as identified by the literature review, but interviews were predominantly participant-led. Findings from the survey were utilised to identify ‘points of departure’ to form proposed interview questions to explore areas of importance identified by participants. Two qualitative researchers conducted the interviews, one facilitated the interview and the other observed the conversation, took detailed notes,

Study	Doos 2015[399]
	made observations and followed up any discussion with prompts and additional questions when appropriate. This information was used during the analysis of the data. Data saturation was reached by the time of the last interview (no new theoretical insights were gained and no new properties of existing themes were revealed). Transcripts were read by two researchers to identify key concepts and emerging themes. Principles of grounded theory, most notably constant comparison, were utilised throughout data analysis, with line-by-line coding and labelling of initial concepts. Early concepts were grouped thematically/relabelled were necessary. Overarching categories emerged and links to existing theory and literature were explored. Analysis and data collection took place in parallel, the topic guide was amended as appropriate to account for, and further explore, key themes.
Findings	Clarity of information on diagnosis and compatible symptoms Patients received very little information about diagnosis and were confused about the sources of their experiences/symptoms; some received contradicting information causing further confusion
Limitations and applicability of evidence	This is a UK study interviewing people who have heart failure and COPD multi-morbidity and their carers. However, it was assigned serious limitations due to lack of information on the role of the researcher, data richness for the sections relevant to this review, the reasons for choosing the methodology and the sample.

Study	Field 2006[463]
Aim	To examine whether heart failure patients' awareness of the purpose and side effects of their medicines equips them to participate in informed discussions about treatments, how they cope with the condition and managed their medication.
Population	People at all stages of heart failure included, those recently diagnosed, those who could not recall being told they had heart failure and people with valvular heart disease who described having been 'in and out of heart failure' for years. People were invited to take part through GPs, cardiologists, specialist nurses and patient support groups. Characteristics: total n=37; age range: 33-84 years; ethnicity: white British n=32, black British n=1, Arab n=2, Asian n=2; number of people taking medication for heart failure n=17 and additional medication for co-morbidity n=20
Setting	NHS UK. Respondents were interviewed throughout the UK in their own homes between February and October 2003. No more information provided.
Study design	Qualitative
Methods and analysis	Maximum variation sampling to include a broad range of participants' experiences; men and women of different age groups, social and ethnic backgrounds, people at different stages of heart failure, people who were single (widowed) and married, those with co-morbidities, those who were/were not supported by heart failure nurses. Researchers were guided in sampling criteria by an expert advisory panel of patients, researchers and clinicians. No access to medical records was obtained. Open-ended narrative interviews were conducted in respondents' own homes by one of the authors, an experienced qualitative researcher. People were encouraged to tell their stories of heart failure from when they first suspected they had a heart problem. They were also prompted to consider specific topics, including medication, their awareness of side effects and their

Study	Field 2006[463]
	understanding of the purpose of medication. No topic guide is mentioned. Interview transcripts were checked by respondents to mark any sections they wished to be deleted from the interview before assigning copyright for use in research, publication, teaching and broadcasting. Data were coded systematically using N6 software and analysed thematically using a modified grounded theory approach, incorporating constant comparison and exploration of deviant cases. Coding framework drew on both existing literature on patients' understanding of heart failure and emerging themes from the current study. Each respondent was assigned to one of three levels of medication awareness on the basis of their whole interview. The levels were developed by two of the authors using the method of constant comparison, which identified emergent themes and considered meanings and significance.
Findings	Level 1: 'Doing what I'm told' Did not fully understand diagnosis of heart failure and consequently importance of medication Had been given information at inappropriate times such as after a surgical procedure in hospital or when they were too shocked by the diagnosis to 'take it in'
	Level 2: 'Leaving it up to your GP' Had good relations with health care professionals and had received enough information for their needs 'Trusted' their doctors; 'a little knowledge is a dangerous thing' Uncertain what would happen as heart failure progressed
	Level 3: Candidates for concordance This group was well informed and equipped for informed exchanges with professionals about heart failure Unusual group as they were younger and with a background in health Acknowledged the uncertainties of their condition and understood that managing heart failure involved being vigilant about their physical and mental state Had high level of interest in their illness
Limitations and applicability of evidence	This is a UK study interviewing people with heart failure. However, serious limitations were assigned due to lack of information on context, role of researcher, data collection and richness of data.

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Study	Horne 2004[637]
Aim	To explore the experiences of patients with severe heart failure and identify their needs for palliative care.
Population	Patients with a clinical diagnosis of heart failure confirmed by echocardiogram were recruited by consultant cardiologists, care of the elderly consultant or heart failure nurse specialist from two teaching hospitals. Patients with comorbidities were not excluded.

Study	Horne 2004[637]
	Characteristics: n=20; male/female: 2/1; mean age (age range): 73 years (60-83); 11 patients were NYHA class IV, 7 patients were class III and 2 were class II; 14 patients lived with their spouse, 1 patient lived with her brother, 5 lived alone
Setting	Doncaster, UK. Urban and rural communities situated in former coal mining area, patients recruited from two teaching hospitals. Semi-structured interviews were conducted in interviewees' own homes between October 2001 and March 2002.
Study design	Qualitative
Methods and analysis	Open semi-structured interviews with key questions carefully selected and approved by the local ethics committee to limit potential distress to the patients. Interviews were conducted by the first author; field notes and a research diary also informed the analysis. Sampling of patients continued until no new themes were identified. Data were coded independently by two researchers using a grounded theory approach. Identification and labelling of main themes and categories. Concurrent data collection and analysis to refine the focus of the study on emergent issues. In the last three patient interviews theoretical sampling was employed using a revised interview schedule, which served to confirm or refute emerging themes. Strategies to ensure validity and trustworthiness were employed throughout the study.
Findings	Information needs Patients wanting more explanation, education and information from their physicians to gain a better understanding of the disease process, the practical limitations, how to get help and how to cope with living with heart failure. Some sense of prognosis and wanting to be told the truth was also important to these participants.
Limitations and applicability of evidence	This is a UK study, but it was assigned serious limitations due to study aims, role of the researcher, rigour of research methods, data richness and relevance of findings.

Study	Macdonald 2016[922]
Aim	To contrast the help-seeking and access to care in cancer and heart disease in order to extend concepts about illness identity, and its relationship to the concept of Candidacy
Population	Data was taken from the Colorectal Cancer Study (2011), End-Stage Heart Failure study (2014) and Stable Heart Failure study (no references given). The 'stable' cohort was recruited via heart failure specialist nurses, but not clear how 'end-stage' cohort recruited. All studies based in Scotland. 30 transcripts used (10 purposively sampled from each of the three studies) out of a pool of 103. Colorectal cancer characteristics: n=10; male/female: 2/3; age range: 50-75 years; 3/10 from most socially deprived area. Heart failure characteristics: n=20; male/female: 11/9; age range 56-86 years; 3/20 from most socially deprived area.
Setting	Scottish NHS. No more information provided.
Study design	Secondary analysis of qualitative data

Study	Macdonald 2016[922]
Methods and analysis	No opportunity to evaluate data collection, although the research team had access to all full transcripts. The process by which the sample is reduced from 103 to 30 transcripts is explained – but not why the number was chosen. Limited explanation of data analysis, but use a form of amplified analysis to fit themes to a framework known as 'Candidacy framework'. Each data set was analysed individually initially for Candidacy. Following each dataset was subjected to additional thematically driven coding that focused on experiences of care and relationships with health professionals. The coding framework progressed through an iterative process and emerged as a framework divided into two time points – pre- and post-diagnosis – each mapped on to the stages of candidacy.
Findings	Post-diagnosis Lack of understanding of heart failure, lack of transparency around prognosis, experience characterised by poor communication and fragmented care Heart failure patients often unaware of their diagnosis, and the term heart failure used rarely Getting information about diagnosis a gradual process, diagnosis often deduced from medications taken Health professionals seem reluctant to be explicit about prognosis
Limitations and applicability of evidence	This is a UK study, but although the paper was published in 2016, the data dates back to 2006. The aim of this paper was not to look at communication of diagnosis and prognosis of heart failure, but rather illness identity and candidacy, which limits the applicability of the findings. It is rated as having serious methodological limitations due to its use of secondary data and the subsequent inability to assess methodology in detail.

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Study	Murray 2002[1030]
Aim	To compare the illness trajectories, needs, and service use of patients with cancer and those with advanced non-malignant disease (heart failure). [Only the information relevant to this review (heart failure patients) has been extracted]
Population	Cardiologists and geriatricians identified outpatients with cardiac failure (NYHA class IV). The research team checked with their GP if the patient was suitable for recruitment (prior to doing so) and sought permission to interview members of the primary care team. Characteristics: n=20 people with heart failure; male/female; mean age: 74; the commonest cause of cardiac failure was ischaemic heart disease, 11 lived with a carer, 7 were alive at the end of the study. Characteristics of healthcare professionals not provided.
Setting	UK study: 4 hospitals in Edinburgh and Livingston, Scotland. In-depth interviews at 3-monthly intervals for up to a year with patients and their main informal carer in the patient's home. No dates provided.
Study design	Qualitative
Methods and analysis	The patient sample was chosen purposively to represent the local demography of each condition with respect to age, sex, deprivation category, living alone or with a carer, and treatment (variables based on data from hospital, register general, and on advice from local specialists).

Study	Murray 2002[1030]
	One of the researchers conducted in-depth interviews at 3-monthly intervals for up to a year with patients and their main informal carer in the patient's home. After each interview the professional carers identified by the patient as being most important to their care (e.g. GPs, hospital doctors, specialist community palliative care nurses, hospital chaplain, occupational therapist, district nurse, specialist cardiac nurse, hospice doctors, and a warden of sheltered accommodation) were approached. At 8-12 weeks after any bereavement carers were interviewed, if appropriate, the GP, and other key professionals. A focus group for each diagnostic group allowed key health and social care professionals, a chaplain, patients, informal carers, and voluntary sector representatives to discuss the issues raised by the interviews and consider alternative service options. The authors conducted concurrent data analysis and fieldwork to allow emergent themes to be fed back into the data collection. These themes and the research questions formed the basis of the coding strategy. NVIVO software was used and the techniques of narrative analysis. A second researcher read all the transcripts and assisted with coding. Regular review and discussion of the evolving themes by the multidisciplinary steering group and the data from the focus group contributed to data synthesis and interpretation.
Findings	Information and understanding of illness and prognosis Patients reported not receiving written information, had poor understanding of their condition and did not connect symptoms to their heart failure Professionals reported wanting patients to understand but also protect them from the potential seriousness of their condition implied by cardiac 'failure' Prognosis was rarely discussed and little acknowledgement that end stage heart failure is a terminal illness Most patients and carers did not feel involved in decision making or empowered to work in partnership with professionals
Limitations and applicability of evidence	This is a UK study with moderate limitations due to lack of explanation of the role of the researcher, data richness lacking for the themes relevant to this review, and a loose link between findings and conclusions.

Study	Selman 2007[1266]; Harding 2008[581]
Aim	Selman 2007: To formulate guidance and recommendations for improving end-of-life care in chronic heart failure. To generate data on patients' and carers' preferences regarding future treatment modalities, and to investigate communication between staff, patients and carers on end-of-life issues. Harding 2008: To generate recommendations for the appropriate provision of feasible and acceptable information to chronic heart failure patients and their family carers, in line with UK and international policy guidelines.
Population	Specialist heart failure nurses recruited patients, and their informal family caregivers, from their outpatient clinic and from hospital wards. Inclusion criteria for patients were a diagnosis of chronic heart failure, NYHA class III or IV, on optimal therapy, not yet seen by palliative care staff, able to communicate in English, and able to give informed consent.

Study	Selman 2007[1266]; Harding 2008[581]
	Characteristics: n=20; male/female: 3/1; mean age (range): 69 (43-83) years; NYHA class III (n=14), NYHA class III-IV (n=2), NYHA class IV (n=4); all except one had previous CHF admission; high rate of co-morbidities (e.g. diabetes, cancer and epilepsy) and invasive cardiac procedures (6 pacemakers, 6 bypass procedures, 3 valve replacements) Carer characteristics: n=11; male/female:1/10; patients' wives (n=8), a niece, a daughter and a son; high rate of co-morbidity (e.g. strokes and cancer) Staff were recruited from the cardiology and palliative care teams. Purposive sampling was used to address staff role and community/inpatient/outpatient care provision. Characteristics: n=12 overall; palliative care (n=6): specialist registrar (n=1), consultant (n=1), specialist inpatient nurses (n=2), specialist community nurses (n=2); cardiology (n=6): specialist nurses (n=3), consultants (n=2), specialist registrar (n=1)
Setting	English NHS. One tertiary hospital (St Thomas' Hospital) in London. No more information provided.
Study design	Qualitative
Methods and analysis	Semi-structured interviews using a topic guide for each population that was drafted based on a literature review and discussion with clinical experts in a steering group. Sequential or interim analysis refined focus to the most relevant clinical and patient perspectives through continuous review of transcripts and exploration of emergent themes. Three researchers conducted the interviews. Interview transcripts were managed with NVIVO software and analysed using a constant comparison approach to formulate analytical categories or themes. Each transcript was coded line by line by one researcher, a sample reviewed by a second researcher to establish interrater reliability and increase validity of findings. Following peer review, initial codes were reviewed for internal consistency and independence of themes. Codes and sub-codes were tabulated, and data from each sample compared and integrated, taking into account relationships between patients and carers.
Findings	Selman 2007: Barriers to improving end-of-life care Specialism specific: cardiac staff confirmed that issues such as future care in the event of an exacerbation, end-of-life preferences etc. are rarely raised with patients; staff reported difficulty handing patient denial, discussing poor prognosis and dealing with emotional involvement with patients and their families; cardiac staff often lack the communication skills necessary to handle these sensitive issues
	Harding 2008: Barriers to effective information provision Disease specific: all staff identified prognostication difficulties. Cardiac staff identified the unpredictable disease trajectory as a reason why future care options are not discussed. Patient specific: patients reported that sensory/memory impairments present communication challenges, lack of insight what questions to ask and lack of empowerment to question clinicians.
	Harding 2008: Recommendations to improve communication and information

Study	Selman 2007[1266]; Harding 2008[581]
	Patients requested open and sensitive relay of poor prognosis by clinicians, family to be involved in communication to support them in their role of family information providers, access to a telephone advice line or support group Clinical staff recommended mutual education and joint working between specialties
Limitations and applicability of evidence	This is a UK study that was assigned very serious limitations due to the limited information on the background and reflection of the researcher, data collection, data richness, relevance of findings and link to conclusions (i.e. no link made to UK and international policy guidelines which they had set out to do). Also the authors do not link the studies to each other despite it becoming apparent from the description of the sample and methodology that the data sets are from the same interviews.

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Study	Simmonds 2015[1289]; Glogowska 2015[523]; Fry 2016[490]
Aim	Simmonds 2015: To identify critical points on heart failure patient pathways where risk of unplanned admission is increased and identify barriers to the implementation of evidence-based interventions. Glogowska 2015: Explore perceptions and experiences of health care professionals working in multi-disciplinary teams that include specialist heart failure nurses when caring for the management of heart failure patients. Fry 2016: Secondary analysis to interrogate the data (exit-interviews) of a subset of 11 patients to explore the experiences of patients living with heart failure. [No findings relevant to this review were reported.]
Population	Simmonds 2015: Adult patients with an unplanned hospital admission for heart failure during the preceding 6 months and who the referring clinician considered had severe or difficult to manage heart failure (with or without physical or mental health co-morbidities). Potential eligible participants were identified at one site by screening of patients on the hospital ward or in heart failure clinics, and at the other two sites by healthcare professionals in heart failure clinics and general practices. Characteristics of patients in main study: n=31; male/female: 1/1; mean age: 72 years; 10 patients lived alone, 5 lived in deprived areas; majority were white British Informal carers of recruited patients were also invited to participate. Characteristics: n=9; no other information provided Health care professionals also took part (observations, impromptu interviews, in-depth interviews) Characteristics: n=55 overall; in-depth interviews with 23: GPs (n=7), community nurses (n=4), heart failure specialist nurses (n=5), senior hospital doctors (n=5) (including 3 consultant cardiologists) and cardiac rehabilitation therapists (n=2).

Study	Simmonds 2015[1289]; Glogowska 2015[523]; Fry 2016[490]
	Glogowska 2015: same as above plus 1 extra community nurse
Setting	UK study conducted during 2011-2013. GP practices (sampled for a range of practice level social deprivation scores and rurality), specialist nurses and secondary care-based services including two teaching hospitals, across three study sites. The three study sites, mix of urban and rural settings, were covering large geographical areas and with variable access to heart failure specialist nurse-led clinics.
Study design	Ethnographic, qualitative study
Methods and analysis	Three social scientists carried out all data collection. Participating patients were followed individually using ethnographic methods (observation, impromptu interviews, field notes, patient and carer diaries, patient medical records) throughout their interactions with healthcare, for a period of up to 11 months. In-depth interviews were made with a subsample of patients or carers/family members (around eight at each site). Recorded fieldwork conversations (impromptu interviews) with patients, carers and healthcare professionals were conducted and analysed as an integral part of the ethnographic fieldwork. The majority of healthcare professionals in the study were caring for study participants and were observed delivering care (observations, impromptu interviews). Those healthcare professionals who were caring for people with heart failure that did not participate in the study took part in pre-arranged in-depth interviews. Interviews took place in primary and secondary healthcare settings and patients' homes. Topic guides (developed through literature review, expert advice from an independent study advisory group and key informant interviews with staff involved with the management of patients with heart failure) were used for in-depth interviews but interviewees were encouraged to speak freely about their experiences and raise topics not covered by the guides. Data analysis using an inductive, thematic approach involving a process of constant comparison between cases using NVIVO software. Data analysis began alongside data collection and informed later data collection in an iterative process. A coding framework was built and gradually added and refined. Observational data, impromptu/fieldwork interviews and documentary materials were analysed at three levels: individual patient cases, across cases within centres, and across research centres to synthesis. Thematic analysis was aided by 'situational analysis'- a grounded theory approach. Qualitative rigour through 'member checking' with both participants and patient/carer advisory group. Coding frames, disconfirming views and development of final themes was regularly discussed with the multi-disciplinary research team.
Findings	Simmonds 2015: Disclosure of diagnosis and educating patients about heart failure Clinicians can find this first conversation difficult, regarding 'heart failure' as a loaded term, which may come as a shock to patients. Talk in euphemistic terms (e.g. 'ageing heart', 'stiff heart', 'heart not pumping efficiently') to avoid upsetting patients and extinguishing hope. Disclosure and explanation of diagnosis during unplanned hospital admission not deemed appropriate by clinicians, patients and carers. Hospitals are busy environment's that do not foster enough time for appropriate and sensitive explanations of heart failure. Patients with good access to hospital and community-based heart failure specialist nursing teams reported more positive experiences of diagnosis. Lack of patient information and education was a strong theme in their study and a key barrier to the development of patient self-help strategies to prevent readmissions. Healthcare professionals emphasised the need for information and guidance to be given to patients as part of an ongoing conversation. Heart failure specialist nurses and GPs were seen as key to the success of this process.
	Glogowska 2015: Communication with patients (healthcare professionals' perspective)

Study	Simmonds 2015[1289]; Glogowska 2015[523]; Fry 2016[490]
	Term 'heart failure' unhelpful in explaining diagnosis and prognosis. Considered 'loaded' term on par with a cancer diagnosis. Some services used a more neutral term 'heart function'. In another location the entire team used 'heart failure' consistently. Explaining diagnosis and prognosis to patients considered challenging. Balancing the need to be honest about the condition (which could raise anxiety) with building trust to maintain hope and a positive outlook in the face of life-threatening illness. Some addressed the issue of prognosis over time, given the uncertainty about the disease course and in response to changing circumstances, particularly when patients might be approaching the end of their life. A common perception was that this type of exchange between clinicians and patients did not take place often enough. Appointments with consultants are too short to relay all the information a patient would need regarding their diagnosis. Providing education delegated to specialist nurses in the outpatient or community setting. Participants agreed that education was best delivered within the context of an ongoing relationship between specialist nurse and patient, in particular during home visits, where patients are more relaxed and there was more time to assimilate information. Community matrons are also able to provide this type of input. Not all patients would take up the education offered. Some would find it challenging and difficult to assimilate, leading to struggles to self-manage their condition. These patients are more likely to be those whose first language was not English, those too ill to benefit from education or in denial about their condition, those attributing their condition to growing older, those with learning difficulties, and those experiencing cognitive decline or living with addictions. Specialist nurses spoke of the necessity to find a balance between the education they offered patients with the patients' capacity to receive it; consequently they tried to identify issues of importance and to personalise the information accordingly. Repetition of these messages may be required over time.
Limitations and applicability of evidence	This is a UK study interviewing people with heart failure and their carers. However, it was assigned moderate limitations due to limitations in context (lacking characteristics of healthcare professionals taking part in impromptu-interviews and observations), reflections on the role of the researcher, and data richness in the sections relevant to this review

Study	Taylor 2017[1363]
Aim	To explore the experiences of patients with a recent diagnosis of heart failure with a focus on symptom onset and diagnosis parts of the pathway to explore how and when patients realised something was wrong and what the term 'heart failure' means to them.
Population	Patients with a recent (<1 year ago) diagnosis of heart failure over the age of 55 who had been referred from primary care were invited for interview. Patients not able to give written informed consent or who were too unwell to take part were excluded. Arrangements for an interpreter to be used where needed were put in place to prevent exclusion of non-English speaking participants. Purposive sampling was planned to achieve demographic variation (considering diversity in age, gender, and ethnicity). Characteristics: n=16; male/female: 2/1; median age (range): 78.5 (52-87) years; all but one participant were white British; 10 of the interviewees were accompanied by a relative
Setting	English NHS. People with heart failure were recruited from a secondary care heart failure clinic serving a large, socioeconomically diverse

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Study	Taylor 2017[1363]
	population in central England, and interviewed between October and December 2014. Interviews were conducted in the interviewees' home, apart from one which was done over the telephone.
Study design	Qualitative
Methods and analysis	Semi-structured interviews with people who had recently received a diagnosis of heart failure, and in some cases with their relative. The interviews, using a topic guide, were conducted by the lead author (a GP and clinical researcher trained in qualitative methods). Early interviews were reviewed and discussed with an experienced medical sociologist with expertise in qualitative methods. Minor modifications to the topic guide were made after two interviews in light of emerging themes from the data. Transcripts of interviews were analysed using the framework method. Transcripts were read and re-read to ensure familiarisation, then initially coded by hand. Coding was reviewed by a second coder, and an independent experienced qualitative research fellow. The coding lists were used to develop an analytical framework organised into categories. All interview transcripts were then coded using NVIVO software. Data for each code were read, re-read and then summarised for each of the participants in the study. Each category was interpreted using an analytical memo to explore emerging themes and concepts.
Findings	Variability in understanding of diagnosis Participants' understanding of their heart failure varied in complexity and depth, some were confused but did not want more information, whilst others actively sought extra information (e.g. online)
	Fear and uncertainty caused by heart failure terminology 'heart failure' associated with fear and that outlook was poor, term had been introduced not initially but later on by specialists
Limitations and applicability of evidence	This is a UK study which was assigned moderate limitations due to limited information on the topic guide and data richness.

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Study	Wingham 2015[1489]
Aim	Identify the needs of caregivers supporting a person with heart failure and inform the development of a caregiver resource to be used as part of a home-based self-management programme.
Population	People who have been caregivers, of people with heart failure for at least six months were contacted by community-based cardiac nurses or the cardiac rehabilitation team in three geographical locations in the UK. Participants were also recruited through a support group for people with an implantable cardiac device, and through advertising by the National Cardiomyopathy Association. Individual interview carer characteristics: n=22; male/female: 3/8; mean age (range): 67 (39-84) years; ethnicity: British White (n=18), Black Caribbean (n=1), British Black (n=1), Indian (n=2); 20 were in spousal or partner relationships; length of time as a caregiver: 6 months to 8 years; 18

Study	Wingham 2015[1489]
	were retired, 3 were employed; at the request of the caregiver the person with heart failure was present at and participated in 12 of the interviews Focus group carer characteristics: n=4 (participants); male/female: 1/3; mean age (range): 62 (42-72) years; ethnicity: British White (n=4); all were in spousal or partner relationships; length of time as a caregiver: 6 months to 6 years; 1 was employed
Setting	UK study with semi-structured interviews and one focus group in three geographical locations reflecting the diversity of the UK population: Cornwall (a rural, stable older white population; interviews and one focus group), and Birmingham and Leicester (ethnically diverse populations). Interviews conducted at a location convenient for the interviewee.
Study design	Qualitative
Methods and analysis	Purposive sampling using maximal variation technique to ensure a mix of demographic and social factors including time as a caregiver, gender, age, socioeconomic status and ethnic diversity. Semi-structured face-to-face interviews with informal (unpaid) caregivers of people with chronic heart failure conducted by one of two of the researchers. A topic guide had been developed with a patient and public involvement group. The researcher made field notes detailing the home environment, geographical location and how interview was performed; reflections on own performance and influence on interview; how caregiver responded to the questions and initial thoughts about the main points arising from the interview. These informed the analysis. Following the interviews, a focus group with a different set of carers was conducted by both researchers together (one led the discussion, the other observed and made notes). Aim was to confirm findings of interviews, ensure all significant caregiver needs had been identified, and refine content and structure of the 'caregiver resource'. Transcripts of audio-recordings were managed and thematically analysed using NVIVO software. The researchers conducted a six-step process which involved familiarisation with the data, generating initial codes, searching for themes, reviewing the themes, defining and naming the themes, and producing the report. The individual interviews were listened to and transcripts and field notes read by two researchers. Small sections of data were assigned a code that summarised the content. Codes with common features were grouped together in emerging themes, before being assigned overarching themes. A third qualitative researcher conducted independent analysis of each transcript before all three researchers met to discuss and agree findings. A copy of the transcript was offered to the interviewee for comments. The focus group data were independently analysed by the construction of simple descriptive summaries by two researchers. The researcher looked for consensus among the group and any differences were explored by seeking an explanation for agreement or disagreement.
Findings	Providing support: variability of heart failure Carers required information about what to do in an emergency, how to recognise when signs and symptoms need urgent attention and how to perform cardiopulmonary resuscitation
	Transition to becoming a caregiver: communicating with health professionals Caregivers want to know about treatment options and contribute to decisions ('know the patient best') Frustration if excluded from consultations either by healthcare professionals or the patient

Study	Wingham 2015[1489]
Limitations and applicability of evidence	This is a UK study but it was assigned moderate limitations due to limitations in context (no information on people with heart failure they cared for), research methods rigour, and data richness.

F.15 Diuretics in advanced heart failure

No clinical evidence was identified.

F.16 Domiciliary oxygen therapy in people with advanced heart failure

Study	Clark 2015[281]
Study type	RCT (Patient randomised; Parallel, prospective, open, pragmatic, multicentre)
Number of studies (number of participants)	1 (n=114)
Countries and setting	Conducted in United Kingdom; Setting: 15 sites all within the UK. At least one trial participant was recruited in 13 of the 15 sites: Hull, Chesterfield, Oldham, Darlington, Dundee, Leicester, Barnet, Durham, Bradford, Ealing, Sunderland, Pinderfields and Plymouth.
Line of therapy	Adjunctive to current care
Duration of study	Intervention + follow up: 24 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	To be included in the study, patients had to: (1) be willing to provide written informed consent and be able to complete patient assessments; (2) be aged 18 years or over; (3) have heart failure from any aetiology; (4) have severe symptoms of heart failure (NYHA class III/IV); (5) have LV systolic dysfunction confirmed by echocardiography, with LVEF less than 40% or graded as at least 'moderately' impaired on visual inspection if an accurate ejection fraction could not be calculated; (6) be receiving maximally tolerated medical

	management of their heart failure as reached target dose of (or be on maximally tolerated dose of, or be intolerant of) an inhibitor of the renin-angiotensin system shown to improve prognosis, reached target dose of (or be on maximally tolerated dose of, or be intolerant of) a beta-adrenoceptor antagonist shown to improve prognosis, reached target dose of (or be on maximally tolerated dose of, or be intolerant of) an aldosterone antagonist
Exclusion criteria	Patients were excluded from the study if they: (1) were unable to provide written informed consent; (2) had had a cardiac resynchronisation therapy device implanted within the previous 3 months; (3) had coexisting malignant disease if this would affect the study in the investigators' opinion; (4) had interstitial lung disease; (5) had COPD likely to fulfil criteria for LTOT, forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) <70% AND fev1 <40% predicted and hypoxia [partial pressure of arterial oxygen (PaO2) <7.3kPa or saturations <90%]; (5) were using any device or medication that would impede their ability to use LTOT or NOT, such as continuous positive airway pressure; (6) were unwilling or unable to comply with safety regulations regarding oxygen use, particularly smoking; (7) were unable to complete patient-related information on entry.
Recruitment/selection of patients	Recruitment was staggered, with sites joining over the course of the trial. Over half of the participants were recruited from the Hull site, where the chief investigator was based. Potential participants were identified from NHS heart failure, cardiology or general medical clinics. Existing lists of likely eligible patients held within the NHS hospitals were also reviewed. In order to aid recruitment some sites used patient identification centres. Potential participants were sent an introduction letter with an invitation to contact the study team if they were interested in taking part in the study. Alternatively, the research nurse could contact the patient directly by telephone.
Age, gender and ethnicity	Age - Mean (SD): 72.3 (11.3). Gender (M:F): 80/34. Ethnicity: Not reported
Extra comments	Participants with NYHA class III or IV LV systolic dysfunction receiving optimal medical therapy
Indirectness of population	No indirectness

Interventions	(n=57) Intervention 1: Domiciliary oxygen therapy-repeated long term use (daily availability). Long term oxygen therapy prescribed for 15 hours per day including overnight hours. Hone oxygen was delivered by concentrators in the patients' homes. The inspired oxygen was increased from 20.9% (normal room air) to approximately 28%.. Duration 24 months. Concurrent medication/care: Best medical therapy. Indirectness: No indirectness (n=57) Intervention 2: No oxygen therapy - No treatment. Patients received the maximally tolerated medical management for their heart failure and reached their target dose of inhibitors of the renin-angiotensin system, a beta-adrenoceptor antagonist and an aldosterone antagonist.. Duration 24 months. Concurrent medication/care: Not reported. Indirectness: No indirectness
Funding	Academic or government funding (National Institute for Health Research (NIHR))

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: REPEATED LONG TERM USE (DAILY AVAILABILITY) versus NO TREATMENT

Protocol outcome 1: Quality of life at 2 weeks
- Actual outcome: MLWHF at 3 months; Group 1: mean 46.5 (SD 1.8); n=53, Group 2: mean 52 (SD 1.8); n=53; Comments: SE reported not SD
Risk of bias: All domain - High, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Indirectness due to length of follow up; Baseline details: The mean NT-proBNP level was higher in the LTOT arm, and the proportion of people taking an aldosterone antagonist was greater. NT-proBNP level was pre-specified as a covariate in the primary analysis to control for this; Group 1 Number missing: 4; Group 2 Number missing: 4
- Actual outcome: EQ-5D-3L at 6 months; Group 1: mean 0.55 (SD 0.23); n=45, Group 2: mean 0.54 (SD 0.3); n=43
Risk of bias: All domain - Very high, Selection - Low, Blinding - Very high, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Indirectness due to length of follow up; Group 1 Number missing: 12; Group 2 Number missing: 13

Protocol outcome 2: Unplanned hospitalisation at 4 weeks
- Actual outcome: Hospitalisation (event rate) at 24 months; Group 1: 35/57, Group 2: 41/57; Comments: Converted to rate ratio (SE) = 0.85 (0.2301)
Risk of bias: All domain - High, Selection - Low, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Indirectness due to length of follow up; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Change in dyspnea at 2 weeks - Actual outcome: NRS for breathlessness (Q1 How bad has your breathlessness felt on average over the past 24 hours?) at 6 months; Risk of bias: All domain - Very high, Selection - Low, Blinding - Very high, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Indirectness due to length of follow up; Group 1 Number missing: 12; Group 2 Number missing: 14 Protocol outcome 4: Change in exercise capacity at 2 weeks - Actual outcome: 6 minute walk test at 6 months; Risk of bias: All domain - Very high, Selection - Low, Blinding - Very high, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Indirectness due to length of follow up; Group 1 Number missing: 16; Group 2 Number missing: 24	
Protocol outcomes not reported by the study	Patient and carer satisfaction at 2 weeks; Change in NYHA class at 2 weeks; Unplanned hospitalisation at 4 weeks (number of bed days)

F.17 Discussing Implantable Cardioverter Defibrillator (ICD) deactivation

Study	Brannstrom 2011[204]
Aim	To describe healthcare professionals' experiences in end of life care for heart failure patients.
Population	15 healthcare professionals (3 cardiologists, 12 internists)
Setting	Sweden
Study design	Interviews
Methods and analysis	The interviewers used open ended questions to encourage narration, and probing questions were then asked as the interview progressed. Interviews lasted from 30 to 90 minutes and thematic content analysis as used to analyse the data. This was initially conducted by identifying codes of the data which were abstracted into subthemes and further into themes.

Study	Brannstrom 2011[204]
Themes	Decision making •Doctors felt that ICD discussions were important but guidelines on how to handle the situation were unclear.
Limitations and applicability of evidence	Severe limitations related to the context of the study, role of the researcher and richness of the data.

Study	Cheang 2015[263]
Aim	To investigate why palliative care in heart failure may be underutilised, in order to identify problems in current practice that may impact the provision of care
Population	Consultants, clinical nurse specialists, other palliative nurses and non-consultant doctors that were mainly based in hospices.
Setting	UK
Study design	Survey
Methods and analysis	A prospective survey was written based on current literature, which identified themes on burden to palliative care services, current practice and professional perception of the role of palliative care in heart failure, palliative care challenges specific to heart failure, and interdisciplinary collaboration. The survey was available on a web-based service to allow online self-administration. Covering letters were sent to the target population of professionals, including to all members of the UK association of palliative medicine, and all adult palliative care teams listed in the UK hospice directory. The free text survey answers were analysed using a framework approach. After familiarisation with the raw data, key themes were identified from the study objectives and issues rose by respondents. These were organised into themes and concepts and associations were highlighted, allowing interpretations to be made.
Themes	Decision making •Healthcare professionals reported many reasons that they were unable to deactivate ICDs. They are unable to do so out of hours, particularly when staff or magnets were unavailable out of hours in community hospitals. Others found healthcare professionals were unavailable to visit dying patients in the community in order to deactivate ICDs. Others spoke of excessive time delays due to a lack of defined process in the community, unavailability of magnets or insufficient education on how to use magnets: confusion of the size of the magnet needed. Others spoke of organisational difficulties, having to make lots of phone calls in order to access technician support for deactivation. Many felt that there was no local or national policy or procedures related to ICD deactivation, which made the process long and difficult.
Limitations and applicability of evidence	Severe limitations as this study sought to assess the quality and utilisation of services, and qualitative analysis of survey results was mentioned only briefly.

Study	Fluur 2013[470]
Aim	To explore future reflections of spouses living with ICD recipients, with a focus on end of life care issues.
Population	Spouses of ICD-recipients at least 6 months post implant, who were in a stable phase of their illness trajectory (mean age 61 years)
Setting	Sweden
Study design	Interviews
Methods and analysis	An interview guide was conducted based on literature reviews and the researchers' own expertise in the area. This was tested in a pilot interview. Introductory question was "please describe your experiences as a spouse of an ICD-recipient". After this they were asked to describe thoughts and expectations related to ICD use, and were asked to consider hypothetical situations in which the ICD may not be replaced. Interviews were semi-structured and ranged between 30 to 60 minutes. Thematic analysis was used whereby initial familirisation with the data was followed by line by line coding and subsequent searches for patterns in these codes, with constant comparison to ensure the categories reflected the original data. Analysis was also validated through discussion with the research team.
Themes	Understanding/attitudes •Thoughts about dying and death were not discussed between healthcare professionals and spouses, and many were unaware of the possibility of deactivating the ICD. For many, the possibility of this came as a surprise. •Many misconceived deactivation to be equivalent to euthanasia, leading to immediate death. In these causes they would only consider deactivation when partners were 'brain dead'. •Participants felt that they would only agree to deactivate the ICD if all hope was gone and their partner no longer had a 'worthy' life. Many expressed that they would not want their partner to suffer and be in pain in their last days of life, which an active ICD could cause. In these cases, they felt there was no reason to prolong the inevitable and cause extra suffering by keeping an ICD going.
	Decision making •Spouses felt that they would rather healthcare professionals make decisions about deactivation so they did not have to make the decisions themselves.
	Discussions •Some participants said that they had brief discussions with healthcare professionals related to the possibility of resetting the device if it was constantly firing. However, spouses did not discuss this further with their partner.
Limitations and applicability of evidence	Minor limitations related to the context of the study

Study	Fluur 2013[469]

Study	Fluur 2013[469]
Aim	To explore patients' experiences of complex issues of battery replacement and deactivation of the ICD
Population	37 ICD recipients with a median time since first implantation of 4.5 years and a mean age of 64 years, and who were not in the palliative phase of a terminal illness.
Setting	Sweden
Study design	Interviews
Methods and analysis	Participants were identified from medical records of ICD clinics at 6 hospitals across Sweden. An interview guide was constructed based on literature reviews and the researchers' own expertise in the area. Interviews lasted between 30 - 60 minutes and were audiotaped. Thematic analysis was used whereby initial familiarisation with the data was followed by line by line coding and subsequent searches for patterns in these codes, with constant comparison to ensure the categories reflected the original data. Analysis was also validated through discussion with the research team.
Themes	Understanding/attitudes •Patients could not define a limit to the number of shocks that would make them want to deactivate the device; however they did feel that multiple shocks would be too painful to bear. •Some participants felt that deactivating the ICD was comparable to active euthanasia. •Some participants were scared about deactivating their ICD •Participants had not thought about deactivation of their device and assumed that this was done automatically without question •People would not consider living without their ICD because they believed it was keeping them alive. Some felt that the ICD should always be replaced when the batteries ran out, regardless of other circumstances. They also described that they would chose life at all costs and would not want to deactivate their ICD when it could extend life. However when discussing hypothetical situations they felt that they would deactivate their device when their quality of life and overall health were so poor that they wouldn't want to continue living. They also did not take into account the impact ICD could have when seriously ill, and envisioned their health to be so poor in these cases that deactivation would cause imminent death. They could not see any disadvantage to keeping a device active, even though those that had experienced shocks understood that they could be painful.
	Discussions •People felt that end of life issues were another phase in their life that were not yet a reality and so they felt that they could make decisions about deactivation nearer the time. They wanted to live in the present after having experiences of heart problems, and had not thought about what would happen if they become sick.
	Decision making •People wanted to put the decision in the hands of healthcare professionals rather than making an active choice themselves about deactivation. They felt that it was difficult for them to make a decision themselves and that clinicians should come up with the suggestion themselves.
Limitations and	Moderate limitations related to data analysis. Themes are repetitive and overlap with many of the same points.

Study	Fluur 2013[469]
applicability of evidence	

1

Study	Goldstein 2008[538]
Aim	To understand barriers to physician initiated discussions about ICD deactivation
Population	12 healthcare professionals (electrophysiologists, cardiologists and generalists)
Setting	USA
Study design	Interviews
Methods and analysis	In depth interviews were conducted using open ended questions from a discussion guide, which began on asking physicians to describe their role in overseeing ICDs, eventually leading to discussions around end of life care issues. Constant comparative method was used for data analysis in order to develop a comprehensive coding system of the open ended data. New codes were added as needed until no new concepts emerged with successive interviews. This was conducted by 3 researchers who met to discuss the coding and reach consensus. These codes were organised to create the themes of the study.
Themes	Discussions •Doctors reported that they rarely had discussions about ICD deactivation, even though they acknowledged the importance of doing so. They found that at a technical level it crossed their mind that it should be switched off, but that for some it wouldn't cross their mind to initiate a conversation with the patient due to this. •Doctors reported that they saw the ICD devices as intrinsic and so different to other treatment management such as medication that they could constantly change the dose of or discontinue treatment. They felt that turning of an ICD is like 'crossing a bridge' by saying that a patient was at the end of their life ow. They felt that this finality was highly different to other treatment decisions they had to make, making it difficult to know when to have the conversation. •Doctors reported that it was hard to bring up discussions about deactivation because this contrasted so much with their discussions about the primary lifesaving role of the devices, which felt as if they were shutting of the hope for patients. •Doctors did not feel like they had a good enough relationship with patients to start talking about ICD deactivation. They felt doing so without a good rapport and relationship would scare patients •Doctors felt it was difficult to remember to have the conversations due to unseen nature of the device in comparison to the larger discussions about advance care planning
	Understanding/attitudes •Some doctors felt that discussions were actually easier than other discussions similar to turning off a respirator because it doesn't automatically led to death and could reduce pain for patients. They felt that for this reason they were not 'killing' the patient.

Study	Goldstein 2008[538]
Limitations and applicability of evidence	Severe limitations related to the methodology and findings of the study

1

Study	Goldstein 2008[537]
Aim	To understand patient barriers to discussions about ICDs in patients with advanced illness
Population	15 ICD-recipients (median age 69 years), 10 patients had their device for over a year and 8 patients had received a shock
Setting	USA
Study design	Interviews
Methods and analysis	Interviewers did not have direct patient care responsibilities. In depth interviews were conducted using open ended questions from a discussion guide, which began on asking patients to describe their understanding of why they needed an ICD, eventually leading to discussions around end of life care issues. Constant comparative method was used for data analysis in order to develop a comprehensive coding system of the open ended data. New codes were added as needed until no new concepts emerged with successive interviews. This was conducted by 2 researchers who met to discuss the coding and reach consensus. These codes were organised to create the themes of the study.
Themes	Understanding/attitudes •Patients had not had discussions about deactivation with their physician and were not aware that deactivation was an option.
	Discussions •Patients in a focus group were not willing to discuss deactivation during the group sessions or willing to have the conversation with their clinicians.
	Understanding/attitudes •Patients felt that deactivation was like an 'act of suicide', because a cardiac arrest was a threat to your life •Patients did not identify any situations in which they would choose to deactivate their device, describing this as a 'no-win situation'.
	Decision making •Patients felt that doctors should be the ones to judge whether or not a device should be deactivated, as they didn't feel qualified to make this decision for themselves
Limitations and applicability of evidence	Severe limitations related to the methodology and findings of the study

Study	Kramer 2011[796]
Aim	To identify nurses' concerns relating to deactivating cardiac devices
Population	14 nurses who were registered from the Division of Cardiovascular Diseases at the Mayo clinic
Setting	USA
Study design	Focus groups
Methods and analysis	Focus groups asked 60 minutes and were led by a trained non-physician facilitator. A semi structured interview guide with discussion questions was used to standardize each group's experience, which began discussions on how nurses viewed their role in helping patients with decision making, which led eventually to end of life care issues. Transcripts were analysed using standard qualitative techniques based in grounded theory, in order to derive themes. Each transcript was reviewed independently by four investigators and disagreements were discussed until a consensus was reached.
Themes	Decision making •Nurses felt that families sometimes put pressure on patients to get a device or to keep a device active
	Discussions •Nurses felt that deactivation was often carried out in reaction to receiving multiple shocks. Nurses felt that they would often bring up the conversation with the family during the dying process when the family started to ask 'why is it taking so long'. •Nurses thought doctors were uncomfortable discussion end of life issues because they are not trained to manage these situations.
	Understanding/attitudes •Nurses reported that any patients were not aware that their device could be deactivated •Nurses supported deactivation when it was with a well-informed patient. They reported that often this would happen when patients were undergoing withdrawal of other life-sustaining treatments, in order to improve patient comfort and avoid shocks.
Limitations and applicability of evidence	Minor limitations related to the richness of the data and context of the study

Study	Lee 2017[854]
Aim	To explore family members' experiences of ICD decision making, in order to inform decision making and improve the quality of end of life care.
Population	6 family members of ICD-recipients (3 children and 3 spouses)
Setting	USA

Study	Lee 2017[854]
Study design	Interview
Methods and analysis	An interview guide with probes was developed for consistency. Interview questions focused on care and issues surrounding decision making at end of life, each interview lasting between 60 to 90 minutes. Thematic analysis then took place, whereby 3 authors coded each transcript and coded individual items, which were eventually combined into themes.
Themes	Understanding/attitudes •Family members were not aware that deactivation of the ICD was an option, and had never considered this.
Limitations and applicability of evidence	Moderate limitations related to data collection, richness of the data and the role of the researcher.

Study	MacIver 2016[924]
Aim	To determine patient awareness and understanding of ICD deactivation
Population	25 heart failure patients with ICDs (mean age 62 years)
Setting	Canada
Study design	Interviews
Methods and analysis	Semi structured face to face interviews were conducted by an undergraduate student with experience in qualitative methods and not a member of the clinical team. Interviews were conducted following an appointment with the heart failure cardiologist. If a patient were unaware that ICDs could be deactivated, the reasoning was explained to them. An interview guide was used to explore emerging concepts. Data were initial coded line by line and broken down into further categories that would eventually make up the themes. This was done by 'axial' coding, and was an iterative process.
Themes	Understanding/attitudes •Many patients were not aware that an ICD could be deactivated. Of these, some felt that they may have been inadvertently told without the information being fully discussed. •Patients would consider ICD deactivation when they were at a terminal deterioration point of their illness, with no hope of a meaningful recovery. This was described as being bedridden, in a coma or on life support. •Some patients said that they would never want their ICD to be activated, and that this was like assisted suicide, with one patient stating that this was against their faith.
	Decision making •Frequency and pain of shocks, overall quality of life and recommendations of the physician. •People said that they trusted healthcare professionals looking after them to know when to bring up ICD deactivation and how to initiate this

Study	MacIver 2016[924]
	discussion.
	Discussions •Many felt that discussions should be initiated by a team member such as a cardiologist, nurse or social worker. •Some felt that healthcare professionals initiating conversations about ICD deactivation would be too emotionally distressing •Patient opinions of when discussions should take place varied. Some felt it should be pre-implant. Many felt that at this time they wanted the issue to be described to them fully, so that they were aware of the issues around deactivation but did not have to make any decisions at that point. They highlighted the role of healthcare professionals in allowing them to make a fully informed decision about ICD implantation. They suggested they could be given written information. •Some patients felt that discussions of deactivation should not happen at the beginning. This is because of the emotional distress it would cause, and how overwhelming the information would be. Others felt that it did not make sense to begin discussions of removing a device before even implanting it •Others felt that ICD deactivation should be discussed if there was a change in their condition, and if their condition had deteriorated. They felt that patients should be of sound mind but had definitely progressed to 'end of life'. Patients felt that physicians could predict when this change could result in death, and that this should be discussed as a reminder of the options and to determine preferences. •Patients did not feel it was appropriate to have discussions about ICD deactivation at the end of life when death was imminent.
Limitations and applicability of evidence	Minor limitations related to the context of the study

Study	Morrison 2010[1016]
Aim	To explore palliative care providers experiences and attitudes of managing ICDs
Population	112 palliative care professionals (51% physicians, 48% nurses and 1% other)
Setting	USA
Study design	Survey
Methods and analysis	A survey was carried out at the 2004 annual assembly of the American Academy of Hospice ad Palliative Medicine and Hospice and Palliative Nurses Association., who attended a session on ICD and were invited to complete a survey. The survey consisted of 18 items related to demographic information, attitudes and experiences in managing ICDs and pacemakers at the end of life, with space to comment after each scale item. Two authors coded the data independently and met to verify the accuracy of the themes and reach consensus
Themes	Decision making •Healthcare professionals felt that 'competent' patients should decide on whether to deactivate their device. They highlighted the importance of

1

Study	Morrison 2010[1016]
	discussions with the patient and family, and felt that all cardiologists thinking about implanting a device should have an end of life discussion.
Limitations and applicability of evidence	Moderate limitations related to the data analysis and richness of the data

1

Study	Mueller 2011[1023]
Aim	To identify issues related to role conflicts and moral distress experienced with the cardiovascular implantable electronic device industry
Population	17 industry employed allied professionals working in a clinical setting to monitor cardiac implantable electronic devices, who had performed at least one device deactivation
Setting	USA
Study design	Focus groups
Methods and analysis	2 focus groups were conducted with 9 people in each group, each lasting 2 hours. Moderators followed a semi structured discussion guide that was developed based on the literature. This included probe questions that sought to draw out experiences of participants. Transcripts were coded independently by 2 investigators, using standard qualitative content analysis and principles of grounded theory. Discrepancies were discussed before developing a final list of themes.
Themes	Understanding/attitudes •Allied healthcare professionals viewed ICD deactivations in seriously ill patients as routine and relatively noncontroversial. This is because they saw this as a means to prevent dying patients from receiving painful shocks.
Limitations and applicability of evidence	Moderate limitations related to the richness of the data and role of the researcher

2

Study	Svanholm 2015[1346]
Aim	To identify areas for improvement in discussions between healthcare professionals and patients related to ICDs.
Population	11 ICD-recipients (mean age 82.8 years) who were expecting a device replacement within 2 years
Setting	Denmark
Study design	Interviews
Methods and	In depth face to face interviews were conducted. Patients were invited from an outpatient clinic to participate. Interviews were conducted by a

Study	Svanholm 2015[1346]
analysis	researcher experienced in qualitative methods, who was not directly involved in the patient care. A topic guide was used which was constructed based on a literature review and researchers' own experiences. After 2 pilot interviews, the guide was adjusted. Introductory question was 'how is your life with an ICD?' which was further probed with follow up questions to expand on the informant's narrative. The phenomenological-hermeneutic approach was utilised whereby researchers re-read and listened to the interviews, and interpreted the text and producing a structural analysis of the content, whereby the text is structured into meaningful units. The research team discussed all themes systematically in order to reach consensus and create the themes.
Themes	Understanding/attitudes •Patients spoke about their quality of life as a factor for whether they'd want their ICD to be deactivated, such as if they were unable to engage in daily activities. •Many elderly patients considered deactivation as an illegal act for the physician, who they felt were obligated to treat them. •Some elderly patients had been seeking information about whether they could refuse an ICD replacement, feeling that they might be ready to die soon. None of the participants reporting discussing these thoughts with loved ones or healthcare professionals
Limitations and applicability of evidence	Minor limitations related to the richness of the data

Study	Strachan 2011[1337]
Aim	Examine patient experiences of end of life care issues
Population	24 ICD recipients and 6 participants who declined an ICD (age 26 to 87 years)
Setting	Canada
Study design	Interviews
Methods and analysis	Participants were recruited from two ICD referral centres, and potential participants were approached one to four weeks after implantation or two weeks to eight months after declining. Interviews were conducted by one researcher and were carried out beyond the point of saturation to make sure no new data emerged. Analysis was undertaken by three members of the research team, using grounded theory approach, and analysis codes were derived from the interview guide. Themes were derived by constant comparisons and discussions with the research team.
Themes	Understanding/attitudes •Patients were not aware that their device could be turned off or removed. They thought this would only happen if the battery had to be changed, or if there was something wrong with the device, or they had an infection or an MRI was required. Most had not considered the dying process in relation to ICDs.

Study	Strachan 2011[1337]
	Discussions •Participants felt that they would like to have discussions about end of life deactivation sooner rather and later, while they were still cognitively intact. Those that had already had this discussion said it was good to do this early while they were already engaged in ICD discussions with their healthcare professionals, and those that hadn't felt that they wanted to do so soon.
Limitations and applicability of evidence	Minor limitations related to the richness of the data

F.18 Identifying patients with an increased risk of mortality

Reference	Allen 2017[56]
Study type	Retrospective cohort
Study methodology	Data source: All ambulatory patients 21 years of age or older with a diagnosis of heart failure during the period from 2005 to 2008 were identified from Kaiser Permanente Colorado, Kaiser Permanente Northwest, and Fallon Health. Baseline covariates for the risk calculators were extracted from electronic health records. Deaths were identified from health plan databases, state death certificates, and Social Security Administration files. The SHFM and MAGGIC risk calculator scores were calculated using the online algorithms. Mimicking the calculators, we imputed the mean values for missing data. NYHA functional class, available in routine care but unavailable in electronic records, was set to functional class III in primary analysis and class IV in secondary analysis. To address concerns about model transportability, we updated the intercept and parameter estimates. The SHFM scores were converted to estimated survival at specific times. The MAGGIC risk calculator estimates for mortality were mapped based on probabilities for the integer scores 0 to 50, as described in the original derivation. Following the published method, we used multiple imputation for the left ventricular ejection fraction, BMI, systolic blood pressure, serum creatinine level, and smoking status.
Number of patients	n= 10,930
Patient characteristics	Ambulatory people with heart failure, 21 years of age or older. Age (mean SD) (years): 75.1 (11.8) Male %: 52%

Reference	Allen 2017[56]
	Ejection fraction: Preserved (≥50%): 4155 (38%) Borderline (41%-49%): 1330 (12.2%) Reduced (≤40%): 3019 (27.6%) Missing: 2426 (22.2%) Family origin not reported Setting: Multicentre Country: USA Inclusion criteria: All ambulatory patients 21 years of age or older with a diagnosis of heart failure during the period from 2005 to 2008. Exclusion criteria: Not reported
Target condition(s)	Mortality at 1 year Number of events: 1661 (15.9%)
Risk tool(s)	Seattle Heart Failure Model MAGGIC project heart failure risk score Derivation: Seattle Heart Failure Model was derived in Levy et al, 2006[873] MAGGIC project heart failure risk score was derived in Pocock 2013[1160]
Statistical measures	Seattle Heart Failure Model At threshold 50% predicted mortality: c-statistic: 0.66 Sensitivity: 0.5 Specificity: 99.9 PPV: 61.5 NPV: 82.2

Reference	Allen 2017[56]
	At threshold 20% predicted mortality: Sensitivity: 20.7 Specificity: 93.1 PPV: 39.6 NPV: 84.4 Hosmer-Lemeshow test X^2: 8.7 <u>MAGGIC project heart failure risk score</u> At threshold 50% predicted mortality: c-statistic: 0.69 Sensitivity: 3.1 Specificity: 99.2 PPV: 45.2 NPV:82.4 At threshold 20% predicted mortality: Sensitivity: 69.7 Specificity: 61.2 PPV: 28.1 NPV:90.3 Hosmer-Lemeshow test X^2:38.6
Source of funding	National Heart, Lung and Blood Institute of the National Institutes of Health, the American Recovery and Reinvestment Act grant and the National Institute on Aging.
Limitations	<u>Seattle Heart Failure Model</u> Risk of bias: Low Indirectness: No indirectness

Reference	Allen 2017[56]
	Usability: Yes MAGGIC project heart failure risk score Risk of bias: High (model showed poor calibration and was not recalibrated) Indirectness: No indirectness Usability: Yes
Comments	

1

Reference	Frankenstein 2009[480]
Study type	Retrospective cohort
Study methodology	Data source: Consecutive patients with heart failure due to left ventricular systolic dysfunction who had undergone evaluation at the heart failure clinic of the Castle Hill Hospital of the University of Hull, UK, between November 2001 and October 2005. The 6 minute walk test was conducted using a standardised protocol. Blood samples for NT-proBNP analysis were taken using EDTA vacutainers and centrifuged at 4 degrees immediately after collection to separate out the plasma. Analysis was made using a fully automated Elecsys Roche Diagnostics Analyser. Samples were stored at -80 degrees until batch analysed.
Number of patients	n= 676
Patient characteristics	People with heart failure due to left ventricular systolic dysfunction Age (years): 73.8 (9.9) Male %: 76 Family origin not reported Setting: Castle Hill Hospital, Hull Country: UK Inclusion criteria: Diagnosis of systolic HF, on stable medication for at least 1 month prior to inclusion.

Reference	Frankenstein 2009[480]
	Exclusion criteria: History of pulmonary disease as identified by a peak expiratory flow <70% expected, valvular heart disease, conditions possibly affecting peripheral muscle function (such as thyroid dysfunction, severe electrolyte disturbance) and cardiac decompensation requiring inotropic support within the 3 months prior to study inclusion.
Target condition(s)	Mortality at 1 year Number of events: 160 (24%)
Risk tool(s)	Untitled (6MWT + NT-proBNP) Derivation: Derived within the same study in a separate cohort of people
Statistical measures	c-statistic: 0.675
Source of funding	Not reported
Limitations	Risk of bias: High (study reported no calibration data) Indirectness: No indirectness Usability: Yes
Comments	

Reference	Kanwar 2017[724]
Study type	Retrospective cohort
Study methodology	Data source: INTERMACS registry, a database of pre- and postimplant variables for patients in the United States who receive mechanical circulatory support devices that are approved by the FDA. Data were collected from over 150 participating institutions. Using the numerical value of HMRS, patients were categorised as low (<1.58), mid (1.58-2.48) or high (>2.48) risk.
Number of patients	n= 11,523
Patient characteristics	People with heart failure with a continuous flow LVAD Age, years (mean (SD)): 57(13) Female %: 21 Family origin not reported

1

Reference	Kanwar 2017[724]
	Setting: Multicentre (over 150 hospitals) Country: United States Follow up: median 3.8 years Inclusion criteria: Patients aged ≥ 18 years who received a continuous flow LVAD as the primary implant between 2010 and 2015 (2010 to ensure that only the latest pump technology was included and 2015 to ensure minimum 90 day follow-up) Exclusion criteria: Patients with missing data points (n=1739) that prevented calculation of HMRS and those where the pump flow was not categorised as continuous flow (n=526).
Target condition(s)	Mortality at 1 year Number of events: 3,146 (reported as 27.3%)
Risk tool(s)	HeartMate II Risk Score (HMRS) Derivation: Derived in Cowger 2013[325]
Statistical measures	AUC: 0.59
Source of funding	Funding provided by the National Institute of Health Division of National Heart, Lung, and Blood Institute Grant.
Limitations	Risk of bias: High (no calibration data reported) Indirectness: No indirectness Usability: Yes
Comments	

1

Reference	Kao 2012[725]
Study type	Retrospective analysis of RCT data
Study methodology	Data source: BEST: Data from the Beta-blocker Evaluation of Survival Trial (BEST) was used in this study. People 18 years or above were recruited from a range of medical centres and hospitals in the USA. All participants had NYHA class III or IV HFREF that was due to a primary or secondary dilated cardiomyopathy as well as a left ventricular ejection fraction of 35% or lower. All participants were required to have received optimal medical therapy, including the use of angiotensin-converting–enzyme inhibitors (if tolerated), for at least one month.

Reference	Kao 2012[725]
Number of patients	n= 1121 (BEST)
Patient characteristics	BEST People with NYHA class III or IV HFREF (LVEF≤35%). Age (years) %: <30: 6.2 30-45: 26.6 45-60: 39.7 >60: 27.5 Male %: 67.4 Family origin: White, non-Hispanic: 59.9 Black, non-Hispanic: 32.1 Hispanic: 6.3 Asian/Pacific Islander: 0.9 American Indian: 0.5 Other: 0.3 Setting: Multicentre Country: USA Inclusion criteria: People with NYHA class III or IV and LVEF≤35% Exclusion criteria: Participants were considered ischemic if they had ≥70% obstruction in a major epicardial coronary artery by angiography or evidence of prior myocardial infarction and were excluded.
Target condition(s)	Mortality at 1 year Number of events: 107 (reported as observed one year mortality of 9.6%)
Risk tool(s)	Seattle Heart Failure Model

Reference	Kao 2012[725]
	Derivation: Seattle Heart Failure Model was derived in Levy et al, 2006[873]
Statistical measures	c-statistic: BEST cohort: 0.713 Predicted versus observed 1 year mortality: 11.0% vs 9.6%
Source of funding	The work in this manuscript was supported by the following United States National Institutes of Health Grants. Kao: NHLBI 2T32 NHL007822-12 (PI: P. Buttrick). Wagner, Robertson, Lowes: NHLBI 5 P20 HL101438-01 (PI: Brian Lowes). The original BEST Study was funded by the Veteran's Administration Cooperative Studies Program, the National Heart, Lung, and Blood Institute, Intercardia Pharmaceutical Company and Arca Biopharma, Inc.
Limitations	Risk of bias: Low Indirectness: Serious indirectness (patients were recruited previous to 2001, when treatment guidelines for CHF changed) Usability: Yes
Comments	

1

Reference	Ketchum 2012[754]
Study type	Retrospective cohort
Study methodology	Data source: The primary efficacy population from the AdreView Myocardial Imaging for Risk Evaluation in Heart Failure (ADMIRE-HF) trial was examined in this study. The population consisted of 961 NYHA II-III heart failure patients with impaired systolic function (ejection fraction ≤35%) who were on guideline recommended medical therapy. Subjects were followed for a maximum of 2 years after cardiac MIBG imaging. The original trail was closed and the primary data analysed after a prespecified number of cardiac end point occurred. 470 of the surviving patients who did not reach 2 years of follow-up were subsequently enrolled in ADMIRE-HFX and underwent additional surveillance to reach two full years of follow-up. The combined dataset from the original and extension trials was used for the present analysis. Baseline clinical data recorded prior to administration of MIBG were used to calculate the SHFM-D.
Number of patients	n= 961
Patient characteristics	People with NHYA class II-III heart failure and impaired systolic function (ejection fraction ≤35%) who were on guideline recommended medical therapy. From July 27, 2005 to February 20, 2008. Age (years): 62±12 Male %: 80

Reference	Ketchum 2012[754]
	Family origin not reported Setting: Multicentre Country: USA Inclusion criteria: People with NHYA class II-III heart failure and impaired systolic function (ejection fraction ≤35%) who were on guideline recommended medical therapy. Exclusion criteria: Functioning cardiac pacemaker (including for resynchronization) or had ever received electrical therapy (defibrillation or pacing, including appropriate ICD shock) for a ventricular arrhythmia.
Target condition(s)	Mortality at 1 year Number of events: 101 deaths in a mean follow-up of 21 months
Risk tool(s)	Seattle Heart Failure Model-D Derivation: Seattle Heart Failure Model-D was derived in Levy et al, 2009[872]
Statistical measures	AUC: 0.69 Predicted versus observed mortality at 1 year: 95.1±0.1% vs 94.6±0.7%
Source of funding	Not reported
Limitations	Risk of bias: Low Indirectness: No indirectness Usability: Yes
Comments	

1

Reference	Ky 2012[818]
Study type	Retrospective cohort
Study methodology	Data source: The Penn Heart Failure Study is a National Heart, Lung, and Blood Institute-sponsored multicentre cohort study of outpatients with chronic heart failure recruited from referral centres at the University of Pennsylvania (Philadelphia, PA), Case Western University (Cleveland,

Reference	Ky 2012[818]
	OH), and the University of Wisconsin (Madison, WI). The resultant cohort spans a full spectrum of heart failure severity ranging from mild disease to severe disease requiring advanced therapies. At the time of study entry, detailed clinical data were obtained using standardised questionnaires administered to the patient and physician, with verification through medical records. Blood samples were obtained at enrolment, processed, and stored at -80ºC UNTIL TIME OF ASSAY. Follow-up events including all-cause mortality and cardiac transplantation were prospectively ascertained every 6 months through patient contact and verified through death certificates, medical records, or contact with patients' families by research personnel.
Number of patients	n= 1513
Patient characteristics	People with a clinical diagnosis of heart failure as determined by a heart failure specialist Age (years): 56 (15) Male %: 66 Aetiology: Systolic heart failure: 86% Ischemic heart failure: 30% Family origin %: White: 74 African American: 22 Other: 4 Setting: Multicentre Country: USA Inclusion criteria: The primary inclusion criterion is a clinical diagnosis of heart failure as determined by a heart failure specialist. Exclusion criteria: Participants with noncardiac condition resulting in an expected mortality of <6 months as judged by the treating physician, or if they were unable to provide consent.

Reference	Ky 2012[818]
Target condition(s)	Mortality at 1 year Number of events: 187 deaths over a maximum follow-up period of 5 years
Risk tool(s)	Seattle Heart Failure Model-D Derivation: Derivation: Seattle Heart Failure Model-D was derived in Levy et al, 2009[872]
Statistical measures	AUC: 0.76 (0.708-0.813) Predicted versus observed 1 year mortality: 93.7% vs 94%
Source of funding	Lead author was supported by the National Institutes of Health and the Heart Failure Society of America Research Fellowship Award. Assay support was provided by Abbott Diagnostics and Critical Diagnostics.
Limitations	Risk of bias: Low Indirectness: Unclear (recruitment dates of cohort not reported) Usability: Yes
Comments	

Reference	Lee 2003[849]
Study type	Retrospective cohort
Study methodology	Data source: Newly admitted patients with a primary diagnosis of heart failure were identified. Of these patients, the cohort was further refined by only including patients with a clinical heart failure presentation who met the Framingham heart failure criteria. Recruited between April 1997 and March 1999). Hospitals included in this study had a minimum yearly volume of more than 100 heart failure patient admissions during the years of sampling. The potential candidate variables were either presentation features (eg, vital signs) or other data abstractable from the clinical records up to the first 24 hours of hospital presentation (eg, laboratory values, pre-existing comorbid conditions and were classified as demographic characteristics, presenting clinical and laboratory features, or pre-existing comorbid conditions. Comorbidity data were subcategorized according to the disease moieties of the Charlson comorbidity index. These included cancer, dementia, diabetes mellitus, chronic obstructive pulmonary disease, cerebrovascular disease, peripheral vascular disease, cirrhotic liver disease, prior myocardial infarction, and renal indices (serum blood urea nitrogen and creatinine concentrations). Hyponatremia and hypokalemia were defined by the lower limit of the normal biochemical range. We also collected information when available on left ventricular function via echocardiography, radionuclide angiography, or cardiac catheterization. Data abstraction from hospital records was conducted by highly experienced cardiology nurse abstractors using a computerized

Reference	Lee 2003[849]
	instrument with preprogrammed range checks.
Number of patients	n= 1407
Patient characteristics	Newly admitted patients with a primary diagnosis of heart failure Age (years): 75.3 (11.8) Female %: 50.5 LVEF<0.40: 47.7% Family origin: Not reported Setting: 14 hospitals Country: Canada Inclusion criteria: Not reported Exclusion criteria: People who developed heart failure after admission (i.e., in hospital complication), patients transferred from another acute care facility, those aged 105 years or older, non-residents and those with an invalid health card number
Target condition(s)	Mortality at 1 year 429 deaths at 1 year (30.5%)
Risk tool(s)	Untitled risk score Derivation: Derived within the same study in a separate cohort (external validation)
Statistical measures	AUC: 0.76
Source of funding	This study was supported by a grant from the Ontario Ministry of Health (Ontario Program for Optimal Therapeutics) and by a grant to the Canadian Cardiovascular Outcomes Research Team from the Canadian Institutes of Health Research and the Heart and Stroke Foundation.
Limitations	Risk of bias: High (no calibration data reported)

Reference	Lee 2003[849]
	Indirectness: Serious indirectness (patients were recruited previous to 2001, when treatment guidelines for CHF changed) Usability: Yes
Comments	

Reference	Levy 2006[873]
Study type	Retrospective cohort
Study methodology	Data source: The study used data previously collected in 6 cohorts of patients with predominantly left ventricular systolic heart failure. One cohort was used to develop the model (the Prospective Randomized Amlodipine Survival Evaluation [PRAISE1]; n=1125), and 5 other cohorts (n=9942) were used to prospectively validate the model. PRAISE1 was a randomized trial of amlodipine versus placebo among 1153 patients in the United States and Canada with ejection fraction (EF) <30% and New York Heart Association (NYHA) functional class IIIB to IV heart failure. We excluded 32 patients with incomplete baseline data. Evaluation of Losartan in the Elderly (ELITE2) was a randomized trial of captopril versus losartan among 3152 patients in 46 countries with EF ≤40%, age ≥60 years, and NYHA class II to IV heart failure. We excluded 165 patients with incomplete baseline data. Valsartan Heart Failure Trial (Val-HeFT) was a randomized trial of valsartan versus placebo in 5010 patients in 16 countries with EF ≤40 and NYHA class II to IV heart failure. Allopurinol use and implantable cardioverter/defibrillator (ICD) use were not available. We excluded 1 patient with probable data entry error for bumetidine. University of Washington (UW) was a prospective cohort study of 148 consecutive outpatients at a tertiary US heart failure clinic. Randomized Enbrel North American Strategy to Study Antagonism of Cytokines (RENAISSANCE) was a randomized trial of etanercept (Enbrel, Amgen, Thousand Oaks, Calif) in 925 patients with NYHA class II to IV heart failure and EF ≤30 in the United States and Canada. Italian Heart Failure Registry (IN-CHF) is a database of consecutive heart failure patients seen by local participating cardiologists in Italy and entered into a national database. There were no exclusion criteria for entry in the registry, and patients with any heart failure etiology, age, EF, or comorbidities could be enrolled. For the IN-CHF, percent lymphocytes were imputed with the use of white blood cell count and other variables. Potassium-sparing diuretic use was not available. In UW, RENAISSANCE, and Val-HeFT, any patients with missing data were assigned the median value for the covariate in that data set, except for missing drug or device variables, in which case they were assigned no drug/device. In PRAISE1, ELITE2, Val-HeFT, RENAISSANCE, and In-CHF, events were classified by a centralized adjudication committees. In the UW cohort, events were classified by one of the study cardiologists (W.C.L.) using review of medical records. For this analysis, the primary outcome was survival free of left ventricular assist device (LVAD) implantation or cardiac transplantation. Death, rather than LVAD implantation or transplantation, represented the majority of events (98%) in these data sets.
Number of patients	• ELITE2, n=2,987 • RENAISSANCE, n=925 • Val-HeFT, n=5010

Reference	Levy 2006[873]			
	• IN-CHF, n=872			
Patient characteristics	ELITE2 (RCT)	RENAISSANCE (RCT)	Val-HeFT (RCT)	IN-CHF (registry data)
	People with EF≤40%, age≥60 years and NYHA class II to IV heart failure Age (years): 71.7±7 Male %: 69 Family origin not reported Setting: Multicentre Country: 46 countries Inclusion criteria: People with EF≤40%, age≥60 years and NYHA class II to IV heart failure Exclusion criteria: Not reported	People with EF≤30% and NYHA class II to IV heart failure Age (years): 62±12 Male %: 78 Family origin not reported Setting: Multicentre Country: USA and Canada Inclusion criteria: Age 18 to 85 years; NYHA class II to IV; ischemic or nonischemic etiology; left ventricular ejection fraction ≤0.30; stable doses of diuretic, ACE inhibitor (unless not tolerated), and β-blocker and/or spironolactone (if taking) for ≥3 months; and 6-minute walk distance of <375 m (or <425 m if hospitalized for CHF within previous 6 months). Exclusion criteria: Severe infection within 1 month, surgically correctable causes of heart failure, other serious illness, acute myocardial infarction or	People with EF≤40% and NYHA class II to IV heart failure Age (years): 63±11 Male %: 80 Family origin not reported Setting: Multicentre Country: 16 countries Inclusion criteria: Men and women 18 years old or older with a history and clinical findings of heart failure for at least three months before screening were eligible. Patients had heart failure of New York Heart Association (NYHA) class II, III, or IV and were clinically stable. To be eligible, they had to have been receiving for at least two weeks a fixed-dose drug regimen that could include ACE inhibitors, diuretics, digoxin, and beta-blockers. In addition, they had to have documented left ventricular dysfunction with an ejection fraction of less than 40 percent	People with heart failure of any etiology, age, EF or comorbidity Age (years): 64±12 Male %: 76 Family origin not reported Setting: Multicentre Country: Italy Inclusion criteria: People with heart failure of any etiology, age, EF or comorbidity Exclusion criteria: No exclusion criteria

Reference	Levy 2006[873]			
		hospitalization (3 months), and recent (3 months) or planned surgery/coronary revascularization.	and left ventricular dilatation with an echocardiographically measured short-axis internal dimension at end diastole greater than 2.9 cm per square meter of body-surface area. Exclusion criteria: Not reported	
Target condition(s)	1 year survival free from LVAD or transplantation. The study reported the composite end point of death, transplantation, and left ventricular assist device implantation. Over 90% of the overall events were mortality. Number of events: • ELITE2: 88.5%±0.6 • RENAISSANCE: 83.3±1.4 • Val-HeFT: 91.0±0.4 • IN-CHF: 86.7±1.2			
Risk tool(s)	Derivation: The tool was derived within the same study using a separate data set comprising participants of the PRAISE trial[1098]			
Statistical measures	1-Year ROC: • ELITE2: 0.679 (0.65-0.71) Predicted versus observed 1 year survival: 90.5±0.1% vs 88.5±0.6% R^2: 0.97 • RENAISSANCE: 0.682 (0.63-0.73) Predicted versus observed 1 year survival: 83.8±0.5% vs 83.3±1.4% R^2: 0.97 • Val-HeFT: 0.694 (0.68-0.72) Predicted versus observed 1 year survival: 90.9±0.1% vs 91.0±0.4% R^2: 0.98 • IN-CHF: 0.749 (0.70-0.80) Predicted versus observed 1 year survival: 89.6±0.4 vs 86.7±1.2% R^2: 0.99			

Reference	Levy 2006[873]
Source of funding	Supported in part by an unrestricted gift from Amgen.
Limitations	ELITE2 Risk of bias: Low Indirectness: Serious indirectness (patients were recruited previous to 2001, when treatment guidelines for CHF changed) Usability: Yes RENAISSANCE Risk of bias: Low Indirectness: Serious indirectness (patients were recruited previous to 2001, when treatment guidelines for CHF changed) Usability: Yes Val-HeFT Risk of bias: Low Indirectness: Serious indirectness (patients were recruited previous to 2001, when treatment guidelines for CHF changed) Usability: Yes IN-CHF Risk of bias: Low Indirectness: Unclear (recruitment dates of cohort not reported) Usability: Yes
Comments	

Reference	May 2007[961]
Study type	Retrospective cohort
Study methodology	Data source: Study participants were drawn from the cardiac catheterization reigistry of the Intermountain Heart Collaborative Study. The population studied included consecutive patients with HF undergoing coronary angiography at LDS Hospital (Salt Lake City, Utah) from 1993 to

Reference	May 2007[961]
	2005. HF was defined as a decrease in left ventricular function characterized by an EF≤40% or a physician reported clinical HF diagnosis (i.e. AmericanCollege of Cardiology/American Heart Association stage B/C). At the time of study entry (i.e., at angiography), patient demographic information was collected including age, gender, HF etiology, NYHA class, blood pressure, and when available EF, as determined by left ventriculography or (in its absence) by echocardiography. Documentation was made regarding whether the patient had a biventricular pacer, an ICD, or a biventricular ICD. Discharge medications were also recorded, including statins, β-adrenergic receptor blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and diuretics. Laboratory assessments made during the index hospitalisation were stored electronically for future use. Diabetes status was categorized as normal (fasting glucose level >100 mg/dl), intermediate (100 to 125 mg/dl), or diabetic (>125 mg/dl) or a clinical diagnosis of diabetes mellitus. Deaths were determined by telephone survey, hospital records, and Utah State Health Department records (death certificates) and were verified through Social Security death records.
Number of patients	n= 4,077
Patient characteristics	People with HF (defined as a decrease in left ventricular function characterized by an EF≤40% or a physician-reported clinical HF diagnosis (i.e., American College of Cardiology/American Heart Association stage B/C) undergoing coronary angiography. Age (years): 67.0 (range 19-96) Male %: 61.4 Family origin not reported Setting: LDS Hospital (Salt Lake City, Utah) Country: USA Inclusion criteria: People with HF (defined as a decrease in left ventricular function characterized by an EF≤40% or a physician-reported clinical HF diagnosis (i.e., American College of Cardiology/American Heart Association stage B/C) undergoing coronary angiography. Exclusion criteria: Not reported
Target condition(s)	Mortality at 1 year Number of events: 917 (20.2%). The study reported the composite end point of death, transplantation, and left ventricular assist device

Reference	May 2007[961]
	implantation. Over 90% of the overall events were mortality.
Risk tool(s)	Seattle Heart Failure Model Derivation: Seattle Heart Failure Model was derived in Levy et al, 2006[873]
Statistical measures	AUC: 0.70 (0.68-0.72) R^2: 0.99
Source of funding	Not reported
Limitations	Risk of bias: Low Indirectness: Serious indirectness (a proportion of patients were recruited previous to 2001, when treatment guidelines for CHF changed) Usability: Yes
Comments	

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Reference	Rector 2006[1189]
Study type	Retrospective cohort
Study methodology	Data source: Inpatient data files were electronically searched to find records that listed heart failure (International Classification of Diseases, 9th Clinical Modification codes 428 to 428.9) as the primary diagnosis between January 1999 and May 2003. Medical records were reviewed to confirm admission to the hospital by the presence of a hospital discharge summary. The first qualifying admission for each person was analysed. Medical records were searched electronically (demographic, vital sign, laboratory result fields) and manually (text of discharge summaries and notes) for data corresponding to the date of admission for heart failure. Comorbidities were abstracted from the discharge summaries. A notification screen identifies electronic medical records of deceased individuals. Records without this notification were reviewed for evidence that medical care was received more than 1 year after the index admission as a confirmation the person was alive.
Number of patients	n= 769
Patient characteristics	People admitted to the Minneapolis VA medical centre with a primary diagnosis of heart failure Age (years): 73±10 Male %: 98 Ischemic heart disease: 68%

Reference	Rector 2006[1189]
	Family origin not reported Setting: Minneapolis VA Medical centre Country: Canada Inclusion criteria: Not reported Exclusion criteria: Cases of heart failure that clearly developed after admission were excluded.
Target condition(s)	Mortality at 1 year Number of events: 194 deaths at 1 year
Risk tool(s)	Untitled risk score Derivation: The untitled risk score was derived in Lee 2003[849]
Statistical measures	c-statistic: 0.71 (0.67-0.76) Observed vs predicted mortality for 5 risk scores: <60: 6.8% vs 7.1% 61 to 90: 14.6% vs 14.2% 91 to 120: 25.7% vs 27.0% 121 to 150: 50.9% vs 47.7% >150: 50.0% vs 67.2%
Source of funding	Supported by resources and facilities at the Minneapolis Veterans Administration Medical Centre, VA Clinical Science Research & Development (grant no. 04S-CRCOE-001) and VA Health Services Research & Development (Grant no HFP-98-001)
Limitations	Risk of bias: Low Indirectness: Serious indirectness (a proportion of patients were recruited previous to 2001, when treatment guidelines for CHF changed) Usability: Yes

Reference	Rector 2006[1189]
Comments	

1

Reference	Regoli 2013[1194]
Study type	Retrospective cohort
Study methodology	Data source: Retrospective data were collected from people who consecutively underwent CRT device implantation between January 2002 and January 2011 at 5 European centres: Division of Cardiology, Fondazione Cardiocentro Ticino, Lugano, Switzerland; Good Hope Hospital, Birmingham, UK; Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; Istituto Clinico Humanitas, Castellanza, Italy; and Presidio Ospedaliero ASL Roma B Policlinico Casilino, Roma, Italy. Because since 2002 clinical practice guidelines on treatment of heart failure and sudden death have changed considerably, CRT (and device type) indication followed the available criteria at the time of implantation. Most patients presented an established indication for CRT: QRS complex duration ≥120MS, left ventricular ejection fraction (LVEF) ≤ 35%, and were receiving optimal medical treatment for HF including beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and diuretics at the highest tolerated dosage. Indications for CRT-P were based on clinical judgement, the presence of co-morbidities and patient willingness. All people were seen at regular time intervals (1,3,6 and 12 months, and at every 6 months thereafter). Device programming and CRT optimization were performed as clinically indicated. At each centre, death events were adjudicated by two independent investigators by reviewing patient medical records. Patients who underwent heart transplant or ventricle assist device implantation were also censored.
Number of patients	n= 1139
Patient characteristics	People who underwent CRT device implantation between January 2002 and January 2011 Age (years): 67.2±10.7 Male %: 77.4% Family origin not reported Setting: 5 centres Country: Europe (Italy, Switzerland and UK) Inclusion criteria: People who underwent CRT device implantation between January 2002 and January 2011

Reference	Regoli 2013[1194]
	Exclusion criteria: Not reported
Target condition(s)	Mortality at 1 year Number of events: 300 deaths during a median follow-up of 40.1 months (IQR 25.2-60.0 months)
Risk tool(s)	Seattle Heart Failure Model Derivation: Seattle Heart Failure Model was derived in Levy et al, 2006[873]
Statistical measures	AUC-ROC: 0.66
Source of funding	Not reported
Limitations	Risk of bias: Low Indirectness: No indirectness Usability: Yes
Comments	Unclear whether or not outcome was a composite of death and transplantation. Only 7 urgent cardiac transplantations were reported, therefore outcome >90% death.

Reference	Sartipy 2014[1246]
Study type	Retrospective cohort
Study methodology	Data source: The Swedish Heart Failure Registry (S-HFR)/RiksSvikt was created in 2003. It is an Internet-based registry in which participating units can record details of their HF patients online directly and transfer data from standardized forms or from computerized patient documentation. During an initiation visit, the registry coordinator trains personnel from the participating units on how to register patients and how to use the registry. The S-HFR consists of about 70 variables including demography, concomitant diseases, diagnostic procedures, haemodynamics, laboratory data, and medication. After 1 year of follow-up, data on mortality and morbidity are collected from National official databases. Information concerning medication, quality of life, and functional capacity are collected from a questionnaire sent out to all patients after 1 year of follow-up (.80% response rate). Sixty of the variables in the registry are obligatory and the other 10 are optional. However, a variable can be recorded as unknown. Patients diagnosed with HF should be registered either at discharge from hospital (within 1 month) or following an out-patient visit and it is recommended that patients are re-registered after every new hospitalization due to HF. Between 11 May 2000 and 1 November 2012, there were 78,692 registrations in the Swedish Heart Failure Registry from 66 of 77 hospitals and

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Reference	Sartipy 2014[1246]
	115 of 1011 primary care outpatient clinics in Sweden, representing 51,064 unique patients.
Number of patients	n= 51,043
Patient characteristics	People with clinician judged heart failure. Age (mean) (years): 75 Female %: 40 Heart failure with preserved EF (EF≥40%): 56% NYHA class I or II: 57% NYHA class III: 38% NYHA class IV: 5% Family origin not reported Setting: Multicentre Country: Sweden Inclusion criteria: Clinician judged heart failure Exclusion criteria: Not reported
Target condition(s)	Mortality at 1 year Number of events: 10,208 (reported as overall mortality at 1 year of 20.2%)
Risk tool(s)	MAGGIC project heart failure risk score Derivation: MAGGIC project heart failure risk score was derived in Pocock 2013[1160]
Statistical measures	<u>MAGGIC project heart failure risk score</u> AROC: 0.777 Predicted versus observed 1 year mortality: 16.8% vs 20.2%

Reference	Sartipy 2014[1246]
Source of funding	The Swedish Heart Failure Registry is funded by the Swedish National Board of Health and Welfare, the Swedish Association of Local Authorities and Regions, the Swedish Society of Cardiology and the Swedish Heart-Lung Foundation. This work was supported by the Swedish Heart-Lung Foundation and the Stockholm County Council.
Limitations	Risk of bias: High (model showed poor calibration and was not recalibrated) Indirectness: Unclear (recruitment dates of cohort unclear) Usability: Yes
Comments	

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Reference	Senni 2013 [1267]
Study type	Prospective and retrospective
Study methodology	Data source: Subjects recruited at 16, from Cardiology and Internal Medicine Units who were able to enrol at least 100 HF participants consecutively during a 6- to 12- month period between 2002 and 2006. Participating institutions had a minimum yearly volume of >100 HF admissions during the sampling period and had taken part in registries or surveys on HF. Participants were recruited either at discharge or in the outpatient clinic. For prospectively enrolled subjects, information was gathered at hospital discharge or at the index outpatient visit. For retrospective enrolment, we reviewed hospital records identified through a primary diagnosis of HF, as well as outpatient clinic records of participants followed up at different institutions. We considered clinical, laboratory, and echocardiographic data within the last 6 months prior to enrolment. Patients were followed up at each centre after the index discharge or outpatient visit (time 0). One-year survival status was ascertained locally by follow-up visits or chart review, telephone interview with the patient, or his/her family, or primary care physician, or by examination of death certificates.
Number of patients	n= 4258
Patient characteristics	People with a diagnosis of heart failure based on symptoms and signs of congestion and objective evidence of cardiac dysfunction at rest. Age (median IQR) (years): 70 (60-77) NYHA class III-IV: 33.6% LVEF<20%: 4.4% LVEF≥50%:26.1%

Reference	Senni 2013 [1267]
	Female %: 38.7 Family origin not reported Setting: Multicentre Country: Countries in Europe Inclusion criteria: A diagnosis of HF based on symptoms and signs of congestion and objective evidence of cardiac dysfunction at rest. People with HF symptoms and a LVEF≥50% had to show lung congestion by chest x-ray. Exclusion criteria: People who died during the index admission, people with an indication for any cardiac surgical procedure, other than transplantation, people with metastatic cancer.
Target condition(s)	Mortality at 1 year Number of events: 534 deaths (12.5%)
Risk tool(s)	3C-HF score Derivation: Derived within the same study in a separate cohort (external validation)
Statistical measures	c-statistic: 0.82 (0.81-0.83) Brier score: 0.082
Source of funding	The work was supported by Fondiazone Credito Bergamasco (CREBERG). The Homburg centre was funded by Deutsche Forschungsgemeinschaft (DFG, KFO 196), BMBF, Kompetenznetzwerk Herzinsuffizienz.
Limitations	Risk of bias: Low Indirectness: No indirectness Usability: Yes
Comments	

Reference	Spinar 2016[1319]
Study type	Retrospective cohort
Study methodology	Data source: The validation AHF dataset of the GREAT registry consists of nine cohorts from Italy (n=1828), Spain (n=1631), France (n=696), Argentina (n=675), Finland (n=584), Switzerland (n=370), USA (n=209), Tunisia (n=186) and Austria (n=136). The cut-off levels for anaemia were haemoglobin <130g/l in men and <120g/l in women, whereas that for hyponatraemia was sodium <135 mmol/l, and creatinine ≥130umol/l. Atrial fibrillation was considered if the patient showed symptoms or a history of any form of AF (paroxysmal, persistent or permanent). Diabetes was considered when present in the patients' history or newly diagnosed.
Number of patients	n= 6315
Patient characteristics	People with acute heart failure Age (mean) (years): 77 (52-91) Female %: 44.5 Family origin not reported Setting: Multicentre Country: Spain, France, Argentina, Finland, Switzerland, USA, Tunisia, Austria Inclusion criteria: Not reported Exclusion criteria: Not reported
Target condition(s)	Mortality at 1 year Number of events: 1995 deaths (31.6%)
Risk tool(s)	AHEAD score Derivation: Derived within the same study in a separate cohort (external validation)
Statistical measures	AUC: 0.631
Source of funding	Supported by a Ministry of Health's project of conceptual development of research organisation grant and the European Regional Development

Reference	Spinar 2016[1319]
	Fund.
Limitations	Risk of bias: Very high (inclusion criteria for cohort unclear, no calibration data reported) Indirectness: Unclear (recruitment dates of cohort unclear) Usability: Yes
Comments	

Appendix G: Health economic evidence tables

G.1 BNP and NT-proBNP in diagnosing heart failure

<table>
<tr><th>Study</th><th colspan="4">Monahan 2017</th></tr>
<tr><th>Study details</th><th>Population & interventions</th><th>Costs</th><th>Health outcomes</th><th>Cost effectiveness</th></tr>
<tr>
<td>Economic analysis: CUA (health outcome: QALYs)

Study design: Decision tree.
Approach to analysis:
Patients categorised in decision tree according to diagnostic strategy pathway based on the diagnostic accuracy of the strategy.
Confirmed diagnosis leads to initiation of drug therapy if HF-REF, no treatment if HF-PEF.
Assumed survival benefit and hospitalisation benefit for early detection.
Missed heart failure diagnosis assumed to delay diagnosis by 6 months.</td>
<td>Population:
Primary care patients aged 55 years or over presenting to GP with symptoms suggestive of HF were recruited across 28 central England practices in the UK

Cohort settings:
Start age: 74
Male: 41%

Intervention 1:
MICE clinical decision rule, upper cut-off – patient presenting with symptoms suggestive of heart failure will be referred straight for echocardiography if they have a history of myocardial infarction, basal crepitations, or is a male with ankle oedema. Otherwise patient receives NT-proBNP test and is referred for echocardiography if they fit one of the following criteria:
Female, without ankle oedema, NT-proBNP ≥1060pg/ml
Male, without ankle</td>
<td>Total costs (mean per patient):
Intervention 1: £167
Intervention 2: £191
Intervention 3: £142
Intervention 4: £241
Intervention 5: £196
Intervention 6: £119
(95% CI: NR; p=NR)

Currency & cost year:
2013/14 UK pounds

Cost components incorporated:
Included costs of GP appointment, echocardiography referral, NT-proBNP test, early treatment drugs, and hospitalisations.</td>
<td>QALYs (mean per patient):
Total QALYs not reported. Incremental compared to do nothing:
Intervention 1: 0.0050
Intervention 2: 0.0057
Intervention 3: 0.0051
Intervention 4: 0.0063
Intervention 5: 0.0059
Intervention 6: -
(95% CI: NR; p=NR)</td>
<td>Full incremental analysis [b]:
<table>
<tr><th>Int [b]</th><th>Cost [b]</th><th>QALY [b]</th><th>Inc cost [d]</th><th>Inc QALY [d]</th><th>ICER [d]</th></tr>
<tr><td>6</td><td>£119</td><td>0</td><td colspan="3">Baseline</td></tr>
<tr><td>1</td><td>£167</td><td>0.0050</td><td colspan="3">Dominated</td></tr>
<tr><td>3</td><td>£142</td><td>0.0051</td><td colspan="3">£4,400</td></tr>
<tr><td>2</td><td>£191</td><td>0.0057</td><td colspan="3">Extendedly dominated</td></tr>
<tr><td>5</td><td>£196</td><td>0.0059</td><td colspan="3">£69,000</td></tr>
<tr><td>4</td><td>£241</td><td>0.0063</td><td colspan="3">£125,100</td></tr>
</table>

Analysis of uncertainty:
Both probabilistic and deterministic sensitivity analyses were undertaken.
The probabilistic sensitivity analysis showed that the probability that Intervention 3 is the optimal strategy at £20,000/QALY is 99.9%.
The following scenarios were explored in the deterministic sensitivity analyses:
Doubling and halving the cost of a NT-proBNP test
Altering drug efficacies to their lower and upper confidence intervals respectively
Substituting in branded drug therapy prices for generic drug therapy prices</td>
</tr>
</table>

Analysis of individual level data for EQ-5D. Unit costs applied. **Perspective:** UK NHS **Time horizon:** Lifetime **Treatment effect duration:**[(a)] 10 years **Discounting:** Costs: 3.5% ; Outcomes: 3.5%	oedema, NT-proBNP ≥ 660pg/ml • Female, with ankle oedema, NT-proBNP ≥520pg/ml **Intervention 2:** MICE clinical decision rule, lower cut-off – patient presenting with symptoms suggestive of heart failure will be referred straight for echocardiography if they have a history of myocardial infarction, basal crepitations, or is a male with ankle oedema. Otherwise patient receives NT-proBNP test and is referred for echocardiography if they fit one of the following criteria: • Female, without ankle oedema, NT-proBNP ≥620pg/ml • Male, without ankle oedema, NT-proBNP ≥ 390pg/ml • Female, with ankle oedema, NT-proBNP ≥190pg/ml **Intervention 3:** 2010 NICE guideline recommended strategy – patient presenting with symptoms suggestive of heart failure referred straight for echocardiography if they have a history of myocardial ischaemia.			- Increasing the proportion of HF-REF patients from 12% to 24% to 50% and 100% respectively. Intervention 3 remains the most cost effective strategy in the scenarios above, except where the proportion of HF-REF is changed to 50% or above. When proportion of HF-REF is 50% intervention 5 is the most cost effective strategy. When proportion of HF-REF is 100% intervention 4 became the most cost effective strategy.

	Otherwise patient receives NT-proBNP test and is referred for echocardiography if level ≥400pg/ml. **Intervention 4:** Echo all – all patients presenting with symptoms of heart failure referred straight for echocardiography. **Intervention 5:** NT-proBNP 125 – all patients presenting with symptoms of heart failure will have a NT-proBNP test carried out and patient is referred for echocardiography if level is ≥125pg/ml. **Intervention 6:** Do nothing – patients presenting with signs and symptoms are not referred for echocardiography or a NT-proBNP test.			

Data sources
Health outcomes: Diagnostic accuracy data was taken from REFER study[1365]. Baseline survival data for untreated patients was taken from the Framingham heart study. The treatment effect on mortality of ACEi and ARBs were taken from systematic reviews [468] and the treatment effect of BB was taken from a meta-analysis[791]. The probability of a heart failure hospitalisation for a treated patient was identified from Mant et al.[932]. The treatment effect of ACEi and BB was identified from two studies and then used to determine the probability of hospitalisation if untreated[468],[791]. **Quality-of-life weights:** EQ-5D UK tariff. **Cost sources:** PSSRU 2014, 2013/14 NHS reference costs, Department of Health, Payment by Results NHS Tariff 2013/14, and NICE Chronic Heart Failure Costing report.
Comments
Source of funding: Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership. **Limitations:** The analysis used diagnostic accuracy data where the level of NT-proBNP was used as a criterion in determining whether or not the patient had heart failure, therefore introducing incorporation bias to the diagnostic

accuracy results. The committee were concerned that the hospitalisation rates applied in the model were overestimated compared to current clinical practice. The model does not report the outcomes for those who do not have heart failure and no assumptions have been reported for this population. **Other:** None.
Overall applicability:[(e)] Directly applicable **Overall quality**[(f)] Potentially serious limitations

Abbreviations: 95% CI: 95% confidence interval; CUA: cost–utility analysis; da: deterministic analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years

(a) Linear extrapolation undertaken to achieve lifetime horizon
(b) Intervention number in order of least to most effective in terms of QALYs
(c) Incremental cost/QALYs compared to do nothing (intervention 6)
(d) Incremental cost/QALYs/cost effectiveness ratio compared to next most effect treatment option that is not ruled out by dominance or extended dominance. An option is ruled out by dominance when another option has higher QALYs and lower costs. An option is ruled out by extended dominance when it has a higher ICER than the next, more effective, option and so this option can never be the most cost effective. ICERs reported rounded to the nearest £100.
(e) Directly applicable / Partially applicable / Not applicable
(f) Minor limitations / Potentially serious limitations / Very serious limitations

G.2 Cardiac Magnetic Resonance Imaging in heart failure

None.

G.3 Salt and fluid restriction

None.

G.4 Beta-blockers in people with heart failure and atrial fibrillation

None.

G.5 Mineralocorticoid Receptor Antagonists

Study	**Lee 2014** [848]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CUA (health outcome: QALYs)	**Population:** Patients with chronic	**Total costs (mean per patient):**	**QALYs (mean per patient):** Intervention 1: 4.98	**ICER (Intervention 2 versus Intervention 1):** £3,520 per QALY gained (pa)

Study design: Discrete-event simulation model based on one RCT. **Approach to analysis:** Patient-level data from EMPHASIS-HF used to determine risk equations for each event by fitting a distribution to each time to event[1221, 1522]. 25,000 patients were simulated and randomly assigned individual time to events based on the risk equations for each model event. Non-CV mortality assumed to be the same for both arms. Patients exit model if death occurs, or ICD or CRT device is implanted. Otherwise patient remained in model until next event occurred. If discontinued treatment with eplerenone, patient returned to standard care. **Perspective:** UK NHS perspective	systolic heart failure (mean LVEF of 26%); New York Heart Association (NYHA) class II symptoms. **Cohort settings:** Start age: 69 Male: 78% **Intervention 1:** Standard therapy (ACEi and BBs - in line with trial protocol) **Intervention 2:** Eplerenone (starting dose of 25mg daily increased to 50mg daily after 4 weeks) in addition to standard therapy (as above)	Intervention 1: £14,275 Intervention 2: £18,559 Incremental (2−1): £4,284 (95% CI: NR; p=NR) **Currency & cost year:** 2011 UK pounds sterling **Cost components incorporated:** Eplerenone drug costs, concomitant medications, eplerenone treatment initiation (two hospital visits and two sets of blood chemistry tests), disease management and monitoring, HF hospitalisation, other cardiovascular hospitalisation, adverse events associated with eplerenone, adverse events associated with standard care, cost of CRT and ICD devices.	Intervention 2: 6.19 Incremental (2−1): 1.22 (95% CI: NR; p=NR)	95% CI: NR Probability Intervention 2 cost-effective (£20K/30K threshold): NR **Analysis of uncertainty:** Deterministic sensitivity analysis: Varied key inputs and assumptions (risk equation parameters and utility decrement associated with age) using one-way parameter sensitivity analysis using the 95% CI of the parameter distributions. In all cases ICER remains below £5,500. Probabilistic sensitivity analysis for time to event: 100 Monte Carlo simulations gave an overall mean ICER of £6,939 (95% CI: £6,656; £7,222). Probability of eplerenone being cost-effective at £20,000/QALY threshold = 100%. Scenario analysis: Using EMPHASIS-HF data with no extrapolation: ICER = £20,730 2 year time horizon: ICER = £20,101 5 year time horizon: ICER = £6,061 No utility decrement for adverse events, AF or hospitalisations: ICER = £3,558 Increased use of devices: ICER = £3,693 No use of devices: ICER = £2,802

Time horizon: Lifetime **Treatment effect duration:**[(a)] 4 years **Discounting:** Costs: 3.5%; Outcomes: 3.5%				
Data sources				
Health outcomes: EMPHASIS-HF RCT[122182] - Outcomes: HF hospitalisation, other cardiovascular hospitalisation, new onset atrial fibrillation, CRT/ICD implantation, adverse events, discontinuation of eplerenone, cardiovascular mortality, and non-cardiovascular mortality. Baseline utility values and hospitalisation utility decrements are taken from Göhler et al. 2009 [529] which are estimated from EPHESUS trial using EQ-5D (this trial has been excluded from this review due to having a post-MI population). Adverse event utility decrements are taken from Sullivan et al. 2011 [1342] catalogue of EQ-5D scores for the UK, and the utility decrement for new-onset atrial fibrillation is from Berg et al. 2010[155]. **Quality-of-life weights:** EQ-5D - UK tariff (Sullivan et al. 2011 and Berg et al. 2010), Western Europe weighting (Göhler et al. 2009[529]). **Cost sources:** British National Formulary 62, 2011, PSSRU 2011, and the Scottish National Tariff (2010/11).				
Comments				
Source of funding: Pfizer Ltd. **Limitations:** The analysis is based on estimates of relative treatment effect and resource use from a single study, so does not reflect all available evidence in this area. There is cross-over between the trial arms. Utility values are not reported directly from patients of the EMPHASIS-HF trial. Potential publication bias due to the sponsor of the study.				
Overall applicability:[(b)] Directly applicable **Overall quality**[(c)] Potentially serious limitations				

Abbreviations: 95% CI: 95% confidence interval; BNF: British National Formulary; CRT: cardiac resynchronisation therapy; CUA: cost-utility analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICD: Implantable cardioverter defibrillator; ICER: incremental cost-effectiveness ratio; NR: not reported; PSSRU: Personal Social Services Research Unit; QALYs: quality-adjusted life years; RCT: randomised controlled trial.
(a) Best fitting parametric survival models were used to describe time- to- event.
(b) Directly applicable / Partially applicable / Not applicable
(c) Minor limitations / Potentially serious limitations / Very serious limitations

Study	**Tilson 2003** [1389]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: - Cost effectiveness analysis - Reporting cost per life-year (LY) gained	**Population:** - Patients with severe chronic heart failure - NYHA class III & IV and LVEF ≤35	**Currency & cost year:** Euro 2002 **Cost components**	**Health outcomes incorporated:** - Probabilities of death and hospitalisation for	**Cost-effectiveness result:** **Analysis** | **Result** Base-case analysis (pDeath = 0.18; pHosp = 0.25; 1 additional outpatient visit | £291/LY

Study design: - Based on the RALES study - Developed using a Markov Model ○ 3 health states: (1) severe CHF; (2) severe CHF + hospitalisation; (3) death ○ 1-year period before possible transition from one state to another. **Perspective:** Irish public healthcare system **Time horizon:** 10 years **Discounting:** Future costs and outcomes were discounted at 5% and 1.5% respectively.	- Mean age of 65 years **Intervention 1:** Optimal medical management (might include diuretics, ACEi, digoxin, BB, or a combination of these) **Intervention 2:** Spironolactone added to optimal medical management	**incorporated:** - Spironolactone treatment cost (*Irish Monthly Index of Medical Specialties*, July 2002) - Hospitalisation cost for severe heart failure (McGowan B. et al. Cost of treating heart failure in an Irish teaching hospital. *Ir Med Sci* 2001; 169:241-44) - Hospital outpatient visit cost (McGowan B. The clinical and economic aspects of the present management of heart failure in an Irish teaching hospital. MSc thesis, Trinity College Dublin 2001).	the placebo cohort were taken from a cohort of patients followed over 12 months in an Irish teaching hospital - The difference in probabilities of death and hospitalisation for the treatment cohort were taken from RALES - Assumed no difference in death and hospitalisation rates between cohorts after the 2-year mean duration of RALES	for spironolactone cohort; hosp cost = €3,019)	
				Two-way sensitivity analysis – variation of probabilities of death (0.16, 0.21) and hospitalisation (0.21, 0.29)	from £193/LY to £390/LY
				One-way sensitivity analysis – additional outpatient visit required to initiate medication for spironolactone group (1, 2, 4)	from £291/LY to £710/LY
				One-way sensitivity analysis – cost of hospitalisation varied (€1,060; €9,319) (£663; £5,826)	from (£455/LY) to spironolactone cohort dominates (more effective and less costly) the placebo cohort
Data sources					
Health outcomes: See above **Cost sources:** See above					
Comments					
Source of funding: NR **Limitations***:* The study did not incorporate a quality of life measure. The mean age of the population of patients in RALES study was lower than the Irish population of patient with chronic heart failure (65 vs 76 years).Some cost data were taken from published studies and not from Government sources, which can affect their					

relevance.	
Overall applicability:[(a)] Partially applicable	**Overall quality**[(b)] Potentially serious limitations

Abbreviations: RALES = Randomised Aldactone Evaluation Study; NYHA = New York Heart Association Classification; CHF = Chronic Heart Failure; BB = Beta-blockers; ACEi = Angiotensin-converting enzyme inhibitors.
(a) Directly applicable / Partially applicable / Not applicable
(b) Minor limitations / Potentially serious limitations / Very serious limitations

G.6 Iron supplementation for iron deficiency in heart failure

Study	**Gutzwiller 2012**[567]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Simple model based on one clinical trial[78, 79, 308, 464, 566, 1162]. **Approach to analysis:** Simple decision tree model applying resource use and associated unit costs and EQ-5D. **Perspective:** UK NHS **Follow-up:** 24 weeks **Discounting:** Costs: n/a ;	**Population:** Iron-deficient CHF patients (NYHA class II or III) with or without anaemia. **Patient characteristics:** N = 459 Mean age: Intervention 1= 67.4 (SD: 11.1) Intervention 2= 67.8 (SD: 10.3) Male: Intervention 1= 45.2% Intervention 2= 47.7% **Intervention 1:** No iron treatment - placebo (saline solution) arm in FAIR-HF trial. **Intervention 2:**	**Total costs (mean per patient):** Intervention 1: £619 Intervention 2: £768 Incremental (2−1): £149 (95% CI: NR; p=NR) **Currency & cost year:** 2009 Pounds sterling **Cost components incorporated:** Drug, drug administration (no wastage), and hospitalisation for CHF. Cost of adverse events were not taken into account (no clinically relevant differences)	**QALYs (mean per patient):** Intervention 1: 0.298 Intervention 2: 0.336 Incremental (2−1): 0.037 (95% CI: 0.017-0.06; p=NR)	**ICER (Intervention 2 versus Intervention 1):** £3,977 per QALY gained (pa) 95% CI: NR Probability Intervention 2 cost-effective (£20K/30K threshold): 99.66%/99.68% **Analysis of uncertainty:** Univariate sensitivity analysis varying the mean duration of hospitalisations for CHF in the UK; the cost of a hospital day by ±30%; drug costs by ±10% as no confidence intervals were available for these parameters. Further varied QALY difference; proportional reduction in hospitalisation days; frequency of hospitalisation in placebo group on basis of confidence intervals. Results ranged from dominance of IV iron strategy to £12,482 per QALY gained. Frequency and duration of hospitalisation, QALY difference, and cost of hospital day

Outcomes: n/a	Iron repletion with ferric carboxymaltose administered as an IV bolus injection - 4mL equivalent to 200mg of iron until repletion was achieved. Patients receive one injection per week until iron repletion achieved (correction phase). Subsequently, an injection was given every 4 weeks (maintenance phase).			were the most influential parameters. Further variations were: calculation of results considering only cases with complete data on utilities; calculation of costs via NYHA class approach; calculation of utilities using EQ-5D VAS scale scores. None of the parameters tested resulted in an ICER above £20,000 per QALY gained.
Data sources				
Health outcomes: QALYs were calculated using patient-level utility data collected at baseline and at 4, 12 and 24 weeks (within-trial analysis of FAIR-HF) **Quality-of-life weights:** EQ-5D UK tariff. **Cost sources:** NHS Reference costs 2008-2009, BNF 2011, PSSRU 2007, Falkirk & District Royal Infirmary 2006.				
Comments				
Source of funding: Vifor Pharma Ltd, Switzerland. **Limitations:** The FAIR-HF trial did not include British participants, but was mostly performed in European countries with a predominantly Caucasian population. This is unlikely to change the conclusions of cost-effectiveness. Short time horizon may not capture full costs and effects of the intervention. Lack of detailed medical resource use data. Within-trial analysis and so does not reflect full body of available evidence for all comparators; FAIR-HF is one of 3 studies comparing IV iron to no iron treatment. **Other:** None.				
Overall applicability:(a) Directly applicable **Overall quality**(b) Potentially serious limitations				

Abbreviations: 95% CI: 95% confidence interval; CUA: cost-utility analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years.
(a) Directly applicable / Partially applicable / Not applicable
(b) Minor limitations / Potentially serious limitations / Very serious limitations

G.7 Pharmacological treatment for heart failure in people with heart failure and chronic kidney disease

None.

G.8 Coronary revascularisation

None.

G.9 Home-based versus centre-based rehabilitation

Study	**Cowie 2014[327]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CC (no health outcomes) **Study design:** Comparative costing **Approach to analysis:** Analysis of individual resource use from patient case notes for the 5 years following those participating in RCT[329] (Cowie 2011[328], Cowie 2014[327]). Unit costs applied. **Perspective:** UK NHS	**Population:** People with heart failure who have been clinically stable for one month and were on optimised medication dosages. **Patient characteristics:** N = 46 Age: 1. 60.4 2. 69.2 3. 63.3 Male: 1. 100% 2. 87% 3. 87%	**Total costs (mean per patient):** Intervention 1: £9,832 Intervention 2: £7,452 Intervention 3: £7,932 Incremental (2−1): saves £2,380 Incremental (3-1): saves £1,900 Incremental (3-2): £480 (95% CI: NR; p=NR) Cost breakdown (intervention) Intervention 1: £0 Intervention 2: £244 Intervention 3: £216[a] Cost breakdown (admission) Intervention 1: £9,832	The paper states quality of life was almost identical between the comparators and therefore not included in the analysis. The associated RCT[329] (Cowie 2011[328], Cowie 2014[327]) reports that there were no significant differences between or within-group findings from any MLHFQ score, or from the physical component summary of the SF-36. The hospital group's mean SF-36 mental component summary was significantly	**ICERs:** n/a **Analysis of uncertainty:** NR.

Follow-up: 5 years **Discounting:** Costs: NR; Outcomes: n/a	**Intervention 1:** Usual care – included specialist HF nursing input **Intervention 2:** Hospital training – one-hour interval training, aerobic circuit class, twice per week, for eight weeks. **Intervention 3:** Home training – one-hour interval training, aerobic circuit DVD which participants completed twice per week, for eight weeks.	Intervention 2: £7,208 Intervention 3: £7,716 **Currency & cost year:** 2013 UK pounds **Cost components incorporated:** Intervention, hospital admissions, heart rate monitors, booklets and support leaflets, reimbursement of travel expenses.	higher (better) than the controls' (p=0.02) after 8 weeks. The hospital group demonstrated a non-significant trend for maintenance of all QoL scores.	
Data sources				
Health outcomes: n/a. **Quality-of-life weights:** n/a **Cost sources:** NHS salaries Agenda for Change, 2013/14; Information Services Division 2011/12 references.				
Comments				
Source of funding: NR. **Limitations:** Does not include any health outcomes. Small sample size, which has significant impact on cost per patient for the home training group. The baseline patient characteristics are not typical with a very high proportion of males. Furthermore, the usual care group nearly 10 years younger than hospital group suggesting there is selection bias. No discounting was undertaken. **Other:** None.				
Overall applicability:[(b)] Partially applicable **Overall quality**[(c)] Very serious limitations				

Abbreviations: CC: comparative cost; 95% CI: 95% confidence interval; ICER: incremental cost-effectiveness ratio; n/a: not applicable; NR: not reported; QALYs: quality-adjusted life years

(a) Authors note that much of the cost incurred by the home programme was attributable to staffing input required to create the DVD. This would remain a non-recurring fixed cost regardless of the number of participants to whom the intervention was provided. Therefore if the group size was larger, then the cost per patient of the intervention for providing home training would decrease. Excluding DVD production costs the ongoing cost of delivering home-training is £64.

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

G.10 Monitoring

Study	Laramée et al. 2013[835]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** Monte Carlo simulation incorporating all-cause mortality, hospitalisation rates, resource use and quality of life. **Perspective:** UK NHS **Time horizon:** Lifetime horizon was used when the number of patients who were alive differed between the compared cohorts at the end of the trial follow-up. When the same numbers of patients were alive in each trial arm at the end of the trial, the trial period was used as the model time horizon. **Treatment effect**	**Population:** Patients with chronic heart failure due to LVSD and patients with heart failure from any cause. **Cohort settings:** **Age:** NR **Male:** NR **Intervention 1:** Usual care – usual care in the community **Intervention 2:** Clinical assessment – management guided by clinical assessment by a specialist **Intervention 3:** Natriuretic peptide monitoring - Management guided by serial measurement of circulating natriuretic peptide concentration by a specialist	***Patients with CHF and LVSD (TIME-CHF, STARS-BNP, Troughton et al. 2000 and PRIMA subgroup)***		
		Total costs (mean per patient): Intervention 1: n/a Intervention 2: £12,869 Intervention 3: £13,972 Incremental (3−2): £1,103 (95% CI: NR; p=NR)	**QALYs (mean per patient):** Intervention 1: n/a Intervention 2: 4.85 Intervention 3: 5.19 Incremental (3−2): 0.34 (95% CI: NR; p=NR)	**ICER (Intervention 3 versus Intervention 2):** £3,304 per QALY gained (da) 95% CI: NR Probability Intervention 3 cost-effective (£20K threshold): 99.08%
		Patients with CHF and LVSD aged <75 (TIME-CHF)		
		Total costs (mean per patient): Intervention 1: n/a Intervention 2: NR Intervention 3: NR	**QALYs (mean per patient):** Intervention 1: n/a Intervention 2: NR Intervention 3: NR	**ICER (Intervention 3 versus Intervention 2):** £2,871 per QALY gained (pa) 95% CI: NR Probability Intervention 3 cost-effective (£20K threshold): 97.92%
		Patients with CHF and LVSD aged ≥75 (TIME-CHF)		
		Total costs (mean per patient): Intervention 1: n/a Intervention 2: NR Intervention 3: NR	**QALYs (mean per patient):** Intervention 1: n/a Intervention 2: NR Intervention 3: NR	**ICER (Intervention 3 versus Intervention 2):** £5,392 per QALY gained (pa) 95% CI: NR Probability Intervention 3 cost-effective (£20K threshold): 67.50%
		Patients with CHF of any cause (BATTLESCARRED and PRIMA)		
		Total costs (mean per patient): Intervention 1: £7,360 Intervention 2: £8,113	**QALYs (mean per patient):** Intervention 1: 4.17 Intervention 2: 4.26	**ICER (Intervention 2 versus Intervention 1):** £8,471 per QALY gained (pa) 95% CI: NR Probability Intervention 2 cost-effective

duration:[(a)] Varied according to the length of follow-up in trial used. **Discounting:** Costs: 3.5%; Outcomes: 3.5%		Intervention 3: £8,414 Incremental (2−1): £753 Incremental (3-2): £301 (95% CI: NR; p=NR)	Intervention 3: 4.28 Incremental (2−1): 0.09 Incremental (3-2): 0.02 (95% CI: NR; p=NR)	(£20K threshold): 99.86% **ICER (Intervention 3 versus Intervention 2):** £14,694 per QALY gained (pa) 95% CI: NR Probability Intervention 3 cost-effective (£20K threshold): 84.18%
		Patients with CHF of any cause aged ≤75 (BATTLESCARRED)		
		Total costs (mean per patient): Intervention 1: NR Intervention 2: NR Intervention 3: NR	**QALYs (mean per patient):** Intervention 1: NR Intervention 2: NR Intervention 3: NR	**ICERs:** Intervention 2 extendedly dominated. Intervention 3 versus Intervention 1: £2,517 per QALY gained (pa) 95% CI: NR Probability Intervention 3 cost-effective (£20K threshold): 98.10%
		Patients with CHF of any cause aged >75 (BATTLESCARRED)		
		Total costs (mean per patient): Intervention 1: NR Intervention 2: NR Intervention 3: NR	**QALYs (mean per patient):** Intervention 1: NR Intervention 2: NR Intervention 3: NR	**ICERs:** Intervention 3 dominated. Intervention 2 versus Intervention 1: £11,508 per QALY gained (pa) 95% CI: NR Probability Intervention 2 cost-effective (£20K threshold): 50.26%

		Currency & cost year: 2011 British pounds **Cost components incorporated:** Hospitalisation, drug usage, outpatient visits, NP measurements, tests of renal function. Post-trial period a yearly cost per patient was applied.		**Analysis of uncertainty:** Probability distributions were applied to each parameter (gamma for unit costs, beta for utility scores, log-normal for risk ratios) and 5,000 Monte Carlo simulations were computed for each analysis.
Data sources				
Health outcomes: Five trials (Troughton et al.2000, TIME-CHF, STARS-BNP, PROTECT, PRIMA subgroup) that compared NP monitoring and clinical assessment by a specialist in patients in patients with CHF due to LVSD were combined in a meta-analysis. BATTLESCARRED and PRIMA main analysis were used to compare NP monitoring, clinical assessment and usual care in patients with CHF due to any cause. BATTLESCARRED and TIME-CHF were used for the age sub-group analysis. **Quality-of-life weights:** EQ-5D determined based on analysis by Göhler et al. 2009 weighted by NYHA class proportions at trial base-line[529]. **Cost sources:** Resource use estimated from clinical trials included in the analysis and unit costs were applied from NHS reference costs 2010-2011, PSSRU 2011 and the BNF.				
Comments				
Source of funding: Work undertaken by the National Clinical Guideline Centre, which receives funding from NICE. It was based on an initial study developed as part of the process to update the NICE clinical guideline on chronic heart failure. **Limitations:** Preference weights of EQ-5D scores were based on subjects region of origin, not necessarily UK tariff (31% US, 52% Western Europe, 14% Latin America). Disease progression not captured in the model. **Other:** None.				
Overall applicability:[(b)] Directly applicable **Overall quality**[(c)] Minor limitations				

Abbreviations: 95% CI: 95% confidence interval; CUA: cost-utility analysis; da: deterministic analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; pa: probabilistic analysis; QALYs: quality-adjusted life years

(a) After the trial end date, it was assumed that there were no differences in mortality between the trial groups. Post-trial mortality estimates were taken from a UK based study of CHF patients by de Guili et al.2005 which reported age and sex-based SMRs that were applied to life tables for England and Wales. [355]

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

Study	Moertl 2012[1005]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** Markov model - number of previous hospitalisations used as a proxy for disease progression. First 18 months relates to clinical trial phase. Beyond 18 months each health state was further dichotomized by proportion of patients receiving beta-blockers and treatment effect of this applied. **Perspective:** Austrian payer perspective (also report results from a Canadian perspective) **Time horizon:** 20 years **Treatment effect duration:**[(a)] 18 months **Discounting:** Costs: 5%;	**Population:** Patients with heart failure discharged after a heart failure hospitalisation **Cohort settings:** Age (SD): Intervention 1: 73 (11) Intervention 2: 71 (13) Intervention 3: 70 (12) Male: Intervention 1: 69% Intervention 2: 70% Intervention 3: 63% **Intervention 1:** Usual care - primary care physician with detailed disease management plan. Visits to outpatient clinic scheduled as usual. **Intervention 2:** Nurse-led multidisciplinary care - 4 home visits by a specialised heart failure nurse after 1, 3, 6 and 12 months and optional telephone support. Deteriorating patients were immediately reported to the HF specialist or advised to seek consultation. **Intervention 3:** NT-proBNP guided, intensive patient management - risk	**Total costs (mean per patient):** Intervention 1: £29,661 Intervention 2: £31,750 Intervention 3: £28,876 Incremental (2−1): £2,089 Incremental (3-1): saves £785 Incremental (3-2): saves £2,874 (95% CI: NR; p=NR) **Currency & cost year:** 2010 Euros (converted here to 2010 UK pounds) **Cost components incorporated:** NT-proBNP testing, nurse intervention, beta-blocker therapy, GP visits, specialist outpatient visits, and hospitalisations. Costs for GP visits and drug costs were not collected and not included in the analysis of the clinical trial phase (first 18 months).	**QALYs (mean per patient):** Intervention 1: 2.36 Intervention 2: 3.04 Intervention 3: 3.20 Incremental (2−1): 0.68 Incremental (3-1): 0.84 Incremental (3-2): 0.16 (95% CI: NR; p=NR)	**ICERs:** Intervention 3 dominates both intervention 2 and 1 **Analysis of uncertainty(da):** Costs were also reported from a Canadian perspective. These are reported below. Intervention 1: £32,689 Intervention 2: £34,824 Intervention 3: £31,679 Using this cost perspective does not alter the conclusions of the analysis. Results appear to be insensitive to changes in parameter values when the following assumptions are adopted: i) No difference in outcomes post-trial period ii) No difference in beta-blocker use post 18 months iii) Utility weights in Markov model derived from a previous study (Göhler et al. 2009) iv) Alternate estimates of mortality and death from previous studies v) Alternate time horizons (18 months, 5 years, 10 years) vi) Different discount rates (3%,

Outcomes: 5%	stratification performed upon NT-proBNP discharge levels. High risk group (>2,200pg/ml) ambulatory visits with HF specialist performed at least bi-weekly in addition to multidisciplinary care (2) for rapid optimization of HF medication. If NT-proBNP fell below 2,200pg/ml 3 or 6 months after discharge, patients managed similarly to those in the multidisciplinary group. If NT-proBNP remains elevated, bi-weekly visits continued until maximal recommended/tolerated doses of HF therapy established. Thereafter time interval between visits was increased to 3 months.			0%).

Data sources

Health outcomes: Within-trial analysis with mortality and hospitalisation rates taken from Berger et al. 2010[157]. **Quality-of-life weights:** Quality of life was assessed in trial using the MLWHFQ during index hospitalisation and 1, 3, 6 and 12 months follow up. These scores were converted to utilities using a previously published algorithm by Havranek et al. 1999[587]. **Cost sources:** Prices for treatment with carvedilol at target dosages were derived from the Vienna Health Insurance Fund for Austria. GP visits were based on the average reimbursement by the Vienna Health Insurance Fund for Austria Hospitalisation costs were estimated from the average cost per day for a hospitalisation in a Viennese hospital, derived from the latest report of the Austrian Federal Ministry of Health. Cost of NT-proBNP tests and HF outpatient clinics fees of a Vienna General Hospital and one of the participating centres was used. The cost of nurse care was based on the invoices issued during the clinical trial.

Comments

Source of funding: Astra Zeneca, Novartis, Roche Diagnostics, Roche Medical, Merck, Medtronic, and Guidant. **Limitations:** Austrian payer perspective. EQ-5D not used to capture quality of life - utility scores converted from MLWHF questionnaire using previously published algorithm. Costs and effects discounted at 5%. Cost of GP visits and drug costs were not collected and not included in the analysis of the clinical trial phase. **Other:** None.

Overall applicability:[(b)] Partially applicable **Overall quality**[(c)] Potentially serious limitations

Abbreviations: 95% CI: 95% confidence interval; CUA: cost-utility analysis; da: deterministic analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; pa: probabilistic analysis; QALYs: quality-adjusted life years
(a) Clinical trial data used to extrapolate beyond 18 month period – details not provided.
(b) Directly applicable / Partially applicable / Not applicable
(c) Minor limitations / Potentially serious limitations / Very serious limitations

Study	Pufulete et al. 2017[1174] (Mohiuddin et al. 2016[1008])			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** Markov model consisting of two health states: 'Alive' and 'Dead' with a cycle length of 3 months. Probability of death and hospitalisation varied over time. **Perspective:** UK NHS **Time horizon:** Lifetime **Treatment effect duration:**[(a)] Assume that BNP-guided therapy would cease after 18 months and that the relative treatment effect would end after four years. **Discounting:** Costs: 3.5%;	**Population:** Patients over 18 years old who were being treated for heart failure in primary or secondary care, recently discharged from hospital following an acute episode. **Cohort settings:** Start age: <75 years: 65 ≥75 years: 81 **Intervention 1:** Specialist-led clinically-guided therapy **Intervention 2:** Specialist-led BNP-guided therapy	***All HF patients aged <75 years***		
		Total costs (mean per patient): Intervention 1: £58,139 Intervention 2: £64,777 Incremental (2−1): £6,638 (95% CI: NR; p=NR)	**QALYs (mean per patient):** Intervention 1: 5.02 Intervention 2: 5.68 Incremental (2−1): 0.66 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** £10,057 per QALY gained (da) 95% CI: NR
		HF-REF patients aged <75 years		
		Total costs (mean per patient): Intervention 1: £58,139 Intervention 2: £63,527 Incremental (2−1): £5,388 (95% CI: NR; p=NR)	**QALYs (mean per patient):** Intervention 1: 5.02 Intervention 2: 5.57 Incremental (2−1): 0.55 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** £9,840 per QALY gained (pa) 95% CI: NR Probability Intervention 2 cost-effective (£20K threshold): NR
		HF-PEF patients aged <75 years		
		Total costs (mean per patient): Intervention 1: £67,694 Intervention 2: £71,097 Incremental (2−1): £3,403 (95% CI: NR; p=NR)	**QALYs (mean per patient):** Intervention 1: 5.86 Intervention 2: 6.23 Incremental (2−1): 0.37 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** £9,066 per QALY gained (pa) 95% CI: NR Probability Intervention 2 cost-effective (£20K threshold): 75%
		All HF patients aged ≥75 years		
		Total costs (mean per patient): Intervention 1: £26,093	**QALYs (mean per patient):** Intervention 1: 2.20	**ICER (Intervention 2 versus Intervention 1):** Intervention 2 dominates intervention 1 Probability Intervention 2 cost-effective

Outcomes: 3.5%		Intervention 2: £25,802 Incremental (2–1): saves £291 (95% CI: NR; p=NR)	Intervention 2: 2.23 Incremental (2–1): 0.03 (95% CI: NR; p=NR)	(£20K threshold): NR
		HF-REF patients aged ≥ 75 years		
		Total costs (mean per patient): Intervention 1: £26,093 Intervention 2: £27,676 Incremental (2–1): £1,583 (95% CI: NR; p=NR)	**QALYs (mean per patient):** Intervention 1: 2.20 Intervention 2: 2.39 Incremental (2–1): 0.19 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** £8,123 per QALY gained (pa) 95% CI: Probability Intervention 2 cost-effective (£20K threshold): 88%
		Currency & cost year: 2013/14 UK pounds **Cost components incorporated:** BNP test, renal testing, up-titration of pharmacotherapy related to BNP monitoring, unscheduled outpatient appointments, on-going cost of managing patients with heart failure in the community, cost of treating patients with heart failure in hospital.		**Analysis of uncertainty:** *Base-case results(pa) at £20,000 threshold:* **Sub-group** — **iNMB (95% CI)** All HF patients < 75 years — £6,426 (£2,402- £10,075) HF-REF patients ages <75 years — £5,424 (£987 - £9,469) HF-PEF patients aged <75 years — £3,155 (-£10,307 - £11,613) All HF patients ≥ 75 years — £869 (-£2,814 - £4,606) HF-REF patients ≥ 75 years — £2,267 (-£1,524 - £6,074) *Sensitivity analyses based on HF-REF patients < 75years at £20,000 threshold (pa)*: **Sensitivity analysis** — **iNMB (95% CI)** SA1:Weibull form of survival function — £5,775 (£963- £10,073)

				SA2: Survival based on Kaplan-Meier curve from Troughton et al.	£ 6,194 (£2,632 - £10,847
				SA3: BNP HR based on HTA IPD meta-analysis	£5,271 (-£1,124 - £10,501)
				SA4: BNP-guided care cease at 2 years	£2,834 (£284 – £5,079)
				SA5: BNP-guided care continues for lifetime	£12,275 (£1,090 - £24,289)
				SA6: Low cost (£12.50) of BNP test	£5,453 (£993 - £9,467)
				SA7: High cost (£37.50) of BNP test	£5,303 (£800- £9,328

Data sources

Health outcomes: Baseline survival estimated using the all-cause mortality rate obtained from CPRD-HES-ONS linked data for the first 8 years of the model. Parametric survival function applied. Beyond the initial period used age-and sex- specific ONS 2011-2013 population life tables for the UK inflating for the heart failure population. All-cause hospitalisation rate also estimated from CPRD-ONS linked data. Used IPD meta-analysis results to estimate the relative effect of BNP guided care on all-cause mortality and all-cause hospitalisations[214].**Quality-of-life weights:** EQ-5D, collected from acutely decompensated heart failure patients in placebo arm of ASCEND-HF multinational trial collected at baseline, 24 hours, discharge and 30 days. **Cost sources:** NHS reference costs 2013-2014, Sanders-van Wijk et al. 2013 (US study)[1243].

Comments

Source of funding: NIHR Health Technology Assessment programme. **Limitations:** Simple two-state Markov model which does not capture disease progression. **Other:** None.

Overall applicability:[(b)] Directly applicable **Overall quality**[(c)] Minor limitations

Abbreviations: 95% CI: 95% confidence interval; CPRD: Clinical Practice Research Datalink; CUA: cost-utility analysis; da: deterministic analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); HES: Hospital Episode Statistics; ICER: incremental cost-effectiveness ratio; pa: probabilistic analysis; ONS: Office for National Statistics; QALYs: quality-adjusted life years; SA=sensitivity analysis

(a) Survival reverted back to baseline data, assuming no benefit beyond four years. This was explored in sensitivity analysis. Applied same monthly hazard rate of hospitalisation throughout the lifetime of patients.

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

G.11 Telemonitoring and self-monitoring

<table>
<tr><th>Study</th><th colspan="4">Pandor et al. 2013[1105], (Thokala et al. 2013[1378])</th></tr>
<tr><th>Study details</th><th>Population & interventions</th><th>Costs</th><th>Health outcomes</th><th>Cost effectiveness</th></tr>
<tr>
<td>Economic analysis: CUA (health outcome: QALYs)

Study design:
Probabilistic decision analytic model
Approach to analysis:
Markov model consisting of two health states: ‘alive at home’ and ‘dead’.
Mortality rates were included in the model were adjusted for time since discharge and type of treatment. Average hospitalisation rates were also applied.
Hazard ratios from a NMA applied for treatment effect.
The same utility value for heart failure patients was applied for all</td>
<td>Population:
Patients with heart failure discharged from hospital within 28 days.

Cohort settings:
Start age: 76 (although not explicitly modelled)
Male: NR

Intervention 1:
Usual care
Intervention 2:
Structured telephone support via human to machine interface (STS HM)
Intervention 3:
Structured telephone support via human to human interface (STS HH)
Intervention 4:</td>
<td>Total costs (mean per patient):
Intervention 1: £8,478
Intervention 2: £9,060
Intervention 3: £9,635
Intervention 4: £9,650

Intervention cost (for 6 months):
Intervention 1: £161
Intervention 2: £715
Intervention 3: £1,075
Intervention 4: £1,051

Currency & cost year:
2011 UK pounds sterling.

Cost components incorporated: cost of remote monitoring interventions</td>
<td>QALYs (mean per patient):
Intervention 1: 2.4137
Intervention 2: 2.4128
Intervention 3: 2.5306
Intervention 4: 2.5908</td>
<td>Full incremental analysis (c):
<table>
<tr><th>Int (b)</th><th>Cost (£)</th><th>QALYs</th><th>Inc. cost (£)</th><th>Inc. QALY</th><th>ICER (£)</th><th>Prob. CE</th></tr>
<tr><td>1</td><td>8,478</td><td>2.4137</td><td colspan="3">Baseline</td><td>0%</td></tr>
<tr><td>2</td><td>9,060</td><td>2.4128</td><td colspan="3">Dominated by 1</td><td>5%</td></tr>
<tr><td>3</td><td>9,635</td><td>2.5306</td><td colspan="3">Extendedly dominated</td><td>12%</td></tr>
<tr><td>4</td><td>9,650</td><td>2.5908</td><td>1,172</td><td>0.1771</td><td>6,616</td><td>83%</td></tr>
</table>

Analysis of uncertainty:
Results were also reported where the predictive distributions of the NMA were used. Using this data does not change the overall outcome of the results and telemonitoring during office hours is the most cost effective intervention.
Scenario analyses undertaken(c):
1. High usual care costs: increased usual care costs from £27 in base-case to £98.70 per patient per month – no change in overall results, although all interventions showed an increase in cost effectiveness.
2. Change in cost of telemonitoring during office hours: min. £133.50 per patient per month; max. £215 per patient per month – no change in overall results; prob. Int. 4 CE: 87%/77% respectively.</td>
</tr>
</table>

strategies. Disutility of 0.1 for heart failure hospitalisation applied for one year. **Perspective:** UK NHS **Time horizon:** Lifetime **Treatment effect duration:**[(a)] 6 months **Discounting:** Costs: 3.5%; Outcomes: 3.5%	Home telemonitoring (TM) during office hours – transmitted data reviewed by medical staff or medical support	(including triage costs, data management, maintenance costs, medical care costs to deal with the events/alerts), emergency room visits, office visits, home visits, telephone calls, clinical assessment, lab tests, HF-hospitalisations, other-cause hospitalisations. Drug prices assumed to be the same across groups.		3. Change in cost of STS HH: min. £175 per patient per month; max. £192 per patient per month – no change in overall results; prob. Int. 4 CE: 84%/83% respectively. 4. 12 months treatment duration – no change in overall results.
Data sources				
Health outcomes: Baseline mortality rates estimated from CHARM study[1310]. The mean number of hospitalisations (both heart failure hospitalisations and other-cause hospitalisations were estimated from a meta-analysis of 21 studies reported by Klersy et al. 2011[770]. Hazard ratios from a NMA for all-cause mortality, all-cause hospitalisations, and heart failure hospitalisations were applied to the baseline rates to estimate the treatment effect of the different interventions[1105]. **Quality-of-life weights:** Review conducted to estimate health related quality of life found four studies, all of which found utility values for recently discharged patients under usual care of 0.57-0.6. Disutility of hospitalisation incorporated based on Yao et al. 2008 who estimated this to be equivalent to the utility of one NYHA class lower – further detail unknown.[1509] **Cost sources:** The resource use of usual care was estimated from the TEN-HMS study conducted across hospitals in Germany, Netherlands and the UK[290]; NHS staff costs from the PSSRU 2010-11 were applied. Hospitalisation costs were elicited from NHS Reference Costs 2009-10. The costs of remote monitoring devices were elicited from an expert advisory group, with monitoring costs estimated from Boyne et al. for STS-HM,[199] and Riegel et al.[1208] for STS-HH. Drug costs assumed the same across all strategies.				
Comments				
Source of funding: NIHR **Limitations:** Assesses structured telephone support with human to machine contact and human to human contact separately. May not reflect full body of available evidence: two additional studies were included in the NMA used to determine treatment effect that were not included in the clinical review of this guideline, and five more recent studies included in the guideline review that were not included in the NMA. Utility decrement of heart failure hospitalisation considered to be overestimated. **Other:** None.				
Overall applicability:[(d)] Directly applicable **Overall quality:**[(e)] Potentially serious limitations				

Abbreviations: 95% CI: 95% confidence interval; CE: cost effective; CUA: cost–utility analysis; da: deterministic analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; NIHR: National Institute for Health Research; NMA: network meta-analysis; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years

(a) Only 6 month intervention, after which patients receive usual care. Therefore after 6 months treatment duration the baseline risks of hospitalisation and mortality are applied.

(b) Intervention number in order of least to most costly

(c) The study reported results both including and excluding the trial data from Home-HF. The results presented here are excluding HOME-HF trial (Dar et al. 2009) as this study was not included in this clinical review as the study did not match the protocol.

(d) Directly applicable / Partially applicable / Not applicable

(e) Minor limitations / Potentially serious limitations / Very serious limitations

G.12 Multi-Disciplinary Teams

Study	**Atienza 2004**[98]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CCA (health outcomes: 1 year mortality rate, all-cause readmissions, quality of life as measured by the MLWHFQ) **Study design:** Within-trial analysis **Approach to analysis:** Analysis of individual level data for health outcomes and resource use. Unit costs applied. **Perspective:** Spanish health care system	**Population:** Patients discharged with primary diagnosis of congestive heart failure from cardiology wards. **Patient characteristics:** N = 338 Age: 1. 67 2. 69 Male: 1. 59% 2. 62% **Intervention 1:** Usual care – follow-up care by primary	**Total costs (mean per patient):** Intervention 1: £4,513 Intervention 2: £2,794 Incremental (2−1): cost saving of £1,719 (95% CI: NR; p=NR) **Currency & cost year:** Euros (presented here as 2004 UK pounds[(a)]) **Cost components incorporated:** Hospitalisations, intervention – staff costs and infrastructure requirements.	**Mortality at 16 months:** Intervention 1: 30/174 Intervention 2: 51/164 **All-cause hospitalisations at 16 months:** Intervention 1: 199 in 174 patients Intervention 2: 126 in 164 patients **Quality of life at 16 months (MLWHFQ):** Intervention 1: 35.5 (SD:7.9) Intervention 2: 28.9 (SD:6.1)	**ICER (Intervention 2 versus Intervention 1):** n/a **Analysis of uncertainty:** None undertaken.

Follow-up: 16 months **Discounting:** Costs: None; Outcomes: None.	care physician (and cardiologist not performing in study). **Intervention 2:** Multidisciplinary team - specialist cardiac nurse, primary care physician and cardiologist.			
Data sources				
Health outcomes: Within-trial analysis of same study. **Quality-of-life weights:** n/a. **Cost sources:** Hospital Accounting Departments provided the rate of the daily average cost for each DRG. Source of salary information is not clear.				
Comments				
Source of funding: Spanish Society of Cardiology, Research Incentive Program from Polytechnic University of Valencia, Spain, and Merck, Sharp & Dohme contributed to the edition and printing of brochure for heart failure patients in the study. **Limitations**: Spanish resource use data and unit costs (year not reported, assumed to be 2004) may not reflect current NHS context. QALYs were not used as the health outcome measure. Within-trial analysis and so does not reflect the full body of available evidence available for this intervention; Atienza 2004 is 1 of 5 studies comparing MDT clinic (long-term intervention) to usual care in high risk patients. No exploration of uncertainty. **Other:** None.				
Overall applicability:[(b)] Partially applicable **Overall quality**[(c)] Potentially serious limitations				

Abbreviations: 95% CI: 95% confidence interval; CCA: cost-consequence analysis; DRG: diagnosis-related group; ICER: incremental cost-effectiveness ratio; n/a: not applicable; NR: not reported; RCT: randomised control trial.
(a) Converted using 2012 purchasing power parities[1088]
(b) Directly applicable / Partially applicable / Not applicable
(c) Minor limitations / Potentially serious limitations / Very serious limitations

See Moertl 2012[1005] in G.10 above.

Study	**Postmus 2011[1168]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CUA (health outcome: QALYs)	**Population:** Patients >18 years old with evidence of structural cardiac dysfunction (PEF and REF)	**Total costs (mean per patient):** Intervention 1: £7,296	**QALYs (mean per patient):** Intervention 1: NR Intervention 2: NR	**ICERs:** Intervention 2 dominates both Intervention 1 and Intervention 3.

Study design: Within-trial analysis of COACH RCT[680] **Approach to analysis:** Analysis of individual level data for mortality, SF-36, and resource use using mixed-effect modelling to test whether the change in utility differed between groups over time. Unit costs applied. **Perspective:** Dutch health care system **Follow-up:** 18 months **Discounting:** Costs: NR; Outcomes: NR	**Patient characteristics:** N = 1,023 Age = 71 (SD: NR) Male = 62% **Intervention 1:** Care as usual – routine follow up by cardiologist (4 visits) **Intervention 2:** Basic support by nurse trained in management of heart failure (education and counselling, 4 visits to cardiologist, 8 visits to HF nurse, in hospital visit by HF nurse, 1 nurse initiated telephone contact in first month, telephone availability of HF nurse during office hours) **Intervention 3:** Intensive support by nurse trained in management of heart failure (education and counselling, 4 visits to cardiologist, 12 visits to HF nurse, in hospital visit by HF nurse, weekly nurse initiated telephone contact in first month, 24 hour telephone availability of HF nurse, 2 home visits by HF nurse, multi-disciplinary advice)	Intervention 2: £7,238 Intervention 3: £8,124 Incremental (2–1): saves £58 Incremental (3-1): £828 Incremental (3-2): £886 (95% CI: NR; p=NR) Cost breakdown (intervention): Intervention 1: £283 Intervention 2: £532 Intervention 3: £794 **Currency & cost year:** 2009 Euros (presented here as 2009 UK pounds[(a)]) **Cost components incorporated:** Included: intervention, cardiovascular and non-cardiovascular-related short stay hospital admission (no overnight stay), hospitalisation (cardiovascular and non-cardiovascular), HF-related diagnostic procedures. Excluded: drug costs, cost of procedures conducted during hospitalisation or short term hospital admission because not rigorously reported in	Intervention 3: NR Incremental (2–1): 0.023 Incremental (3-1): 0.019 Incremental (3-2): -0.004 (95% CI: NR; p=NR)	95% CI: NR Probability most-cost effective option at €20K (£15,000) threshold: Intvn 1: 30% Intvn 2: 62% Intvn 3: 8% *Sub-group analysis for severe (NYHA class III or IV) and less severe (NYHA class I or II) HF patients:* *Patients with less severe HF* **ICER:** Intervention 2 dominates both Intervention 1 and Intervention 3. *Patients with severe HF* **ICER:** Intvn 2: Extendedly dominated Intvn 3 vs 1: £44,625 per QALY gained **Analysis of uncertainty:** Varied fraction of time that a patient spends in a coronary care unit from 0% – 60% and assessed the consequences of doubling and halving unit cost of outpatient visit (main determinant of intervention cost) – allowed the two parameter values to vary simultaneously. Results showed that there were some combinations for which basic support no longer dominated usual care, but ICERs never exceeded £10,500 per QALY gained.

		COACH.		Basic support dominated intensive support for all considered combinations.
Data sources				
Health outcomes: Within-trial analysis based on COACH study[680]. **Quality-of-life weights:** Within-trial analysis, SF-36. **Cost sources:** Dutch Manual for Costing				
Comments				
Source of funding: Supported by the Competence Network of Heart Failure funded by the Federal Ministry of Education and Research. **Limitations:** This analysis has been undertaken from a Dutch perspective using 2009 unit costs and therefore may not reflect current NHS context. Does not include important cost aspects such as procedures during hospital admission. EQ-5D was not used. Probabilistic sensitivity analysis was not presented at £20k/QALY. No discounting was undertaken; however the follow-up was only 18 months and so is unlikely to have a significant effect. . **Other:** None.				
Overall applicability:[(b)] Partially applicable **Overall quality**[(c)] Potentially serious limitations				

1 *Abbreviations: 95% CI: 95% confidence interval; CUA: cost-utility analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years;SF-36: Short-form 36 questionnaire.*
3 *(a) Converted using 2009 purchasing power parities[1088]*
4 *(b) Directly applicable / Partially applicable / Not applicable*
5 *(c) Minor limitations / Potentially serious limitations / Very serious limitations*
6

Study	**Pulignano 2010** [1176]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CEA (health outcomes: death or readmission for heart failure and all-cause admission rate) **Study design:** Within-trial analysis of a RCT study [368] **Approach to analysis:** Analysis of individual level data for health outcomes and resource use. Unit costs applied.	**Population:** Heart failure patients aged 70 years or over with reduced and normal ejection fraction, discharged home after a hospitalisation. **Patient characteristics:** N = 173 Age: 77 Male: 1. 53% 2. 51% **Intervention 1:** Usual care – patients receive all treatments and services	**Total costs (mean per patient):** Intervention 1: £4,323 Intervention 2: £3,602 Incremental (2−1): cost saving of £721 (95% CI: NR; p=NR) Cost breakdown: <u>Outpatient</u> Intervention 1: £812 Intervention 2: £1,017 <u>Inpatient</u>	**Mortality at 2 years:** Intervention 1: 32/87 Intervention 2: 27/86 **All-cause admissions at 2 years:** Intervention 1: 65/87 Intervention 2: 48/86	**ICER (Intervention 2 versus Intervention 1):** Intervention 2 saves £4,042 per death and/or heart failure-related admission avoided. Intervention 2 saves £2,155 per all-cause admission avoided. Probability Intervention 2 cost-effective (£20K/30K threshold): NR **Analysis of uncertainty:** None undertaken.

Perspective: Italian national health care system **Follow-up:** 2 years **Discounting:** Costs: None; Outcomes: None.	ordered by their primary care physician and/or personal cardiologist. **Intervention 2:** Multidisciplinary team - disease management programme run by a team consisting of a cardiologist, experienced in geriatrics (case managers), two to four specialised nurses, and the patient's primary care physician.	Intervention 1: £3,511 Intervention 2: £2,584 **Currency & cost year:** Euros (presented here as 2010 UK pounds[(a)]) **Cost components incorporated:** Pre-discharge education, multidimensional assessment, medications, management programme, usual care, hospitalisations.		
Data sources				
Health outcomes: Within-trial analysis based on RCT by Del Sindaco et al. 2007[368]. **Quality-of-life weights:** None. **Cost sources:** Italian NHS charges using DRG codes, Annual National Therapeutic Formulary (no references provided).				
Comments				
Source of funding: ADRIANO – Italian Association for Research on Cardiac Disease in Older Patients. **Limitations:** Italian national health service resource use and unit costs may not reflect current UK NHS context. QALY data was not reported clearly enough to report and therefore were not used as the health outcome measure. Discounting was not applied. Within-trial analysis and therefore does not reflect the full body of evidence available for this comparison; Pulignano 2010 is 1 of 5 studies comparing MDT clinic (long-term intervention) to usual care in high risk patients. No exploration of uncertainty. **Other:** None.				
Overall applicability:[(b)] Partially applicable **Overall quality**[(c)] Potentially serious limitations				

Abbreviations: 95% CI: 95% confidence interval; CEA: cost-effectiveness analysis; DRG: Diagnostic Related Groups; ICER: incremental cost-effectiveness ratio; n/a: not applicable; NR: not reported; RCT: randomised control trial.
(a) Converted using 2012 purchasing power parities[1088]
(b) Directly applicable / Partially applicable / Not applicable
(c) Minor limitations / Potentially serious limitations / Very serious limitations

Study	**Sahlen 2016** [1235]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost-effectiveness**
Economic analysis: CUA	**Population:** Adults with a confirmed	**Total costs (mean per**	**QALYs net of baseline**	**ICER (Intervention 2 versus**

(health outcome: QALYs) **Study design:** Within-trial analysis of a RCT study[203] **Approach to analysis:** Analysis of individual level resource use and EQ-5D. Unit costs applied. **Perspective:** Swedish hospital **Follow-up:** 6 months **Discounting:** Costs: n/a ; Outcomes: n/a.	diagnosis of chronic heart failure with NYHA class III-IV symptoms and at least one marker of severity: i) hospitalisation requiring IV diuretics, despite being on "optimal" medication ii) needing frequent IV support iii) chronic poor quality of life (<50 on visual analogue scale) iv) cachexia v) life expectancy <1y. **Patient characteristics:** N = 72 Age: 1. 76.6 (SD:10.2) 2. 81.9 (SD:7.2) Male: 1. 69.4% 2. 72.2% **Intervention 1:** Usual care - provided mainly by general practitioners and/or the nurse-led HF clinic at the department of geriatric medicine. **Intervention 2:** Multidisciplinary approach - collaboration between specialists in palliative care and heart failure care, including heart failure nurse, palliative care nurse, cardiologist, palliative care physician, physiotherapist and occupational	**patient):** Intervention 1: £5,269 Intervention 2: £3,752 Incremental (2−1): cost saving of £1,517 (95% CI: NR; p=NR) Cost breakdown (upfront): Intervention 1: £380 Intervention 2: £2,159 **Currency & cost year:** Euros (presented here as 2012 UK pounds[(a)]) **Cost components incorporated:** Staffing costs, health care services, emergency care, and in-hospital care. Travel expenses not included.	**(mean per patient):** Intervention 1: -0.024 Intervention 2: +0.006 Incremental (2−1): 0.03 (95% CI: NR; p=NR)	**Intervention 1):** Intervention 2 dominates intervention 1 (more effective and less costly) Probability Intervention 2 cost-effective (£20K/30K threshold): NR **Analysis of uncertainty:** Sensitivity analysis was performed using a standard cost model for Sweden made on behalf of the Swedish Association of Local Authorities and Regions. Includes overhead costs and travel expenses. The sensitivity analysis provides similar results to the base case with intervention 2 dominating intervention 1.

	therapist. Offered person-centred care at home. The team took responsibility for "total care" i.e. including co-morbidities. Rounds were scheduled every 2 weeks with all team members.			
Data sources				
Health outcomes: Within-trial analysis based on PREFER study[203]. **Quality-of-life weights:** Within-trial analysis: EQ-5D, EU tariff. **Cost sources:** Statistics Sweden 2012, accounting records of Västerbotten County, 2012.				
Comments				
Source of funding: Swedish Association of Local Authorities and Regions, the Strategic Research Program in HealthCareSciences, "Bridging Rsearch and Practice for Better Health, Sweden", the Swedish Heart and Lung Association, konung Gustav V och drottning Viktorias frimurarstiftelse, and the Rönnbäret Fund Skellefteå Municipality. **Limitations:** Single centre study from a county council hospital in Västerbotten County, Sweden and therefore resource use and 2012 costs may not reflect current UK NHS context. Short time horizon may not capture full costs and effects of the intervention. EQ-5D reported differently to the clinical trial evidence. Only minimal sensitivity analyses were carried out to quantify uncertainty.. **Other:** None.				
Overall applicability:[(b)] Partially applicable **Overall quality**[(c)] Potentially serious limitations				

Abbreviations: 95% CI: 95% confidence interval; CUA: cost-utility analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); EU: European Union; ICER: incremental cost-effectiveness ratio; n/a: not applicable; NR: not reported; RCT: randomised control trial.
(a) Converted using 2010 purchasing power parities[1088]
(b) Directly applicable / Partially applicable / Not applicable
(c) Minor limitations / Potentially serious limitations / Very serious limitations

G.13 Transition between heart failure care settings

None.

G.14 Communication needs regarding diagnosis and prognosis

None.

G.15 Diuretics in advanced heart failure

None.

G.16 Domiciliary oxygen therapy in people with advanced heart failure

None.

G.17 Discussing Implantable Cardioverter Defibrillator (ICD) deactivation

None.

G.18 Identifying patients with an increased risk of mortality

None.

Appendix H: GRADE tables

H.1 BNP and NT-proBNP in diagnosing heart failure

No clinical evidence was identified.

H.2 Cardiac Magnetic Resonance Imaging in heart failure

No clinical evidence was identified.

H.3 Salt and fluid restriction

Table 28: Clinical evidence profile: Programme for low sodium diet vs Programme for moderate sodium diet for heart failure

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Advice for low sodium diet	Advice for moderate sodium diet	Relative (95% CI)	Absolute	
Quality of Life (follow-up mean 6 months; measured with: Kansas City Cardiomyopathy Questionnaire; range of scores: 0-100; Better indicated by higher values)											
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	[2]	none	19	19	-	median 7.8 lower	⊕⊕OO LOW
Renal function (follow-up mean 6 months; measured with: Creatinine (umol/L); Better indicated by lower values)											
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	[2]	none	19	19	-	median 4 lower	⊕⊕OO LOW
Unplanned hospitalisations - not measured											
0	-	-	-	-	-	none	-	-	-	-	

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Imprecision cannot assessed due to reporting of median and inter-quartile range

Table 29: Clinical evidence profile: Programme for fluid restriction vs Advice on fluid restriction for heart failure

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Programme for fluid restriction	Advice on fluid restriction	Relative (95% CI)	Absolute	
Quality of Life at 6 months (follow-up mean 6 months; measured with: EQ5D - visual analogue scale; range of scores: 0-100; Better indicated by higher values)											
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	11	10	-	MD 8.68 lower (24.96 lower to 7.6 higher)	⊕OOO VERY LOW
Oedema (follow-up mean 3 months; measured with: Congestion score; range of scores: 0-5; Better indicated by lower values)											
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	very serious[4]	none	12	11	-	MD 0.07 higher (1.1 lower to 1.24 higher)	⊕OOO VERY LOW
Unplanned hospitalisations - not measured											
0	-	-	-	-	-	none	-	-	-	-	

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 or 2 increments because the majority of evidence was from an indirect population (chosen as in a monitoring trial)
[3] Downgraded by 2 increments because the majority of evidence was from an indirect population (in a monitoring trial) and was looking at congestion, which includes things other than oedema (the protocol outcome)
[4.] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

H.4 Beta-blockers in people with heart failure and atrial fibrillation

Table 30: Clinical evidence profile: Beta-blockers versus placebo in people with CHF and concomitant atrial fibrillation

Quality assessment							No of participants		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Beta-blocker	Placebo	Relative (95% CI)	Absolute		
All-cause mortality (follow-up mean 3.3 years)												
9	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	-	15.7%[2]	HR 1.02 (0.85 to 1.23)	3 more per 1000 (from 22 fewer to 32 more)	⊕⊕⊕O MODERATE	CRITICAL
First heart-failure related hospital admission (follow-up mean 3.3 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[4]	no serious imprecision	none	-	14.9%[2]	HR 0.93 (0.77 to 1.12)	10 fewer per 1000 (from 32 fewer to 16 more)	⊕⊕⊕O MODERATE	CRITICAL
Non-fatal stroke at 3.3 years (follow-up mean 3.3 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	-	[3]	HR 1.11 (0.71 to 1.74)	[3]	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both
[2] The control group risk was calculated as a median from data included within the original CIBIS-II[1429], SENIORS [1025]and US-HF[701] publications in order to estimate an absolute effect, this information could not be obtained from the IPD.
[3] Not estimable as only the summary statistic was reported by Kotecha 2014[791] and no additional information regarding the event rates were available from the original papers

[4]Downgraded by 1 increment due to indirectness of the outcome which only reported first heart-failure related hospital admission rather than all-cause hospital admissions

H.5 Mineralocorticoid Receptor Antagonists

Table 31: Clinical evidence profile: Mineralocorticoid receptor antagonists in heart failure with preserved ejection fraction

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mineralocorticoid receptor antagonist	Placebo	Relative (95% CI)	Absolute		
All-cause mortality (time to event)(follow-up 3.3 years)												
1	randomised trials	no serious risk of	no serious inconsistency	no serious indirectness	serious[2]	none	252/1722 (14.6%)	274/1723 (15.9%)	HR 0.91 (0.77 to 1.08)	13 fewer per 1000 (from 34 fewer to	⊕⊕⊕O MODERATE	CRITICAL

		bias								12 more)		
All-cause mortality (dichotomous)(follow-up 1 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/205 (0.49%)	0%	Peto Odds Ratio 7.07 (0.14 to 356.74)	Unable to calculate[3]	⊕OOO VERY LOW	CRITICAL
Quality of life (Kansas City)(follow-up 1 years; measured with: Kansas City Cardiomyopathy Questionnaire; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Unable to calculate[4]	-	-	MD 1.35 higher (0.21 to 2.49 higher)	⊕⊕OO LOW	CRITICAL
Quality of life (EQ-VAS)(follow-up time unclear[5]; measured with: EQ-VAS[6]; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Unable to calculate[4]	-	-	MD 0.47 higher (0.27 lower to 1.21 higher)	⊕⊕OO LOW	CRITICAL
Quality of life (Minnesota)(follow-up 1 years; measured with: Minnesota Living with Heart Failure Questionnaire; range of scores: 0-105; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	204	196	-	MD 0 higher (3.54 lower to 3.54 higher)	⊕⊕⊕O MODERATE	CRITICAL
Quality of life (SF-36 Physical Functioning)(follow-up 1 years; measured with: SF-36 Physical Functioning scale; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	204	196	-	MD 2 lower (6.61 lower to 2.61 higher)	⊕⊕⊕O MODERATE	CRITICAL
All-cause hospitalisation (count rate)(follow-up 3.3 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	Unable to calculate[7]	Unable to calculate[7]	Rate Ratio 0.94 (0.87 to 1.02)	12 fewer events per 1000 person-years (from 26 fewer to 4 more)	⊕⊕⊕⊕ HIGH	CRITICAL
All-cause hospitalisation (dichotomous)(follow-up 1 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	60/204 (29.4%)	50/204 (24.5%)	RR 1.2 (0.87 to 1.65)	49 more per 1000 (from 32 fewer to 159 more)	⊕⊕⊕O MODERATE	CRITICAL
Participants with NYHA class I status(follow-up 1 years)												
1	randomised trials	serious[1]	no serious inconsistency	serious[8]	very serious[2]	none	8/204 (3.9%)	11/196 (5.6%)	RR 0.7 (0.29 to 1.7)	17 fewer per 1000 (from 40 fewer to 39 more)	⊕OOO VERY LOW	IMPORTANT
Hyperkalaemia(follow-up 1-3.3 years; assessed with: serum potassium > or ≥5.5mm/L)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	326/1926 (16.9%)	160/1919 (8.3%)	RR 2.04 (1.71 to 2.43)	87 more per 1000 (from 59 more to 119 more)	⊕⊕⊕O MODERATE	IMPORTANT
Worsening renal function(follow-up 1-3.3 years; assessed with: various[9])												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	253/1926 (13.1%)	14.5%	RR 1.53 (1.27 to 1.83)	77 more per 1000 (from 39 more to 120 more)	⊕⊕⊕O MODERATE	IMPORTANT

Gynaecomastia(follow-up 1-3.3 years; assessed with: various[10])											
2	randomised trials	serious[1]	no serious inconsistency	serious[8]	no serious imprecision	none	50/1926 (2.6%)	0.4%	Peto Odds Ratio 5.23 (3.07 to 8.9)	17 more per 1000 (from 8 more to 32 more)	⊕⊕OO LOW	IMPORTANT

[1]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3]Unable to calculate as there were zero events in the control arm
[4]Unable to calculate as the control group risk was not reported
[5]Time outcome reported unclear. Study states that 'impacts of therapy on changes in [the scores] over time were examined using a repeated -measure analysis of covariance (using all follow-up time points (4, 12 24, 36, 48 and 60 months)'.'
[6]Not the full EQ5D, just the VAS component
[7]Not estimable from rate ratio
[8]Downgraded by 1 increment because the study had indirect outcomes
[9]TOPCAT used serum creatinine level ≥2 times the baseline value and above the upper limit of the normal range; ALDO-DHF used eGFR < 30mL/min/1.73m2, or eGFR decrease > 15mL/min/1.73m2 versus baseline.
[10]TOPCAT: Breast tenderness or enlargement leading to study drug discontinuation; ALDO-DHF: "Gynaecomastia" (not defined)

Table 32: Clinical evidence profile: Mineralocorticoid receptor antagonists in heart failure with reduced ejection fraction

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mineralocorticoid receptor antagonist	Placebo	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 1-2 years)												
3	randomised trials	no serious risk of bias	serious[1] inconsistency	Serious[2]	Serious[3]	none	472/2297 (20.5%)	15.5%[4]	HR 0.78 (0.61 to 1.00)	32 fewer per 1000 (from 57 fewer to 0 more)	⊕OOO VERY LOW	CRITICAL
All-cause hospitalisation (follow-up 1.75-2 years)												
2	randomised trials	no serious risk of bias	serious [9]	Serious[2]	Serious[3]	none	-	39.7%[4]	Rate Ratio 0.79 (0.71 to 0.87)	83 fewer per 1000 (from 52 fewer to 115 fewer)	⊕OOO VERY LOW	CRITICAL
Hospitalisation for any cause (dichotomous) (follow-up mean 1 years)												
1	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	Serious[3]	none	45/111 (40.5%)	52.7%	RR 0.77 (0.58 to 1.02)	121 fewer per 1000 (from 221 fewer to 11 more)	⊕OOO VERY LOW	CRITICAL
Change in NYHA class - Improved (follow-up 0.7-2 years)												
2	randomised trials	Serious[5]	no serious inconsistency	Serious[2]	Serious[3]	none	278/717 (38.8%)	33%[6]	RR 1.27 (1.1 to 1.46)	89 more per 1000 (from 33 more to 152 more)	⊕OOO VERY LOW	IMPORTANT
Hyperkalaemia (follow-up 0.7-2 years; assessed with: various[7])												
4	randomised trials	Serious[5]	serious[8]	no serious indirectness	no serious imprecision	none	336/2386 (14.1%)	6.4%[6]	RR 1.97 (1.18 to 3.27)	62 more per 1000 (from 12 more to	⊕⊕OO LOW	IMPORTANT

										145 more)		
Renal function (change in creatinine (umol / L) - continuous) (follow-up 1.75 years; Better indicated by lower values)												
1	randomised trials	Serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1360	1369	-	MD 4.5 higher (1.94 to 7.06 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Renal function (change in eGFR (ml/min/173m^2) - continuous) (follow-up 1.75 years; Better indicated by higher values)												
1	randomised trials	Serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1364	1373	-	MD 1.89 lower (3.26 to 0.52 lower)	⊕⊕⊕O MODERATE	IMPORTANT
Renal function (creatinine increased - dichotomous) (follow-up 0.7 years)												
1	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	very serious[3]	none	11/117 (9.4%)	6/109 (5.5%)	RR 1.71 (0.65 to 4.46)	39 more per 1000 (from 19 fewer to 190 more)	⊕OOO VERY LOW	IMPORTANT
Renal function (30% reduction in eGFR (ml/min/1.73 m^2) from baseline) (follow-up 3 months)												
1	randomised trials	Serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	140/822 (17%)	59/841 (7%)	RR 2.43 (1.82 to 3.24)	100 more per 1000 (from 58 more to 157 more)	⊕⊕⊕O MODERATE	IMPORTANT
Renal impairment (dichotomous - undefined) (follow-up mean 1 years)												
1	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/111 (4.5%)	9.1%	RR 0.5 (0.18 to 1.4)	46 fewer per 1000 (from 75 fewer to 36 more)	⊕OOO VERY LOW	IMPORTANT
Renal failure (follow-up 1.75 years; assessed with: (not defined))												
1	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	very serious[3]	none	38/1360 (2.8%)	41/1369 (3%)	RR 0.93 (0.6 to 1.44)	2 fewer per 1000 (from 12 fewer to 13 more)	⊕OOO VERY LOW	IMPORTANT
Gynecomastia - Spironolactone (follow-up 2 years)												
1	randomised trials	Serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	55/603 (9.1%)	8/614 (1.3%)	RR 7 (3.36 to 14.57)	78 more per 1000 (from 31 more to 177 more)	⊕⊕⊕O MODERATE	IMPORTANT
Gynecomastia (or other breast disorders) - Eplerenone (follow-up 1-1.75 years)												
2	randomised trials	Serious[5]	no serious inconsistency	no serious indirectness	very serious[3]	none	10/1471 (0.68%)	0.5%	Peto odds ratio 0.72 (0.32 to 1.61)	1 fewer per 1000 (from 3 fewer to 3 more)	⊕OOO VERY LOW	IMPORTANT
Hypotension (follow-up 0.7-1.75 years)												
3	randomised trials	Serious[5]	no serious inconsistency	no serious indirectness	Serious[3]	none	59/1588 (3.7%)	3.7%[46]	RR 1.22 (0.84 to 1.78)	8 more per 1000 (from 6 fewer to 29 more)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 or 2 increments because: Heterogeneity, I2=63%, unexplained by subgroup analysis.

[2] Downgraded by one increment as the majority of the evidence included an indirect population (not on beta-blockers)
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

[4] Control group risk based on risk reported in EMPHASIS, as that population were on current first line treatment including beta-blockers.
[5] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[6] Control group risk based on risk reported in EMPHASIS, as it carries the vast majority of the weight in the meta-analysis
[7] EMPHASIS - serum potassium > 5.5 mmol/L. RALES - serum potassium ≥5.5 mmol/L. Udelson 2010 - no definition. Tsutsui 2017 – no definition.

8 Downgraded by 1 or 2 increments because: Heterogeneity, I2=79%, unexplained by subgroup analysis.
9 Downgraded by 1 or 2 increments because: Heterogeneity, I2=59%, unexplained by subgroup analysis.

H.6 Iron supplementation for iron deficiency in heart failure

Table 33: Clinical evidence profile: IV iron versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intravenous iron	Placebo	Relative (95% CI)	Absolute		
Mortality (follow-up 3-12 months)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	20/495 (4%)	5.9%	RR 0.86 (0.47 to 1.58)	8 fewer per 1000 (from 31 fewer to 34 more)	⊕OOO VERY LOW	CRITICAL
Quality of life (follow-up 5.5 months; measured with: EQ5D; range of scores: 0-1; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	304	155	-	MD 0.08 higher (0.03 to 0.12 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Quality of life (follow-up 5.5-12 months; measured with: EQ5D VAS; range of scores: 0-100; Better indicated by higher values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	418	261	-	MD 4.02 higher (1.52 to 6.52 higher)	⊕⊕OO LOW	CRITICAL
Quality of life (follow-up 5.5-12 months; measured with: KCCQ; range of scores: 0-100; Better indicated by higher values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	418	261	-	MD 5.43 higher (2.84 to 8.02 higher)	⊕⊕OO LOW	CRITICAL
Quality of life (follow-up 6 months; measured with: MLWHFQ ; range of scores: 0-105; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	20	20	-	MD 18 lower (22.66 to 13.34 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
Improvement in NYHA class (follow-up 3 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	2/10 (20%)	16.7%	RR 1.2 (0.14 to 10.58)	33 more per 1000 (from 144 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL

Hospitalisation due to HF (follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	no serious imprecision	none	0/20 (0%)	25%	Peto Odds Ratio 0.11 (0.02 to 0.69)	250 fewer per 1000 (from 450 fewer to 50 more)	⊕⊕OO LOW	CRITICAL
Hospitalisation all cause (follow-up 6-12 months)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/455 (0%)	37.1%[4]	Rate Ratio 0.66 (0.5 to 0.85)	126 fewer per 1000 (from 56 fewer to 185 fewer)	⊕⊕OO LOW	CRITICAL
Exercise tolerance (follow-up 5.5-12 months; measured with: 6MWT, distance; Better indicated by higher values)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	413	275	-	MD 39.5 higher (25.11 to 53.88 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Haemoglobin in anaemic patients (follow-up 6 months; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	30	30	-	MD 2.1 higher (1.8 to 2.4 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Discontinuation: adverse events (follow-up 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	14/152 (9.2%)	12.5%	RR 0.74 (0.38 to 1.42)	32 fewer per 1000 (from 78 fewer to 52 more)	⊕OOO VERY LOW	IMPORTANT
Ischaemic stroke (follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/305 (0.66%)	0%	Peto Odds Ratio 4.52 (0.24 to 85.34)	10 more per 1000 (from 10 fewer to 20 more)	⊕OOO VERY LOW	IMPORTANT
Drug related vascular disorders (not defined) (follow-up 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	1/152 (0.66%)	0.66%	Peto Odds Ratio 1.00 (0.06 to 16.06)	0 fewer per 1000 (from 20 fewer to 20 more)	⊕OOO VERY LOW	IMPORTANT
Gastrointestinal disorders (not defined) (follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	24/305 (7.9%)	3.3%	RR 2.42 (0.94 to 6.23)	47 more per 1000 (from 2 fewer to 173 more)	⊕⊕OO LOW	IMPORTANT
Drug related gastrointestinal disorders (not defined) (follow-up 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/152 (1.3%)	0%	Peto Odds Ratio 7.44 (0.46 to 119.46)	10 more per 1000 (from 10 fewer to 40 more)	⊕OOO VERY LOW	IMPORTANT
Nausea (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	1/30 (3.3%)	3.3%	RR 1 (0.07 to 15.26)	0 fewer per 1000 (from 31 fewer to 471 more)	⊕⊕OO LOW	IMPORTANT
Abdominal pain (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	0/30 (0%)	3.3%	Peto Odds Ratio 0.14 (0.00 to 6.82)	30 fewer per 1000 (from 120 fewer to 50 more)	⊕⊕OO LOW	IMPORTANT

Systolic blood pressure (follow-up 6 months; Better indicated by lower values)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	30	30	-	MD 1.3 higher (1.95 lower to 4.55 higher)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MID
[3] Downgraded by 1 increment as the outcome is indirect
[4] Mean control group rate per 100 patient-years

Table 34: Clinical evidence profile: oral iron versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral iron	Placebo	Relative (95% CI)	Absolute		
Mortality (follow-up 3 months)												
2	randomised trials	Very serious[1]	serious[5]	no serious indirectness	very serious[2]	none	3/118 (2.5%)	1.7%	Peto Odds Ratio 1.48 (0.25 to 8.66)	8 more per 1000 (from 13 fewer to 128 more)	⊕OOO VERY LOW	CRITICAL
Improvement in NYHA class (follow-up 3 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	serious[2]	none	6/7 (85.7%)	16.7%	RR 5.14 (0.84 to 31.57)	691 more per 1000 (from 27 fewer to 1000 more)	⊕OOO VERY LOW	IMPORTANT
Permanent study drug discontinuation (follow-up 4 months)												
1	randomised trials	No serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	15/111 (13.5%)	14.9%	RR 0.91 (0.48 to 1.72)	13 fewer per 1000 (from 78 fewer to 107 more	⊕⊕OO LOW	IMPORTANT
Adverse events (follow-up 4 months)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	serious[2]	none	39/111 (35.1%)	39.5%	RR 0.89 (0.63 to 1.25)	43 fewer per 1000 (from 146 fewer to 99 more)	⊕OOO VERY LOW	IMPORTANT
Serious adverse events (follow-up 4 months)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	11/111 (9.9%)	8.8%	RR 1.13 (0.5 to 2.55)	11 more per 1000 (from 44 fewer to 136 more)	⊕OOO VERY LOW	IMPORTANT
Change in peak VO2 ml/kg/min (follow-up 4 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	[4]	none				The median change in peak VO2 in the oral iron group was	⊕⊕OO LOW	IMPORTANT

										0.5 higher		
Change in 6 minute walk test distance (follow-up 4 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	[4]	none				The median 6 minute walk test distance in the oral iron group was 31 lower	⊕⊕OO LOW	IMPORTANT
Change in KCCQ clinical summary score (higher score is better; follow-up at 4 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	[4]	none				The median KCCQ in the oral iron group was 3.6 higher	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[3] Downgraded by 1 increment as the outcome is indirect
4 Unable to assess imprecision as the study reported the results as median and IQR
5 Downgraded by 1 increment due to inconsistency, I^2=51%

Table 35: Clinical evidence profile: IV iron versus oral iron

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intravenous iron	Oral iron	Relative (95% CI)	Absolute		
Mortality (follow-up 3 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/10 (20%)	0%	Peto Odds Ratio 6.13 (0.33 to 112.36)	200 more per 1000 (from 100 fewer to 500 more)	⊕OOO VERY LOW	CRITICAL
Improvement in NYHA class (follow-up 3 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	serious[2]	none	2/10 (20%)	85.7%	RR 0.23 (0.07 to 0.84)	660 fewer per 1000 (from 137 fewer to 797 fewer)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[3] Downgraded by 1 increment as the outcome is indirect

H.7 Pharmacological treatment for heart failure in people with heart failure and chronic kidney disease

Table 36: Clinical evidence profile: ACE-inhibitor versus Placebo (CKD stages 3-4)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ACE-inhibitor versus Placebo (CKD stages 3-4)	Control	Relative (95% CI)	Absolute		
All-cause mortality - CKD stages 3-4 (follow-up mean 41 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	242/498 (48.6%)	207/538 (38.5%)	HR 0.88 (0.73 to 1.06)	37 fewer per 1000 (from 86 fewer to 18 more)	⊕OOO VERY LOW	CRITICAL
All-cause mortality - CKD stage 3b and 4 only (follow-up mean 41 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/134 (0%)	53/134 (39.6%)	HR 0.76 (0.54 to 1.07)	78 fewer per 1000 (from 158 fewer to 21 more)	⊕OOO VERY LOW	CRITICAL
All-cause hospitalisation												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	233/498 (46.8%)	260/538 (48.3%)	HR 0.88 (0.73 to 1.06)	43 fewer per 1000 (from 101 fewer to 20 more)	⊕OOO VERY LOW	CRITICAL
Quality of life												
0	No evidence available					none	-	-	-	-		CRITICAL
Renal function (change in serum creatinine mmol/l) (follow-up mean 12 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	466	501	-	MD 0.06 higher (0.02 to 0.1 higher)	⊕⊕OO LOW	IMPORTANT

Hyperkalaemia (follow-up mean 41 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	9/467 (1.9%)	6/503 (1.2%)	RR 1.62 (0.58 to 4.5)	7 more per 1000 (from 5 fewer to 42 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 37: Clinical evidence profile: ACE-inhibitor high dose versus low dose (CKD stages 3b-4)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ACE-inhibitor high dose**	**Low dose**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up median 46 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	-	52%[3]	HR 1.02 (0.86 to 1.21)	7 more per 1000 (from 52 fewer to 69 more)	⊕OOO VERY LOW	CRITICAL
Mortality or Hospitalisation (follow-up median 46 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	-	87%[3]	HR 1.02 (0.89 to 1.16)	5 more per 1000 (from 33 fewer to 36 more)	⊕OOO VERY LOW	CRITICAL
Quality of life												
0	No evidence available					none	-	-	-	-		CRITICAL
Renal dysfunction or hyperkalaemia (follow-up median 46 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[4]	none	40.3%	31.8%	RR 1.27 (1.07 to 1.50)	86 more per 1000 (from 22 more to 159 more)	⊕OOO VERY LOW	IMPORTANT
Hypotension/Dizziness (follow-up median 46 months)												

1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	36.9%	23.5%	RR 1.56 (1.28 to 1.89)	133 more per 1000 (from 66 more to 211 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment because the majority of evidence was from an indirect population (defined CKD in terms of creatinine, not eGFR)
[3] Data insufficient to calculate control group, overall risk for CKD group given
[4] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 38: Clinical evidence profile: Angiotensin receptor antagonist (ARB) versus placebo (CKD class 3b-4)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Angiotensin receptor antagonist (ARB)	Placebo	Relative (95% CI)	Absolute		
All-cause mortality (follow-up mean 23 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	362/1478 (24.5%)	341/1439 (23.7%)	HR 1.01 (0.85 to 1.2)	2 more per 1000 (from 32 fewer to 40 more)	⊕OOO VERY LOW	CRITICAL
Combined outcome: cardiovascular mortality or HF admission (follow-up mean 3.2 years)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	53/84 (63.1%)	44/70 (62.9%)	HR 0.92 (0.79 to 1.07)	31 fewer per 1000 (from 86 fewer to 25 more)	⊕OOO VERY LOW	CRITICAL
Morbid event (includes hospitalisation and death) (follow-up mean 23 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	499/1476 (33.8%)	549/1441 (38.1%)	HR 0.86 (0.74 to 1)	43 fewer per 1000 (from 82 fewer to 0 more)	⊕OOO VERY LOW	CRITICAL
Quality of life												
0	No evidence available					none	-	-	-	-		CRITICAL

Renal function: change in eGFR (follow-up mean 23 months; Better indicated by higher values)											
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	1105	1074	-	MD 3.6 lower (4.31 to 2.89 lower)	⊕OOO VERY LOW	IMPORTANT
Renal failure - progression to dialysis (follow-up mean 3.2 years)											
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	0/1476 (0%)	0/1435 (0%)	-[4]	[4]-	⊕OOO VERY LOW	IMPORTANT
Hyperkalaemia (follow-up mean 30 months)											
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	139/1560 (8.9%)	7.3%	RR 1.85 (1.4 to 2.43)	62 more per 1000 (from 29 more to 104 more)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of
[2] Downgraded by 1 increment due to indirectness, as compound outcome rather than numbers of admissions
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] Unable to calculate as zero events in both arms

Table 39: Clinical evidence profile: ARB high dose versus low dose (CKD class 3a/b)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ARB high dose	Low dose	Relative (95% CI)	Absolute		
Combined outcome: death or HF hospitalisation (follow-up mean 4.7 years)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	395/495 (79.8%)	369/450 (82%)	HR 0.98 (0.85 to 1.13)	6 fewer per 1000 (from 53 fewer to 36 more)	⊕OOO VERY LOW	CRITICAL
Quality of life												
0	No evidence available					none	-	-	-	-		CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded 1 increment due to indirectness as outcome was compound rather than numbers of admissions

Table 40: Clinical evidence profile: Beta-blocker versus Placebo (CKD stages 3-4)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Beta-blocker	Placebo	Relative (95% CI)	Absolute		
All-cause mortality - CKD class 3a (follow-up mean 1.1 years)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	6.25%[3]	HR 0.69 (0.51 to 0.91)	19 fewer per 1000 (from 5 fewer to 30 fewer)	⊕⊕OO LOW	CRITICAL
All-cause mortality - CKD class 3b-4 (follow-up mean 1.1 years)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	8.92%[3]	HR 0.55 (0.32 to 0.94)	39 fewer per 1000 (from 5 fewer to 60 fewer)	⊕⊕OO LOW	CRITICAL
All-cause mortality - CKD class 3-4 (follow-up mean 1.8 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	71/348 (20.4%)	92/356 (25.8%)	HR 0.76 (0.56 to 1.03)	55 fewer per 1000 (from 104 fewer to 7 more)	⊕OOO VERY LOW	CRITICAL
Combined outcome: death or hospitalisation - CKD class 3a (follow-up mean 1.3 years)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[4]	serious[2]	none	0/361 (0%)	46.4%[5]	HR 0.72 (0.57 to 0.91)	102 fewer per 1000 (from 31 fewer to 165 fewer)	⊕OOO VERY LOW	CRITICAL
Combined outcome: death or hospitalisation - CKD class 3b-4 (follow-up mean 1.3 years)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[4]	serious[2]	none	-	55.3%[5]	HR 0.82 (0.64 to 1.05)	70 fewer per 1000 (from 150 fewer to 18 more)	⊕OOO VERY LOW	CRITICAL
Hospitalisation (time to event) - CKD class 3a (follow-up mean 1 years)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	161/370 (43.5%)	187/500 (37.4%)	HR 0.9 (0.73 to 1.11)	30 fewer per 1000 (from 84 fewer to 31 more)	⊕OOO VERY LOW	CRITICAL
Hospitalisation (time to event) - CKD class 3b-4 (follow-up mean 1 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	105/204 (51.5%)	121/137 (88.3%)	HR 0.61 (0.47 to 0.79)	153 fewer per 1000 (from 67 fewer to 248 fewer)	⊕OOO VERY LOW	CRITICAL
Hospitalisation for cardiovascular disorder - CKD class 3-4 (follow-up mean 1.8 years)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[6]	serious[2]	none	100/348 (28.7%)	104/356 (29.2%)	HR 0.93 (0.7 to 1.24)	17 fewer per 1000 (from 77 fewer to 56 more)	⊕OOO VERY LOW	CRITICAL
HF hospitalisation - CKD class 3a (follow-up mean 1.3 years)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[6]	serious[2]	none	-	16.7%[5]	HR 0.66 (0.45 to 0.97)	53 fewer per 1000 (from 5 fewer to 88 fewer)	⊕OOO VERY LOW	CRITICAL
HF hospitalisation - CKD class 3b-4 (follow-up mean 1.3 years)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[6]	serious[2]	none	-	22%[5]	HR 0.76 (0.51 to 1.13)	48 fewer per 1000 (from 101 fewer to 25 more)	⊕OOO VERY LOW	CRITICAL
Quality of life												
0	No evidence available					none	-	-	-	-		CRITICAL
Renal failure (not defined) (follow-up mean 1.8 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[7]	none	0/440 (0%)	0/446 (0%)	-[7]	-[7]	⊕⊕OO LOW	IMPORTANT
Bradycardia (follow-up mean 1.8 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	Serious[2]	none	12/440 (2.7%)	9/446 (2%)	RR 1.35 (0.58 to 3.18)	7 more per 1000 (from 8 fewer to 44 more)	⊕OOO VERY LOW	IMPORTANT

Hypotension (follow-up mean 1.8 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/440 (0.45%)	0/446 (0%)	Peto Odds Ratio 7.51 (0.47 to 120.22)	0 more per 1000 (from 0 more to 10 more)[9]	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID and downgraded by 2 increments if the confidence intervals crossed both MIDs
[3] Control risk taken from MERIT-HF
[4] Downgraded 1 increment for indirectness as compound outcome rather than numbers of admissions
[5] Data insufficient to calculate control risk. Overall risk given
[6] Downgraded 1 increment for indirectness as outcome is subset of protocol all-cause hospitalisation specified in protocol
[7] Unable to calculate as zero events in both arms
[9] Absolute risk difference calculated using RevMan software

Table 41: Clinical evidence profile: Digoxin versus placebo (CKD class 3-5)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Digoxin	Placebo	Relative (95% CI)	Absolute		
All-cause mortality - CKD class 3a/b (follow-up mean 3 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none		38%[2]	HR 0.95 (0.85 to 1.06)	15 fewer per 1000 (from 46 fewer to 18 more)	⊕OOO VERY LOW	CRITICAL
All-cause mortality - CKD class 4-5 (follow-up mean 3 years)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none		58%[2]	HR 0.93 (0.65 to 1.33)	26 fewer per 1000 (from 149 fewer to 105 more)	⊕OOO VERY LOW	CRITICAL
Death or Hospitalisation - CKD class 3a/b (follow-up mean 3 years)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[4]	no serious imprecision	none		38%[5]	HR 0.84 (0.76 to 0.93)	49 fewer per 1000 (from 21 fewer to 75 fewer)	⊕OOO VERY	CRITICAL

											LOW	
Death or Hospitalisation - CKD class 4-5 (follow-up mean 3 years)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[4]	serious[3]	none		58%[5]	HR 0.77 (0.55 to 1.08)	93 fewer per 1000 (from 201 fewer to 28 more)	⊕OOO VERY LOW	CRITICAL
Quality of Life												
0	No evidence available					none	-	-	-	-		CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Data not sufficient to calculate control risk. Overall risk for given for participants with eGFR around 45 or below 34 respectively
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] Downgraded as compound outcome rather than protocol
[5] Data not sufficient to calculate. Overall mortality risk given

Table 42: Clinical evidence profile: Ivabradine versus placebo (CKD class 3a/b)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ivabradine	Placebo	Relative (95% CI)	Absolute		
All-cause mortality												
0	No evidence available					none	-	-	-	-		CRITICAL
Hospitalisations												
0	No evidence available					none	-	-	-	-		CRITICAL
Quality of Life												
0	No evidence available					none	-	-	-	-		CRITICAL
Renal function: change in eGFR (follow-up mean 23 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	437	428	-	MD 0.2 higher (2 lower to 2.4 higher)	⊕OOO VERY LOW	IMPORTANT
Renal failure												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	79/780 (10.1%)	85/799 (10.6%)	RR 0.95 (0.71 to 1.27)	5 fewer per 1000 (from 31 fewer to 29 more)	⊕OOO VERY LOW	IMPORTANT

Hyperkalaemia (follow-up mean 23 months)											
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	14/780 (1.8%)	27/799 (3.4%)	RR 0.53 (0.28 to 1.01)	16 fewer per 1000 (from 24 fewer to 0 more)	⊕OOO VERY LOW	IMPORTANT
Bradycardia (symptomatic only) (follow-up mean 23 months)											
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	35/780 (4.5%)	14/799 (1.8%)	RR 2.56 (1.39 to 4.72)	27 more per 1000 (from 7 more to 65 more)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 43: Clinical evidence profile: Mineralocorticoid Receptor Antagonist (MRA) versus placebo (CKD class 3a/b)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MRA	Placebo	Relative (95% CI)	Absolute		
All-cause mortality (RR) (follow-up mean 2 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness[2]	serious[3]	none	32/390 (8.2%)	48/402 (11.9%)	RR 0.69 (0.45 to 1.05)	37 fewer per 1000 (from 66 fewer to 6 more)	⊕⊕OO LOW	CRITICAL
Combined outcome: cardiovascular mortality or HF admission (RR) - CKD class 3a/b (follow-up mean 2 years)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[4]	serious[3]	none	107/439 (24.4%)	163/473 (34.5%)	RR 0.71 (0.58 to 0.87)	100 fewer per 1000 (from 45 fewer to 145 fewer)	⊕OOO VERY LOW	CRITICAL
HF hospitalisation (RR) - CKD class 3a/b (follow-up mean 2 years)												
1	randomised trials	serious[1]	no serious inconsistency	serious[5]	serious[3]	none	30/390 (7.7%)	44/402 (10.9%)	RR 0.7 (0.45 to 1.09)	33 fewer per 1000 (from 60 fewer to 10 more)	⊕OOO VERY LOW	CRITICAL
Quality of Life												
0	No evidence available					none	-	-	-	-		CRITICAL

Renal function change in eGFR CKD class 3a/b (follow-up mean 2 years; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	422	461	-	MD 2.11 lower (4.23 lower to 0.01 higher)	⊕OOO VERY LOW	
Hyperkalaemia during study (follow-up mean 2 years)												
2	randomised trials	very serious[1]	no serious inconsistency[6]	no serious indirectness	no serious imprecision	none	170/812 (20.9%)	77/863 (8.9%)	RR 2.32 (1.37 to 3.91)	118 more per 1000 (from 33 more to 260 more)	⊕⊕OO LOW	

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Reports mortality as relative risk, rather than protocol time to event but not downgraded
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] Downgraded 1 increment for indirectness as reporting compound outcome rather than numbers of hospitalisations
[5] Downgraded 1 increment for indirectness as reporting only proportion having HF hospitalisations, not numbers of all cause hospitalisations
[6] Statistical heterogeneity, but both have results suggesting clinical harm. Subgroup analysis not done as insufficient studies

H.8 Coronary revascularisation

Table 44: Clinical evidence profile: CABG + Medical therapy versus medical therapy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CABG	Medical therapy	Relative (95% CI)	Absolute		
All-cause mortality (follow-up median 9.8 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	359/610 (58.9%)	398/602 (66.1%)	HR 0.80 (0.7 to 0.93)	82 fewer per 1000 (from 27 fewer to 130 fewer)	⊕⊕⊕O MODERATE	CRITICAL

All-cause mortality (follow-up 30 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	22/610 (3.6%)	7/602 (1.2%)	HR 3.12 (1.33 to 7.32)	24 more per 1000 (from 4 more to 70 more)	⊕⊕⊕O MODERATE	CRITICAL
Quality of life - EQ-5D (follow-up 12 months; range of scores: 0-1; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	610	602	-	MD 0.05 higher (0.02 to 0.09 higher)	⊕⊕OO LOW	CRITICAL
Quality of life - EQ5D-VAS (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	610	602	-	MD 5.9 higher (3.2 to 8.5 higher)	⊕⊕⊕O MODERATE	CRITICAL
Quality of life - KCCQ (quality of life domain) (follow-up 12 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	610	602	-	MD 8.8 higher (5.4 to 12.2 higher)	⊕⊕⊕O MODERATE	CRITICAL
Quality of life - SF-12 (Physical component) (follow-up 12 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	610	602	-	MD 1.5 higher (0.5 to 2.5 higher)	⊕⊕⊕O MODERATE	CRITICAL
Quality of life - SF-12 (Mental Component) (follow-up 12 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	610	602	-	MD 2.2 higher (0.5 to 3.9 higher)	⊕⊕⊕O MODERATE	CRITICAL
All-cause hospitalisations (follow-up median 4.7 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	290/610 (47.5%)	340/602 (56.5%)	RR 0.84 (0.75 to 0.94)	90 fewer per 1000 (from 34 fewer to 141 fewer)	⊕⊕⊕O MODERATE	CRITICAL

Subsequent procedures - CABG (follow-up median 4.7 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/610 (0.16%)	100/602 (16.6%)	Peto Odds Ratio 0.12 (0.08 to 0.17)	146 fewer per 1000 (from 138 fewer to 153 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
Subsequent procedures - PCI (follow-up median 4.7 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	26/610 (4.3%)	37/602 (6.1%)	RR 0.69 (0.43 to 1.13)	19 fewer per 1000 (from 35 fewer to 8 more)	⊕⊕OO LOW	IMPORTANT
NYHA Class I (follow-up median 4.7 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[2]	none	255/610 (41.8%)	206/602 (34.2%)	RR 1.22 (1.06 to 1.41)	75 more per 1000 (from 21 more to 140 more)	⊕⊕OO LOW	IMPORTANT
Stroke (follow-up median 9.8 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	47/610 (7.7%)	41/602 (6.8%)	RR 1.13 (0.76 to 1.69)	9 more per 1000 (from 16 fewer to 47 more)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if majority of the evidence was rated high risk of bias, downgraded by 2 increments if majority of the evidence was rated very high risk of bias
[2] Downgraded by 1 increment if the confidence intervalcrossed one MID, downgraded by 2 increments if the confidence interval crossed both MIDs
[3] Downgraded by 1 increment due to indirectness of the outcome (protocol outcome – change in NYHA class; extracted outcome no. in NYHA class I).

Table 45: Clinical evidence profile: Invasive strategy + medical therapy versus medical therapy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Invasive strategy**	**Medical therapy**	**Relative (95% CI)**	**Absolute**		
All-cause mortality (follow-up 4.9 years)												
1	randomised	serious[1]	no serious	no serious	very	none	26/68	25/68	RR 1.04	15 more per 1000	⊕OOO	CRITICAL

	trials		inconsistency	indirectness	serious[2]		(38.2%)	(36.8%)	(0.67 to 1.61)	(from 121 fewer to 224 more)	VERY LOW	
Quality of life - EQ-5D (follow-up 6 months; range of scores: 0-1; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	68	68	-	MD 0.02 lower (0.14 lower to 0.10 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life - MLWHF (follow-up 6 months; range of scores: 0-105; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	68	68	-	MD 3.9 lower (11.35 lower to 3.55 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if majority of the evidence was rated high risk of bias, downgraded by 2 increments if majority of the evidence was rated very high risk of bias.
[2] Downgraded by 1 increment if the confidence intervalcrossed one MID, downgraded by 2 increments if the confidence interval crossed both MIDs.

H.9 Home-based versus centre-based rehabilitation

Table 46: Clinical evidence profile: Home-based exercise training versus centre-based exercise training

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Home-based care		Relative (95% CI)	Absolute		
All-cause mortality (follow-up 2 to 6 months)												
5	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/165 (2.4%)	4/170 (2.4%)	Peto odds ratio 1.01 (0.23 to 4.48)	0 more per 1000 (from 18 fewer to 82 more)	⊕OOO VERY LOW	CRITICAL
Quality of life - SF-36 PCS (follow-up 2 to 6 months; Better indicated by higher values)												

2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	90	71	-	MD 0.56 lower (5.45 lower to 4.33 higher)	⊕⊕OO LOW	CRITICAL
Quality of life - SF-36 MCS (follow-up 2 to 6 months; Better indicated by higher values)												
2	randomised trials	very serious[1]	serious[3]	no serious indirectness	serious[2]	none	90	71	-	MD 0.72 higher (5.74 lower to 7.18 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life - EQ-5D utility (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0	-	-	MD 0.06 lower (0.16 lower to 0.04 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Quality of life - MLWHFQ (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	23	26	-	MD 4 lower (17 lower to 9 higher)	⊕⊕⊕O MODERATE due to imprecision	CRITICAL
Exercise capacity - ISWT (follow-up 2 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	90	71	-	MD 6 higher (104.42 lower to 116.22 higher)	⊕OOO VERY LOW	IMPORTANT
Exercise capacity - 6MWT (follow-up 2 months; Better indicated by higher values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	98	103	-	MD 0.82 higher	⊕⊕⊕O	IMPORTANT

										(23.52 lower to 25.16 higher)	MODERATE	
Exercise Capacity VO2max (follow-up 2 to 6 months; Better indicated by higher values)												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	122	99	-	MD 0.09 higher (1.27 lower to 1.46 higher)	⊕⊕OO LOW	IMPORTANT
Exercise capacity - 10 metre walk test (fast) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	23	26	-	MD 1.0 higher (0.9 to 1.1 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Completers (follow-up 2 to 6 months)												
4	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	137/149 (91.9%)	114/146 (78.1%)	RR 1.18 (1.07 to 1.3)	141 more per 1000 (from 55 more to 234 more)	⊕OOO VERY LOW	IMPORTANT
Adherence to intervention (Cowie 2012) (follow-up 2 months)												
1	randomised trials	serious[1]	no serious inconsistency[4]	no serious indirectness	very serious[2]	none	11/15 (73.3%)	12/15 (80%)	RR 0.92 (0.62 to 1.36)	64 fewer per 1000 (from 304 fewer to 288 more)	⊕OOO VERY LOW	IMPORTANT
Adherence to intervention (Daskapan 2005) (follow-up 3 months)												
1	randomised trials	very serious[1]	no serious inconsistency[4]	no serious indirectness	serious[2]	none	14/15 (93.3%)	11/14 (78.6%)	RR 1.19 (0.88 to 1.61)	149 more per 1000 (from 94 fewer to	⊕OOO VERY LOW	IMPORTANT

										479 more)		
Adherence to intervention (Karapolat 2009) (follow-up 2 months)												
1	randomised trials	serious[1]	no serious inconsistency[4]	no serious indirectness	no serious imprecision[2]	none	32/37 (86.5%)	33/37 (89.2%)	RR 0.97 (0.82 to 1.15)	27 fewer per 1000 (from 161 fewer to 134 more)	⊕⊕⊕O MODERATE	IMPORTANT
Adherence to intervention (Piotrowicz 2010) (follow-up 2 months)												
1	randomised trials	very serious[1]	no serious inconsistency[4]	no serious indirectness	serious[2]	none	77/77 (100%)	59/75 (78.7%)	RR 1.27 (1.13 to 1.43)	212 more per 1000 (from 102 more to 338 more)	⊕OOO VERY LOW	IMPORTANT
Adherence to intervention (hwang 2017) (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	23	26	-	MD 6 higher (2 to 10 higher)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Heterogeneity, I2=54%, downgraded by 1 increment

H.10 Monitoring

Table 47: Clinical evidence profile: [NP monitoring versus clinical monitoring]

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NP monitoring**	**Clinical monitoring**	**Relative (95% CI)**	**Absolute**		
Mortality (HR) - Age <75 years (follow-up 6-36 months)												
9	randomised trials	Serious[1]	no serious inconsistency[2]	no serious indirectness	Serious[3]	none		24.8%[4]	HR 0.74 (0.55 to 1)	58 fewer per 1000 (from 103 fewer to 0 more)	⊕⊕OO LOW	CRITICAL
Mortality (HR) - Age 75 and over (follow-up 6-36 months)												
9	randomised trials	Serious[1]	no serious inconsistency[2]	no serious indirectness	Serious[3]	none		35.3%[4]	HR 1.22 (0.81 to 1.85)	59 more per 1000 (from 56 fewer to 200 more)	⊕⊕OO LOW	CRITICAL
Mortality (RR) - All ages (follow-up range 1-2 years)												
2	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	Serious[3]	none	70/472 (14.8%)	14.4%	RR 0.88 (0.65 to 1.18)	17 fewer per 1000 (from 50 fewer to 26 more)	⊕⊕OO LOW	CRITICAL
All-cause hospitalisation (HR) - Age <75 years (follow-up 6-36 months)												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[3]	none		69.6%[5]	HR 0.81 (0.66 to 0.99)	77 fewer per 1000 (from 4 fewer to 152 fewer)	⊕⊕⊕O MODERATE	CRITICAL
All-cause hospitalisation (HR) - Age 75 and over (follow-up 6-36 months)												

4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[3]	none		69.9%[5]	HR 1.03 (0.84 to 1.27)	11 more per 1000 (from 64 fewer to 83 more)	⊕⊕⊕O MODERATE	CRITICAL
All-cause hospitalisation (RR) - All ages (follow-up mean 15 months)												
1	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	Serious[3]	none	52/110 (47.3%)	60/110 (54.5%)	RR 0.87 (0.67 to 1.12)	71 fewer per 1000 (from 180 fewer to 65 more)	⊕⊕OO LOW	CRITICAL
All-cause hospitalisation (Rate Ratio) - All ages (follow-up median 9 months)												
1	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	17/33 (51.5%)	25/36 (69.4%)	Rate Ratio 0.74 (0.4 to 1.37)	181 fewer per 1000 (from 417 fewer to 257 more)	⊕OOO VERY LOW	CRITICAL
HF hospitalisation (HR) - All ages (follow-up 6-36 months)												
5	randomised trials	Serious[1]	no serious inconsistency	Serious[6]	Serious[3]	none		24.5%[7]	HR 0.78 (0.61 to 0.99)	48 fewer per 1000 (from 2 fewer to 87 fewer)	⊕OOO VERY LOW	CRITICAL
HF hospitalisation (RR) - All ages (follow-up mean 2 years)												
1	randomised trials	very serious[1]	no serious inconsistency	Serious[6]	Serious[3]	none	6/26 (23.1%)	13/26 (50%)	RR 0.46 (0.21 to 1.03)	270 fewer per 1000 (from 395 fewer to 15 more)	⊕OOO VERY LOW	CRITICAL
HF hospitalisation (Rate Ratio) – All ages (follow-up 12 to 24 months years)												

1	randomised trials	Serious[1]	no serious inconsistency	Serious[6]	Serious[3]	none	350/446 (78.5%)	277/448 (61.8%)	Rate Ratio 1.26 (1.08 to 1.48)	161 more per 1000 (from 49 more to 297 more)	⊕OOO VERY LOW	CRITICAL
Quality of life MLWHFQ (follow-up mean 12 months; measured with: final score; range of scores: 0-105; Better indicated by lower values)												
2	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	231	231	-	MD 1.4 higher (2.23 lower to 5.02 higher)	⊕⊕⊕O MODERATE	CRITICAL
Quality of life - KCCQ (follow-up mean 9 months; measured with: change score; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	126	124	-	MD 2.6 lower (7.19 lower to 1.99 higher)	⊕⊕OO LOW	CRITICAL
Quality of life SF36 physical (follow-up mean 12 months; measured with: final score; range of scores: 0-100; Better indicated by higher values)												
2	randomised trials	Serious[1]	very serious[9]	no serious indirectness	no serious imprecision	none	210	208	-	MD 0.33 lower (5.13 lower to 4.47 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life SF36 mental (follow-up mean 12 months; measured with: final score; range of scores: 0-100; Better indicated by higher values)												
2	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	210	208	-	MD 0.06 higher (1.9 lower to 2.02 higher)	⊕⊕⊕O MODERATE	CRITICAL
Renal function - All ages (follow-up 6-12 months; measured with: eGFR, creatinine clearance and creatinine level; Better indicated by lower values)												

4	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	329	325	-	MD 0.76 lower (3.8 lower to 2.09 higher)[8]	⊕⊕⊕O MODERATE	IMPORTANT
Creatinine rise >30% (follow-up mean 3 months)												
1	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	7/110 (6.4%)	9/110 (8.2%)	RR 0.78 (0.3 to 2.01)	18 fewer per 1000 (from 57 fewer to 83 more)	⊕OOO VERY LOW	IMPORTANT
Acute Kidney Injury - Age <75 years (follow-up median 18 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	32/108 (29.6%)	28/102 (27.5%)	RR 1.08 (0.7 to 1.66)	22 more per 1000 (from 82 fewer to 181 more)	⊕⊕OO LOW	IMPORTANT
Acute Kidney Injury - Age 75 and over (follow-up median 18 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	42/146 (28.8%)	47/143 (32.9%)	RR 0.88 (0.62 to 1.24)	39 fewer per 1000 (from 125 fewer to 79 more)	⊕⊕OO LOW	IMPORTANT
Acute Kidney Injury - All ages (follow-up median 10 months)												
1	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	4/76 (5.3%)	3/75 (4%)	RR 1.32 (0.3 to 5.68)	13 more per 1000 (from 28 fewer to 187 more)	⊕OOO VERY LOW	IMPORTANT
Worsening renal function - all ages (follow-up 12-24 months)												
1	randomised	serious[1]	no serious	no serious	serious[2]	none	16/446	9/448	RR	16 more	⊕⊕OO	IMPORTANT

	trials		inconsistency	indirectness			(3.6%)	(2%)	1.79 (0.80 to 4.00)	per 1000 (from 4 fewer to 60 more)	LOW	
Hyperkalaemia - Age <75 years (follow-up median 18 months)												
1	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	20/108 (18.5%)	15/102 (14.7%)	RR 1.26 (0.68 to 2.32)	38 more per 1000 (from 47 fewer to 194 more)	⊕OOO VERY LOW	IMPORTANT
Hyperkalaemia - Age 75 and over (follow-up median 18 months)												
1	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	34/143 (23.8%)	35/146 (24%)	RR 0.99 (0.66 to 1.50)	2 fewer per 1000 (from 82 fewer to 120 more)	⊕OOO VERY LOW	IMPORTANT
Hyperkalaemia - All ages (follow-up 18-24 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/446 (2.5%)	6/448 (1.3%)	RR 1.84 (0.69 to 4.94)	11 more per 1000 (from 4 fewer to 53 more)	⊕OOO VERY LOW	IMPORTANT
Hypotension - Age <75 years (follow-up median 18 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	Serious[3]	none	48/108 (44.4%)	38/102 (37.3%)	RR 1.19 (0.86 to 1.66)	71 more per 1000 (from 52 fewer to 246 more)	⊕OOO VERY LOW	IMPORTANT
Hypotension - Age 75 and over (follow-up median 18 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	Serious[3]	none	68/143 (47.6%)	44/146 (30.1%)	RR 1.58 (1.17 to 2.13)	175 more per 1000 (from 51	⊕OOO VERY LOW	IMPORTANT

										more to 341 more)		
Hypotension - All ages (follow-up 10-24 months)												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	18/555 (3.2%)	6/559 (1.1%)	Peto odds ratio 3.08 (1.34 to 7.07)	22 more per 1000 (from 4 more to 65 more)	⊕⊕OO LOW	IMPORTANT
Bradycardia - Age <75 years (follow-up median 18 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	13/108 (12%)	8/102 (7.8%)	RR 1.53 (0.66 to 3.55)	42 more per 1000 (from 27 fewer to 200 more)	⊕⊕OO LOW	IMPORTANT
Bradycardia - Age 75 and over (follow-up median 18 months)												
1	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	21/143 (14.7%)	18/146 (12.3%)	RR 1.19 (0.66 to 2.14)	23 more per 1000 (from 42 fewer to 141 more)	⊕OOO VERY LOW	IMPORTANT
Symptomatic bradycardia - all ages (follow-up 12-24 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/446 (0%)	0/448 (0%)	Not estimable[10]	[10]	⊕⊕⊕O MODERATE	IMPORTANT
Significant Ventricular Arrhythmia - All ages (follow-up median 10 months)												
1	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	7/76 (9.2%)	4/75 (5.3%)	RR 1.73 (0.53 to 5.66)	39 more per 1000 (from 25 fewer to 249 more)	⊕OOO VERY LOW	IMPORTANT

New Atrial Fibrillation - All ages (follow-up median 10 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	2/76 (2.6%)	5/75 (6.7%)	RR 0.39 (0.08 to 1.97)	41 fewer per 1000 (from 61 fewer to 65 more)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Heterogeneity could not be formally assessed due to use of pooled data, which comprised seven of the nine included studies for the outcome. The paper reporting the pooled data did not report any statistics related to heterogeneity[214]
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4] The age-specific control risk was calculated from TIME-CHF and BATTLESCARRED
[5] The age-specific control risk was taken from TIME-CHF
[6] Downgraded by 1 increment because the outcome is an indirect indicator for the protocol outcome
[7] The control rate refers to the overall control risk in the Troughton meta-analysis (11 studies)
[8] Scores estimated using a standardised mean difference of -0.04 (-0.2 to 0.11)
[9] Downgraded by 1 increment as point estimates were inconsistent with little overlap of confidence intervals, not enough studies to perform sub-group analysis, I^2=81%
[10] Unable to estimate as zero events were reported in both arms of the study

Table 48: Clinical evidence profile: NP monitoring vs no monitoring protocol

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**NP monitoring**	**No protocol**	**Relative (95% CI)**	**Absolute**		
Mortality (HR) - Age <75 years (follow-up median 11 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none		31.25%[3]	HR 0.11 (0.01 to 0.86)	272 fewer per 1000 (from 37 fewer to 309 fewer)	⊕⊕OO LOW	CRITICAL
Mortality (HR) - Age 75 and over (follow-up median 11 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none		34.48%[3]	HR 1.48 (0.35 to 6.26)	120 more per 1000 (from 207 fewer to 584 more)	⊕OOO VERY LOW	CRITICAL

Mortality (RR) - Age <75 years (follow-up median 12 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[2]	none	9/58 (15.5%)	20/64 (31.3%)	RR 0.5 (0.25 to 1)	156 fewer per 1000 (from 234 fewer to 0 more)	⊕⊕⊕O MODERATE	CRITICAL
Mortality (RR) - Age 75 and over (follow-up median 12 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[2]	none	31/63 (49.2%)	20/58 (34.5%)	RR 1.43 (0.92 to 2.2)	148 more per 1000 (from 28 fewer to 414 more)	⊕⊕⊕O MODERATE	CRITICAL
Mortality (RR) - All ages (follow-up median 3 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	20/92 (21.7%)	35/90 (38.9%)	RR 0.56 (0.35 to 0.89)	171 fewer per 1000 (from 43 fewer to 253 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
All-cause hospitalisation (HR) - Age <75 years (follow-up median 11 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none		69.6%[4]	HR 1.08 (0.55 to 2.12)	28 more per 1000 (from 215 fewer to 224 more)	⊕OOO VERY LOW	CRITICAL
All-cause hospitalisation (HR) - Age 75 and over (follow-up median 11 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	Serious[2]	none		69.9%[4]	HR 1.66 (0.81 to 3.4)	165 more per 1000 (from 77 fewer to 284 more)	⊕OOO VERY LOW	CRITICAL
HF hospitalisation (RR) - Age <75 years (follow-up median 12 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	Serious[5]	very serious[2]	none	17/58 (29.3%)	23/64 (35.9%)	RR 0.82 (0.49 to 1.37)	65 fewer per 1000 (from 183 fewer to 133 more)	⊕OOO VERY LOW	CRITICAL
HF hospitalisation (RR) - Age 75 and over (follow-up median 12 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	Serious[5]	Serious[2]	none	27/63 (42.9%)	18/58 (31%)	RR 1.38 (0.86 to 2.23)	118 more per 1000 (from 43 fewer to 382 more)	⊕⊕OO LOW	CRITICAL
HF hospitalisation (RR) - All ages (follow-up median 12 months)												

1	randomised trials	no serious risk of bias	no serious inconsistency	Serious[5]	no serious imprecision	none	26/92 (28.3%)	55/90 (61.1%)	RR 0.46 (0.32 to 0.67)	330 fewer per 1000 (from 202 fewer to 416 fewer)	⊕⊕⊕O MODERATE	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Age-specific control rate taken from BATTLESCARRED usual care group
[4] Age-specific control rate taken from TIME-CHF clinically guided group (no usual care control available)
[5] Downgraded by one increment because the outcome was an indirect indicator of the protocol outcome

Table 49: Clinical Evidence Profile (Q2) NP monitoring vs Clinical monitoring for people with CHF and CKD

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NP monitoring	Clinical monitoring	Relative (95% CI)	Absolute		
All-cause mortality (follow-up 9.5-36 months)												
8	randomised trials	serious[1]	serious[5]	no serious indirectness	Very serious[2]	none		27.5%[3]	HR 1.04 (0.58 to 1.84)	9 more per 1000 (from 105 fewer to 172 more)	⊕OOO VERY LOW	CRITICAL
All-cause hospitalisation (days in hospital) (Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[4]	serious[2]	none	81	82	-	MD 0.38 higher (2.81 lower to 3.57 higher)	⊕OOO VERY LOW	CRITICAL

[1] Control group risk not available, approximated from risk for both arms combined, will under-estimate effect
[2]Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[3]Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[4]Downgraded by 1 increment for indirectness as proxy for the protocol outcome of rate ratio of all-cause admissions
[5] Downgraded by 1 increment as point estimates were inconsistent, not enough studies to perform subgroup analysis, I^2=73%

H.11 Telemonitoring and self-monitoring

Table 50: Clinical evidence profile: Structured telephone support versus usual care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Impact of structured telephone support and in heart failure	Control	Relative (95% CI)	Absolute		
All-cause mortality: Recent admission (follow-up 3 to 24 months)												
15	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	267/2692 (9.9%)	304/2667 (11.4%)	RR 0.84 (0.72 to 0.98)	18 fewer per 1000 (from 2 fewer to 32 fewer)	⊕⊕OO LOW	CRITICAL
All-cause hospitalisation: Recent admission												
11	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	996/2286 (43.6%)	980/2263 (43.3%)	RR 1 (0.94 to 1.07)	0 fewer per 1000 (from 26 fewer to 30 more)	⊕⊕OO LOW	CRITICAL
Quality of life: SF-36 (Physical health component): Recent admission (follow-up 180 days; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	352	363	-	MD 1.5 higher (0.04 to 2.96 higher)	⊕⊕⊕O MODERATE	CRITICAL
Quality of life: SF-36 (Physical functioning component): Recent admission (follow-up 180 days; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	352	363	-	MD 4.1 higher (0.4 to 7.8 higher)	⊕⊕⊕O MODERATE	CRITICAL
Quality of life: MLWHFQ: Recent admission (follow-up 6 months; Better indicated by lower values)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	69	65	-	MD 0.80 lower (6.48 lower to 4.88 higher)	⊕⊕OO LOW	CRITICAL
Quality of life: EQ-5D: Recent admission (follow-up 6 months; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	69	65	-	MD 0.04 lower (0.03 lower to 0.11 higher)	⊕⊕⊕O MODERATE	CRITICAL
Quality of life: HFSS: Recent admission (follow-up 30 days; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	303	302	-	MD 1.2 higher (2.4 lower to 4.8 higher)	⊕⊕OO LOW	CRITICAL
Adherence to intervention: Weight self daily: Recent admisssion (follow-up 3 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	141	146	-	MD 1.5 higher (0.62 to 2.38 higher)	⊕OOO VERY LOW	IMPORTANT
Adherence to intervention: Check ankles and feet for swelling: Recent admission (follow-up 3 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	141	146	-	MD 0.4 higher (0.15 to 0.65 higher)	⊕OOO VERY LOW	IMPORTANT
Adherence to intervention: Follow fluid recommendations: Recent admission (follow-up 3 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	141	146	-	MD 0.4 higher (0.13 to 0.67 higher)	⊕OOO VERY LOW	IMPORTANT
Adherence to intervention: Follow low-salt diet: Recent admission (follow-up 3 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	141	146	-	MD 0.3 higher (0.12 to 0.48 higher)	⊕OOO VERY LOW	IMPORTANT
Adherence to intervention: Take medication: Recent admission (follow-up 3 months; Better indicated by higher values)												
1	randomised	very serious[1]	no serious	no serious	no serious	none	141	146	-	MD 0.1 higher	⊕⊕OO	IMPORT

	trials		inconsistency	indirectness	imprecision					(0.04 lower to 0.24 higher)	LOW	ANT
All-cause mortality: STS vs UC - Community (follow-up 3 to 24 months)												
9	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	216/2408 (9%)	216/2087 (10.3%)	RR 0.88 (0.73 to 1.05)	12 fewer per 1000 (from 28 fewer to 5 more)	⊕⊕OO LOW	CRITICA L
All-cause hospitalisation: STS vs UC - Community (follow-up 3 to 24 months)												
6	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	426/1333 (32%)	541/1361 (39.8%)	RR 0.81 (0.73 to 0.89)	76 fewer per 1000 (from 44 fewer to 107 fewer)	⊕⊕OO LOW	CRITICA L
Quality of life: MLWHFQ: Community (follow-up 3 to 24 months; Better indicated by lower values)												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1061	1042	-	MD 4.28 lower (6.43 to 2.14 lower)	⊕⊕⊕⊕ HIGH	CRITICA L
Quality of life: Health distress score: Community (follow-up 3 months; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	36	16	-	MD 1.11 lower (1.97 to 0.25 lower)	⊕OOO VERY LOW	CRITICA L
All-cause mortality: STS vs UC - Mixed (follow-up mean 11.6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/94 (7.4%)	9/160 (5.6%)	RR 1.32 (0.51 to 3.44)	18 more per 1000 (from 28 fewer to 137 more)	⊕OOO VERY LOW	CRITICA L
All-cause hospitalisation: STS vs UC - Mixed (follow-up mean 11.6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	34/94 (36.2%)	48/160 (30%)	RR 1.21 (0.84 to 1.72)	63 more per 1000 (from 48 fewer to 216 more)	⊕⊕OO LOW	CRITICA L
Quality of life: MLWHFQ: Mixed (follow-up 16 weeks; Better indicated by lower values)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	25	25	-	MD 20.76 lower (23.78 to 17.74 lower)	⊕OOO VERY LOW	CRITICAL
Quality of life: KCCQ HRQoL: Mixed (Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	25	25	-	MD 12.9 higher (1.96 to 23.84 higher)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Funnel plots constructed by the Cochrane authors showed asymmetry and the potential of a strong publication bias in the studies included within the review

Table 51: Clinical evidence profile: Telemonitoring versus usual care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Impact of telemonitoring in heart failure**	**Control**	**Relative (95% CI)**	**Absolute**		
All-cause mortality: Recent admission (follow-up 3 to 24 months)												
9	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	69/793 (8.7%)	101/687 (14.7%)	RR 0.56 (0.42 to 0.74)	65 fewer per 1000 (from 38 fewer to 85 fewer)	⊕⊕OO LOW	CRITICAL
All-cause hospitalisation: Recent admission (not explained by subgrouping for age, publication date or intensity) (follow-up 3 to 24 months)												
8	randomised trials	serious[1]	very serious[4]	no serious indirectness	serious[2]	reporting bias[3]	387/753 (51.4%)	395/647 (61.1%)	RR 0.81 (0.66 to 0.98)	116 fewer per 1000 (from 12 fewer to 208 fewer)	⊕OOO VERY LOW	CRITICAL
Quality of life: SF-12 Physical: Recent admission (follow-up 6 months; Better indicated by higher values)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	138	142	-	MD 2.4 higher (0.15 lower to 4.95 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Quality of life: SF-12 Mental: Recent admission (follow-up 6 months; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	138	142	-	MD 0.7 higher (2.1 lower to 3.5 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Quality of life: Health distress score: Recent admission (follow-up 6 months; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	138	142	-	MD 0.7 lower (2.7 lower to 1.3 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Quality of life: MLWHFQ: Recent admission (follow-up 3 to 6 months; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	177	176	-	MD 3.01 lower (6.88 lower to 0.87 higher)	⊕⊕⊕O MODERATE	CRITICAL
Quality of life: SF-36 Mental component summary: Recent admission (follow-up 12 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	28	29	-	MD 5 higher (0.52 lower to 10.52 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life: SF-36 Physical component summary: Recent admission (follow-up 12 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	28	29	-	MD 0 higher (5.71 lower to 5.71 higher)	⊕OOO VERY LOW	CRITICAL
All-cause mortality: Community (follow-up 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/10 (20%)	3/10 (30%)	RR 0.67 (0.14 to 3.17)	99 fewer per 1000 (from 258 fewer to	⊕OOO VERY LOW	CRITICAL

										651 more)		
All-cause mortality: Mixed (follow-up 3 to 24 months)												
8	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	155/1147 (13.5%)	166/1213 (13.7%)	RR 0.96 (0.79 to 1.16)	5 fewer per 1000 (from 29 fewer to 22 more)	⊕⊕OO LOW	CRITICAL
All-cause hospitalisation: Mixed (not explained by subgrouping for age) (follow-up 3 to 24 months)												
6	randomised trials	no serious risk of bias	serious[5]	no serious indirectness	no serious imprecision	reporting bias[3]	463/999 (46.3%)	473/1053 (44.9%)	RR 1.02 (0.88 to 1.18)	9 more per 1000 (from 54 fewer to 81 more)	⊕⊕OO LOW	CRITICAL
Quality of life: SF-36 Physical functioning component: Mixed (follow-up 24 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	354	356	-	MD 2.1 higher (1.89 to 2.31 higher)	⊕⊕OO LOW	CRITICAL
Quality of life: MLWHFQ: Mixed (follow-up 6 to 12 months; Better indicated by lower values)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	140	145	-	MD 5.98 lower (11.37 to 0.58 lower)	⊕OOO VERY LOW	CRITICAL
Quality of life: SF-36 Mental component summary: Mixed (follow-up 12 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	102	101	-	MD 3 lower (5.76 to 0.24 lower)	⊕OOO VERY LOW	CRITICAL
Quality of life: SF-36 Physical component summary: Mixed (follow-up 12 months; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	102	101	-	MD 0 higher (2.89 lower to 2.89 higher)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

[3] Funnel plots constructed by the Cochrane authors showed asymmetry and the potential of a strong publication bias in the studies included within the review.
[4] Heterogeneity, I^2=83%, unexplained by subgroup analysis for age, year of publication and intensity of intervention
[5] Heterogeneity, I^2=55%, unexplained by subgroup analysis for age

Table 52: Clinical evidence profile: Structured telephone support + telemonitoring versus usual care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Impact of structured telephone support and telemonitoring in heart failure	Control	Relative (95% CI)	Absolute		
All-cause mortality: STS + TM vs UC - Recent admission (follow-up 180 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	100/715 (14%)	144/722 (19.9%)	RR 0.7 (0.56 to 0.89)	60 fewer per 1000 (from 22 fewer to 88 fewer)	⊕⊕OO LOW	CRITICAL
All-cause hospitalisation: STS + TM vs UC – Recent admission (follow-up 180 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	363/715 (50.8%)	355/722 (49.2%)	RR 1.03 (0.93 to 1.15)	15 more per 1000 (from 34 fewer to 74 more)	⊕⊕⊕O MODERATE	CRITICAL
Quality of life: MLHWFQ: Recent admission (follow-up 180 days; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	722	715	-	MD 4.13 lower (7.6 to 0.66 lower)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

1 # H.12 Multi-Disciplinary Teams

3 Studies arranged by name / first author

4 **Table 53: Clinical Evidence Profile: Agvall 2013: Nurse-led (MDTcm) vs Primary care (1 control), >6 months for low-risk HFrEF**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MDTcm	Control	Relative (95% CI)	Absolute		
Hospitalisations (follow-up mean 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	36/79 (45.6%)	51/81 (63%)	rate ratio 0.72 (0.47 to 1.11)	176 fewer per 1000 (from 334 fewer to 69 more)	⊕⊕OO LOW	CRITICAL
Quality of life - not reported												
0	-	-	-	-	-	none	-	-	-	-		
Death (follow-up mean 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/79 (5.1%)	5/81 (6.2%)	RR 0.82 (0.23 to 2.94)	11 fewer per 1000 (from 48 fewer to 120 more)	⊕OOO VERY LOW	CRITICAL
Prescribed ACE-I or ARB (follow-up mean 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	79/79 (100%)	68/81 (84%)	RR 1.19 (1.08 to 1.31)	160 more per 1000 (from 67 more to 260 more)	⊕⊕OO LOW	IMPORTANT
Prescribed beta-blocker (follow-up mean 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	58/79 (73.4%)	63/81 (77.8%)	RR 0.94 (0.79 to 1.13)	47 fewer per 1000 (from 163 fewer to 101 more)	⊕⊕OO LOW	IMPORTANT
Renal function (follow-up mean 12 months; measured with: Serume creatinine; Better indicated by lower values)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	79	79	-	MD 1.90 lower (11.88 lower to 8.08 higher)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 54: Clinical Evidence Profile: Auckland-HF (Doughty 2002): Long MDT clinic (MDTc) vs Primary +/- Secondary care in high risk HF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MDT clinic	Control	Relative (95% CI)	Absolute		
Hospitalisations (follow-up mean 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	120/100 (120%)	154/97 (158.8%)	rate ratio 0.76 (0.6 to 0.96)	381 fewer per 1000 (from 64 fewer to 635 fewer)	⊕⊕OO LOW	CRITICAL
Death (follow-up mean 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	19/100 (19%)	24/97 (24.7%)	RR 0.77 (0.45 to 1.31)	57 fewer per 1000 (from 136 fewer to 77 more)	⊕OOO VERY LOW	CRITICAL
Quality of life (follow-up mean 12 months; measured with: Minnesota LWHFQ (change score) lower=better; range of scores: 0-105; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	100	97	-	MD 7 lower (7.82 to 6.18 lower)	⊕⊕OO LOW	CRITICAL
Prescribed ACE-I (follow-up mean 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	67/81 (82.7%)	53/73 (72.6%)	RR 1.14 (0.96 to 1.35)	102 more per 1000 (from 29 fewer to 254 more)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by one increment as confidence interval cross one MID or two increments as confidence interval crosses both MID

Table 55: Clinical Evidence Profile: Berger 2010: Long case-management (MDTcm) vs Primary +/- secondary care (1/2 control), for >6 months high risk HFrEF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MDTcm	Control	Relative (95% CI)	Absolute		
Hospitalisations - dichotomous (follow-up mean 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	64/85 (75.3%)	39/47 (83%)	RR 0.91 (0.76 to 1.08)	75 fewer per 1000 (from 199 fewer to 66 more)	⊕OOO VERY LOW	CRITICAL
Death (follow-up mean 18 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	21/96 (21.9%)	35/90 (38.9%)	RR 0.56 (0.36 to 0.89)	171 fewer per 1000 (from 43 fewer to 249 fewer)	⊕⊕OO LOW	CRITICAL
Quality of life - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Prescribed ACE-I or ARB (follow-up mean 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	88/90 (97.8%)	87/90 (96.7%)	RR 1.01 (0.96 to 1.06)	10 more per 1000 (from 39 fewer to 58 more)	⊕⊕⊕O MODERATE	IMPORTANT
Prescribed beta-blocker (follow-up mean 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	92/96 (95.8%)	76/90 (84.4%)	RR 1.13 (1.03 to 1.25)	110 more per 1000 (from 25 more to 211 more)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded one increment as "count rate" was the protocol outcome for hospitalisation, and this is proportion who were hospitalised at least once
[3] Downgraded by one increment as confidence interval cross one MID or two increments as confidence interval crosses both MID

Table 56: Clinical Evidence Profile: Capomolla 2002: Long MDT clinic (MDTc) vs Cardiology clinic in high risk HFrEF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MDT clinic	Control	Relative (95% CI)	Absolute		
Hospitalisations (follow-up mean 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	13/112 (11.6%)	78/122 (63.9%)	rate ratio 0.18 (0.1 to 0.33)	524 fewer per 1000 (from 428 fewer to 575 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Cardiac Death (follow-up mean 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	3/112 (2.7%)	21/122 (17.2%)	RR 0.16 (0.05 to 0.51)	145 fewer per 1000 (from 84 fewer to 164 fewer)	⊕⊕OO LOW	CRITICAL
Utility (proxy for Quality of life) (follow-up mean 12 months; measured with: higher=better; range of scores: 0-1; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	serious[4]	none	109	101	-	MD 0.09 higher (0.04 to 0.14 higher)	⊕OOO VERY LOW	CRITICAL
ACE-I dose prescribed (long acting only) (follow-up mean 12 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	109	101	-	MD 8 higher (5.5 to 10.5 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Beta-blocker dose prescribed (follow-up mean 12 months; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	101	109	-	MD 21 higher (13.9 to 28.1 higher)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias bias
[2] Downgraded one increment as the outcome was not the protocol all-cause mortality
[3] Downgraded as not a protocol outcome for quality of life
[4] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 57: Clinical Evidence Profile: COACH basic (Jaarsma 2008): Long Nurse-led clinic (MDTn) vs Cardiology clinic in high risk HF

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**MDTn**	**Control**	**Relative (95% CI)**	**Absolute**		
Hospitalisations (follow-up mean 18 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	377/340 (110.9%)	376/339 (110.9%)	rate ratio 1.01 (0.88 to 1.17)	11 more per 1000 (from 133 fewer to 189 more)	⊕⊕⊕O MODERATE	CRITICAL
Death (follow-up mean 18 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	90/340 (26.5%)	99/339 (29.2%)	HR 0.88 (0.66 to 1.18)	30 fewer per 1000 (from 88 fewer to 43 more)	⊕⊕OO LOW	CRITICAL
Quality of life - not reported												
0	-	-	-	-	-	none	-	-	-	-		

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 58: Clinical Evidence Profile: COACH intensive (Jaarsma 2008): Long Home based MDT (MDThome) vs Cardiology clinic in high risk HF

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**MDT home**	**Control**	**Relative (95% CI)**	**Absolute**		
Hospitalisations (follow-up mean 18 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	408/344 (118.6%)	376/339 (110.9%)	rate ratio 1.10 (0.96 to 1.27)	111 more per 1000 (from 44 fewer to 299 more)	⊕⊕OO LOW	CRITICAL
Death (follow-up mean 18 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	83/344 (24.1%)	99/339 (29.2%)	HR 0.81 (0.6 to 1.08)	48 fewer per 1000 (from 105 fewer to 19 more)	⊕⊕OO LOW	CRITICAL

Quality of life - not reported												
0	-	-	-	-	-	none	-	-	-	-		

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 59: Clinical Evidence Profile: DEAL-HF (De la Porte 2007): Long MDT clinic (MDTc) vs Cardiology clinic for high risk HF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MDT clinic	Control	Relative (95% CI)	Absolute		
Hospitalisation (follow-up mean 12 months; assessed with: Days in hospital)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	359/118 (304.2%)	644/122 (527.9%)	Rate Ratio 0.56 (0.49 to 0.64)	2310 fewer per 1000 (from 1890 fewer to 2680 fewer)[2]	⊕⊕⊕O MODERATE	CRITICAL
Death (follow-up mean 12 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	12/118 (10.2%)	23/122 (18.9%)	RR 0.54 (0.28 to 1.03)	87 fewer per 1000 (from 136 fewer to 6 more)	⊕⊕⊕O MODERATE	CRITICAL
Renal function (follow-up mean 12 months; measured with: mean creatinine levels (umol/l); Better indicated by lower values)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	118	122	-	MD 17 lower (0 to 0 higher)[5]	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded one increment as not protocol outcome for hospitalisation of count rates
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[4] Imprecision could not be assessed

Table 60: Clinical Evidence Profile: Del Sindaco 2007: Long MDT clinic (MDTc) vs Primary / secondary care for high risk HF

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MDT clinic	Control	Relative (95% CI)	Absolute		
Hospitalisations - dichotomous (follow-up mean 24 months)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	48/86 (55.8%)	65/87 (74.7%)	RR 0.75 (0.6 to 0.93)	187 fewer per 1000 (from 52 fewer to 299 fewer)	⊕OOO VERY LOW	CRITICAL
Death (follow-up mean 24 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	27/86 (31.4%)	27/86 (31.4%)	RR 0.85 (0.56 to 1.29)	47 fewer per 1000 (from 138 fewer to 91 more)	⊕OOO VERY LOW	CRITICAL
Quality of life - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by one increment as not the protocol outcomes for hospitalisations, count rate
[3] Downgraded by one increment as confidence interval crosses one MID or downgraded by two increments as confidence interval crosses both MIDs

Table 61: Clinical evidence Profile: Driscoll 2014: Mid-length Nurse-led clinic (MDTn) vs Primary / secondary care for high risk HFrEF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MDT nurse	Control	Relative (95% CI)	Absolute		
Hospitalisations (follow-up mean 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/12 (8.3%)	3/13 (23.1%)	rate ratio 0.67 (0.07 to 6.41)	76 fewer per 1000 person years (from 215 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Death (follow-up mean 6 months)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/12 (8.3%)	0/13 (0%)[3]	peto OR 8.03 (0.16 to 406)	80 more per 1000 (from 120 fewer to 280 more)[4]	⊕OOO VERY LOW	CRITICAL
Quality of life (follow-up mean 12 months; measured with: MLWHFQ (change score) lower=better; range of scores: 0-105; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12	13	-	MD 2.80 lower (13.68 lower to 8.08 higher)	⊕⊕OO LOW	CRITICAL
Prescribed "optimal" dose beta-blocker (follow-up mean 6 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	9/11 (81.8%)	5/13 (38.5%)	RR 2.13 (1.01 to 4.47)	435 more per 1000 (from 4 more to 1000 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded one increment as confidence interval crossed one MID or two increments as confidence interval crossed both MIDs
[3] Cannot be estimated as no events in control arm
[4] Absolute difference calculated by RevMan

Table 62: Clinical evidence Profile: Ducharme 2005: Mid-length MDT clinic (MDTc) vs Primary / secondary care for high risk HF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MDT clinic	Control	Relative (95% CI)	Absolute		
Hospitalisations (follow-up mean 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	77/115 (67%)	113/115 (98.3%)	rate ratio 0.68 (0.51 to 0.91)	314 fewer per 1000 (from 88 fewer to 481 fewer)	⊕⊕OO LOW	CRITICAL
Death (follow-up mean 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12/115 (10.4%)	19/115 (16.5%)	RR 0.63 (0.32 to 1.24)	61 fewer per 1000 (from 112 fewer to 40 more)	⊕⊕OO LOW	CRITICAL
Quality of life - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both

Table 63: Clinical evidence Profile: Ekman 1998: Mid-length Nurse-led clinic (MDTn) vs Primary care (1 control) 3-6 months for high risk HF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MDT nurse	Control	Relative (95% CI)	Absolute		
Hospitalisations (follow-up mean 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	87/79 (110.1%)	95/79 (120.3%)	rate ratio 0.92 (0.68 to 1.22)	96 fewer per 1000 (from 385 fewer to 265 more)	⊕⊕OO LOW	CRITICAL
Death (follow-up mean 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious	none	21/79 (26.6%)	17/79 (21.5%)	RR 1.24 (0.71 to 2.16)	52 more per 1000 (from 62 fewer to 250 more)	⊕OOO VERY LOW	CRITICAL
NYHA class change (a proxy for QoL) (follow-up mean 6 months; measured with: mean level (I-IV), lower=better; range of scores: 1-4; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	no serious imprecision	none	79	79	-	MD 0.10 higher (0.15 lower to 0.35 higher)	⊕⊕OO LOW	CRITICAL
Prescribed ACE-I (follow-up mean 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	49/70 (70%)	47/75 (62.7%)	RR 1.12 (0.89 to 1.41)	75 more per 1000 (from 69 fewer to 257 more)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by one increment as confidence interval cross one MID or downgraded by two increments as confidence interval crosses both MID
[3] Downgraded by one increment as a proxy measure of quality of life

Table 64: Clinical evidence Profile: Gonzalez-Guerrero 2014: Mid-length MDT clinic (MDTc) vs Primary care +/- Geriatric clinic for high risk HF

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MDT clinic	Control	Relative (95% CI)	Absolute		
Hospitalisations (follow-up mean 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	42/59 (71.2%)	45/58 (77.6%)	rate ratio 0.92 (0.6 to 1.4)	62 fewer per 1000 (from 310 fewer to 310 more)	⊕OOO VERY LOW	CRITICAL
Death (follow-up mean 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	13/59 (22%)	22/58 (37.9%)	RR 0.58 (0.32 to 1.04)	159 fewer per 1000 (from 258 fewer to 15 more)	⊕⊕OO LOW	CRITICAL
Quality of life - not reported												
0	-	-	-	-	-	none	-	-	-	-		

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by one increment as confidence interval crosses one MID or two increments as confidence interval crosses both MIDs

Table 65: Clinical Evidence Profile: HICMann (Peters-Klimm 2010): Long non-specialist Case management (MDTcm) vs Primary care (1 control) >6 months for low risk (HFrEF)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MDT cm	Control	Relative (95% CI)	Absolute		
Hospitalsations (follow-up mean 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	40/87 (46%)	34/91 (37.4%)	rate ratio 1.23 (0.78 to 1.94)	86 more per 1000 (from 82 fewer to 351 more)	⊕OOO VERY LOW	CRITICAL
Death (follow-up median 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/92 (5.4%)	5/98 (5.1%)	RR 1.07 (0.32 to 3.56)	4 more per 1000 (from 35 fewer to 131 more)	⊕OOO VERY LOW	CRITICAL

Quality of life (follow-up mean 12 months; measured with: Kansas City Cardiomyopathy Questionnaire, higher=better; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	87	93	-	MD 1.70 higher (3.28 lower to 6.68 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (physical) (follow-up mean 12 months; measured with: SF-36 physical health composite, higher=better; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	61	70	-	MD 0.3 lower (3.25 lower to 2.65 higher)	⊕⊕OO LOW	CRITICAL
Quality of life (mental) (follow-up mean 12 months; measured with: SF-36 mental health composite, higher=better; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	61	70	-	MD 0.1 lower (3.5 lower to 3.5 higher)	⊕⊕OO LOW	CRITICAL
Prescribed double therapy of ACE-I/ARB and B-blocker (follow-up mean 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	63/87 (72.4%)	67/93 (72%)	RR 1.01 (0.84 to 1.2)	7 more per 1000 (from 115 fewer to 144 more)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded one increment as confidence interval crosses one MID or two increments as confidence interval cross both MIDs

Table 66: Clinical Evidence Profile: J-HOMECARE (Tsuchihashi-Makaya 2013): Mid-length Case management (MDTcm) vs Cardiology clinic for high risk HF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**MDT home**	**Control**	**Relative (95% CI)**	**Absolute**		
Hospitalisations (follow-up mean 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	0/51 (0%)	10/47 (21.3%)[4]	HR 0.52 (0.28 to 0.98)	96 fewer per 1000 (from 4 fewer to 148 fewer)	⊕OOO VERY LOW	CRITICAL
Death (follow-up mean 12 months)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	8/79 (10.1%)	8/82 (9.8%)	RR 1.04 (0.41 to 2.63)	4 more per 1000 (from 58 fewer to 159 more)	⊕OOO VERY LOW	CRITICAL
Quality of life (physical) (follow-up mean 12 months; measured with: SF-8 physical component, higher=better; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious	no serious inconsistency	no serious indirectness	serious[3]	none	70	68	-	MD 2.00 higher (1.18 lower to 5.18 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (mental) (follow-up mean 12 months; measured with: SF-8 mental health component, higher=better; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	70	68	-	MD 2 higher (0.67 lower to 4.67 higher)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded one increment as not protocol outcome of count rates for hospitalisations
[3] Downgraded one increment as confidence interval crosses one MID or two increments as confidence interval crosses two MID
[4] Used estimated control rate

Table 67: Clinical evidence Profile: Ledwidge 2003: Short MDT clinic (MDTc) vs Primary +/- secondary care for high risk HF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**MDT clinic**	**Control**	**Relative (95% CI)**	**Absolute**		
Hospitalisations (follow-up mean 3 months)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	2/51 (3.9%)	12/47 (25.5%)	rate ratio 0.15 (0.03 to 0.69)	217 fewer per 1000 (from 79 fewer to 248 fewer)	⊕⊕OO LOW	CRITICAL
Death (follow-up mean 3 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/51 (5.9%)	3/47 (6.4%)	RR 0.92 (0.2 to 4.34)	5 fewer per 1000 (from 51 fewer to 213 more)	⊕OOO VERY LOW	CRITICAL
Quality of life - not reported												

0	-	-	-	-	-	none	-	-	-	-		CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias bias
[2] Downgraded by one increment as not protocol outcome of all-cause hospitalisations
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both

Table 68: Clinical Evidence Profile: Martensson 2005: Long non-specialist Case management (MDTcm) vs Primary care (1 control) > 6 months for low risk HF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MDT cm	Control	Relative (95% CI)	Absolute		
Hospitalisation - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Deaths (follow-up mean 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	10/76 (13.2%)	3/73 (4.1%)	RR 3.20 (0.92 to 11.17)	90 more per 1000 (from 3 fewer to 418 more)	⊕OOO VERY LOW	
Quality of life - not reported												
0	-	-[1]	-	-	-[3]	none	79	81	-	-[3]		CRITICAL
Prescribed ACE-I at target dose (follow-up mean 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30/62 (48.4%)	39/68 (57.4%)	RR 0.84 (0.61 to 1.17)	92 fewer per 1000 (from 224 fewer to 97 more)	⊕OOO VERY LOW	IMPORTANT
Prescribed beta-blocker at target dose (follow-up mean 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	14/62 (22.6%)	16/68 (23.5%)	RR 0.96 (0.51 to 1.8)	9 fewer per 1000 (from 115 fewer to 188 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by one increment as confidence interval crosses one MID or two increments as confidence interval crosses both MID
[3] Precision cannot be assessed

Table 69: Clinical Evidence Profile: Northstar (Schou 2013): Extended follow-up in MDT clinic (MDTc) vs Primary care (1 control) >6 months for low risk HF (stable HFrEF)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MDT clinic	Control	Relative (95% CI)	Absolute		
Hospitalisations (follow-up median 2 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	655/460 (142.4%)	694/460 (150.9%)	rate ratio 0.94 (0.85 to 1.05)	91 fewer per 1000 (from 226 fewer to 75 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Hospitalisations per year (follow-up mean 1809 patient-years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	340/460 (73.9%)	346/460 (75.2%)	rate ratio 0.98 (0.88 to 1.1)	15 fewer per 1000 (from 90 fewer to 75 more)	⊕⊕⊕⊕ HIGH	
Death (follow-up median 2 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	60/460 (13%)	64/460 (13.9%)	HR 1.05 (0.74 to 1.5)	6 more per 1000 (from 34 fewer to 62 more)	⊕⊕OO LOW	CRITICAL
Quality of life (follow-up median 2 years; measured with: Minnesota LWHFQ (change score) lower=better; range of scores: 0-105; Better indicated by lower values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision[3]	none	372	351	-	MD 1 lower (1 lower to 1 higher)[3]	⊕⊕⊕O MODERATE	CRITICAL
Prescribed ACE-I (follow-up median 2 years)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	405/460 (88%)	407/460 (88.5%)	RR 1.00 (0.95 to 1.04)	0 fewer per 1000 (from 44 fewer to 35 more)	⊕⊕⊕O MODERATE	IMPORTANT
Prescribed beta-blocker (follow-up median 2 years)												

1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	403/460 (87.6%)	403/460 (87.6%)	RR 1.00 (0.95 to 1.05)	0 fewer per 1000 (from 44 fewer to 44 more)	⊕⊕⊕O MODERATE	IMPORTANT
Adverse - serum creatinine increase >50% during follow-up (follow-up median 2 years)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	13/372 (3.5%)	13/372 (3.5%)	RR 0.94 (0.44 to 2.01)	2 fewer per 1000 (from 20 fewer to 35 more)	⊕OOO VERY LOW	IMPORTANT
Adverse - hyperkalaemia (potassium > 5.0mmol/l) at follow-up (follow-up median 2 years)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	13/372 (3.5%)	22/351 (6.3%)	RR 0.56 (0.29 to 1.09)	28 fewer per 1000 (from 45 fewer to 6 more)	⊕⊕OO LOW	IMPORTANT
Adverse - hypotension (follow-up mean 12 months)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	3/372 (0.81%)	2/351 (0.57%)	RR 1.42 (0.24 to 8.42)	2 more per 1000 (from 4 fewer to 42 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by one increment as confidence interval crosses one MID or two increments as confidence interval crosses both MID
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[3] Precision cannot be formally assessed, but interquartile range suggests small confidence interval

Table 70: Clinical evidence Profile: Nucifora 2006: Mid-length MDT clinic (MDTc) vs Primary care for high risk HF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MDT clinic	Control	Relative (95% CI)	Absolute		
Hospitalisations (follow-up mean 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	79/99 (79.8%)	81/101 (80.2%)	rate ratio 1.00 (0.73 to 1.36)	0 fewer per 1000 (from 217 fewer to 289 more)	⊕OOO VERY LOW	CRITICAL
Deaths (follow-up mean 6 months)												
1	randomised	serious[1]	no serious	no serious	very serious[2]	none	14/99	8/101	RR 1.79 (0.78	63 more per 1000 (from	⊕OOO	CRITICAL

	trials		inconsistency	indirectness			(14.1%)	(7.9%)	to 4.07)	17 fewer to 243 more)	VERY LOW	
Quality of life (follow-up mean 6 months; measured with: Minnesota LWHFQ (change score) lower=better; range of scores: 0-105; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	74	76	-	MD 4 higher (1.82 lower to 9.82 higher)	⊕OOO VERY LOW	CRITICAL
Prescribed ACE-I (follow-up mean 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	68/85 (80%)	75/93 (80.6%)	RR 0.99 (0.86 to 1.15)	8 fewer per 1000 (from 113 fewer to 121 more)	⊕⊕⊕O MODERATE	IMPORTANT
Prescribed beta-blocker (follow-up mean 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	12/85 (14.1%)	18/93 (19.4%)	RR 0.73 (0.37 to 1.42)	52 fewer per 1000 (from 122 fewer to 81 more)	⊕OOO VERY LOW	IMPORTANT
Taking prescribed medication (follow-up mean 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	74/85 (87.1%)	78/93 (83.9%)	RR 1.04 (0.92 to 1.17)	34 more per 1000 (from 67 fewer to 143 more)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by one increment as confidence interval crosses one MID or two increments as confidence interval crosses both MIDs

Table 71: Clinical Evidence Profile: OPTIMAL (Mejhert 2004):Long Nurse-led clinic (MDTn) vs Primary care for high risk HF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MDT nurse	Control	Relative (95% CI)	Absolute		
Hospitalisations (follow-up mean 37 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	453/103 (439.8%)	514/105 (489.5%)	rate ratio 0.90 (0.79 to 1.02)	490 fewer per 1000 (from 1000 fewer to 98 more)	⊕⊕OO LOW	CRITICAL
Death (follow-up mean 37 months)												
1	randomised	serious[1]	no serious	no serious	serious[2]	none	40/103	34/105	RR 1.20 (0.83	65 more per 1000 (from	⊕⊕OO	CRITICAL

	trials		inconsistency	indirectness			(38.8%)	(32.4%)	to 1.73)	55 fewer to 236 more)	LOW	
Quality of life (follow-up mean 12 months; measured with: Nottingham Health Profile Part 1, lower=better; range of scores: 0-600; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	103	105	-	MD 9 higher (21 lower to 39 higher)	⊕⊕OO LOW	CRITICAL
Prescribed ACE-I (follow-up mean 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	68/103 (66%)	77/105 (73.3%)	RR 0.9 (0.75 to 1.08)	73 fewer per 1000 (from 183 fewer to 59 more)	⊕OOO VERY LOW	IMPORTANT
Prescribed beta-blockers (follow-up mean 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	57/103 (55.3%)	65/105 (61.9%)	RR 0.89 (0.71 to 1.12)	68 fewer per 1000 (from 180 fewer to 74 more)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 72: Clinical evidence Profile: PREFER (Brannstrom 2014): Mid-length Home-based MDT (MDThome) vs Primary +/- secondary care for high risk HF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**MDT home**	**Control**	**Relative (95% CI)**	**Absolute**		
Hospitalisations												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/36 (33.3%)	53/36 (147.2%)	rate ratio 0.28 (0.16 to 0.5)	1060 fewer per 1000 (from 736 fewer to 1237 fewer)[1]	⊕⊕⊕⊕ HIGH	CRITICAL
Death (follow-up mean 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	8/36 (22.2%)	4/36 (11.1%)	RR 2.00 (0.66 to 6.06)	111 more per 1000 (from 38 fewer to 562 more)	⊕⊕OO LOW	CRITICAL

Quality of life (follow-up mean 6 months; measured with: EQ-5D (appears to be EQ-5D visual analogue scale), higher=better; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	36	36	-	MD 8.1 higher (2.03 lower to 18.23 higher)	⊕OOO VERY LOW	CRITICAL

[1] Manually calculated as rate above 100%
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 73: **Clinical Evidence Profile: PRICE (Atienza 2004): Long MDT clinic (MDTc) vs Cardiology for high risk HF**

Quality assessment							**No of patients**		**Effect**		**Quality**	**Importance**
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**MDT clinic**	**Control**	**Relative (95% CI)**	**Absolute**		
Hospitalisations (follow-up mean 16 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	126/164 (76.8%)	199/174 (114.4%)	rate ratio 0.67 (0.54 to 0.84)	377 fewer per 1000 (from 183 fewer to 526 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Death (follow-up mean 16 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	No serious imprecision	none	51/164 (31.1%)	30/174 (17.2%)	RR 1.80 (1.21 to 2.68)	138 more per 1000 (from 36 more to 290 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Quality of life (follow-up mean 16 months; measured with: Minnesota LWHFQ, lower=better; range of scores: 0-105; Better indicated by lower values)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	110	110	-	MD 6.60 lower (8.47 to 4.73 lower)	⊕⊕OO LOW	CRITICAL
Prescribed ACE-I (follow-up mean 16 months)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	51/76 (67.1%)	53/77 (68.8%)	RR 0.97 (0.78 to 1.21)	21 fewer per 1000 (from 151 fewer to 145 more)	⊕⊕OO LOW	IMPORTANT

Prescribed beta-blocker (follow-up mean 16 months)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	48/76 (63.2%)	30/77 (39%)	RR 1.62 (1.17 to 2.25)	242 more per 1000 (from 66 more to 487 more)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[2] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 74: Clinical evidence Profile: Rao 2007: Short MDT clinic (MDTc) vs Primary care for high risk HF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**MDT clinic**	**Control**	**Relative (95% CI)**	**Absolute**		
Hospitalisations (follow-up median 9 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	23/59 (39%)	13/53 (24.5%)	Rate Ratio 1.59 (0.81 to 3.14)	145 more per 1000 (from 47 fewer to 525 more)	⊕⊕⊕O MODERATE	CRITICAL
Death (follow-up mean 9 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	1/59 (1.7%)	2/53 (3.8%)	RR 0.45 (0.04 to 4.81)	21 fewer per 1000 (from 36 fewer to 144 more)	⊕⊕OO LOW	CRITICAL
Quality of life - not reported												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Prescribed ACE-I (follow-up mean 3 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	50/59 (84.7%)	34/53 (64.2%)	RR 1.32 (1.05 to 1.66)	205 more per 1000 (from 32 more to 423 more)	⊕⊕⊕O MODERATE	IMPORTANT
Prescribed beta-blocker (follow-up mean 3 months)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	30/59 (50.8%)	1/53 (1.9%)	peto OR 11.29 (4.95 to 25.77)	194 more per 1000 (from 75 more to 467 more)	⊕⊕⊕⊕ HIGH	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 75: Clinical Evidence Profile: Varma 1999: Long Pharmacist-led clinic (MDT pharm) vs Primary care (1 control) >6 months for low risk HF

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	MDT clinic	Control	Relative (95% CI)	Absolute		
Hospitalisations (follow-up mean 12 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	14/42 (33.3%)	27/41 (65.9%)	rate ratio 0.51 (0.27 to 0.97)	323 fewer per 1000 (from 20 fewer to 481 fewer)	⊕OOO VERY LOW	CRITICAL
Death (follow-up mean 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/42 (16.7%)	7/41 (17.1%)	RR 0.98 (0.38 to 2.54)	3 fewer per 1000 (from 106 fewer to 263 more)	⊕OOO VERY LOW	CRITICAL
Quality of life (follow-up mean 12 months; measured with: Minnesota LWHFQ, lower=better; range of scores: 0-105; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	26	23	-	MD 6.40 lower (0.76 to 12.04 lower)	⊕OOO VERY LOW	CRITICAL
Taking prescribed medication (follow-up mean 12 months; assessed with: Self-report)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	26/26 (100%)	22/23 (95.7%)	RR 1.05 (0.93 to 1.18)	48 more per 1000 (from 67 fewer to 172 more)	⊕⊕OO LOW	IMPORTANT
Taking prescribed medication (follow-up mean 12 months; assessed with: Automated measure)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	10/13 (76.9%)	3/10 (30%)	RR 2.56 (0.95 to 6.92)	468 more per 1000 (from 15 fewer to 1000 more)	⊕OOO VERY	IMPORTANT

											LOW	

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by one increment as confidence interval crosses one MID or two increments as confidence interval crosses both MID

H.13 Transition between heart failure care settings

None.

H.14 Communication needs regarding diagnosis and prognosis

None.

H.15 Diuretics in advanced heart failure

None.

H.16 Domiciliary oxygen therapy in people with advanced heart failure

Table 76: Clinical evidence profile: [long term oxygen therapy versus best medical therapy]

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Long term oxygen therapy	Best medical therapy	Relative (95% CI)	Absolute		

Quality of life (MLWHF) (follow-up 3 months; Better indicated by lower values)											
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	53	53	-	MD 5.5 lower (10.49 to 0.51 lower)	⊕⊖⊖⊖ VERY LOW	CRITICAL
Quality of life (EQ-5D-3L) (follow-up 6 months; Better indicated by lower values)											
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	45	43	-	MD 0.01 higher (0.1 lower to 0.12 higher)	⊕⊖⊖⊖ VERY LOW	CRITICAL
Hospitalisation (follow-up 24 months)											
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	35/57 (61.4%)	41/57 (71.9%)	Rate ratio 0.85 (0.54 to 1.33)	54 fewer events per 1000 person-years (from 165 fewer to 119 more)	⊕⊖⊖⊖ VERY LOW	CRITICAL
NRS for breathlessness (follow-up 6 months; range of scores: 0-10; Better indicated by lower values)											
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	45	43	-	MD 0.63 lower (1.57 lower to 0.31 higher)	⊕⊖⊖⊖ VERY LOW	IMPORTANT
Quality of life (MLWHF) (follow-up 3 months; Better indicated by lower values)											

1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	41	33	-	MD 0.64 higher (34.54 lower to 35.82 higher)	⊕⊖⊖⊖ VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

[2] The majority of the evidence was from studies with follow up periods longer than stated by the review protocol

[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

H.17 Discussing Implantable Cardioverter Defibrillator (ICD) deactivation

None.

H.18 Identifying patients with an increased risk of mortality

None.

Appendix I: Excluded clinical studies

I.1 BNP and NT-proBNP in diagnosing heart failure

Reference	Reasons for exclusion
Abhayaratna 2006[6]	Inappropriate reference standard
Ahn 2013[35]	Inappropriate population and reference standard (conference abstract)
Ajuluchukwu 2010[39]	Inappropriate study design
Alehagen 2003[52]	Inappropriate reference standard
Anonymous 2013[427]	Inappropriate study design
Anonymous 2010[83]	Inappropriate study design
Anonymous 2014[84]	Inappropriate study design (conference abstract)
Antlanger 2015[87]	Inappropriate study design (conference abstract)
Anwaruddin 2006[89]	Inappropriate population
Arques 2007[94]	Inappropriate population
Baggish 2004[111]	Inappropriate study design
Balion 2014[116]	Inappropriate study design
Barak 2010[121]	Inappropriate study design
Bayram 2009[140]	Inappropriate population
Bionda 2006[170]	Inappropriate study design (no accuracy data)
Blonde-Cynober 2011[175]	Inappropriate population and sample size
Booth 2014[187]	Inappropriate study design (systematic review)
Brito 2015[209]	Not in English
Burri 2012[222]	Inappropriate study design
Christenson 2010[274]	Inappropriate population
Collerton 2014[302]	Inappropriate reference standard
Cong 2014[310]	Unavailable
Cost 2000[321]	Inappropriate study design (accuracy data not reported)
David 2008[350]	Excluded due to incorrect sample size
deFilippi 2007[365]	Inappropriate population
Devroey 2011[377]	Inappropriate study design
Dhar 2009[379]	Inappropriate study design (narrative review)
Diercks 2009[385]	Inappropriate study design (commentary)
Dong 2006[396]	Inappropriate reference standard
Du 2012[409]	Inappropriate population
Duan 2013[411]	Inappropriate population (conference abstract)
Eckstein 2012[423]	Inappropriate population
Ejaz 2015[430]	Inappropriate reference standard and sample size
Fazal 2015[454]	Inappropriate study design and population
Fu 2013[491]	Inappropriate population
Fu 2015[492]	Inappropriate study design and population
Galasko 2005[497]	Inappropriate population
Goode 2009[544]	Inappropriate reference standard (conference abstract)

Reference	Reasons for exclusion
Guo 2014[564]	Inappropriate population
Han 2015[579]	Inappropriate study design (systematic review)
Herrmann 2003[601]	Inappropriate study design
Hess 2005[602]	Inappropriate population
Hettwer 2007[603]	Inappropriate reference standard
Hildebrandt 2010[606]	Inappropriate study design (systematic review)
Hobbs 2004[613]	Inappropriate population and reference standard
Hobbs 2002[614]	Inappropriate population
Hutcheon 2002[655]	Inappropriate population, target condition and reference standard
Islamoglu 2008[672]	Inappropriate reference standard
Jafri 2013[687]	Inappropriate study design
Jafri 2013[686]	Inappropriate study design
Jeevanantham 2007[694]	Inappropriate population
Jeyaseelan 2007[696]	Inappropriate target condition
Jose 2003[709]	Inappropriate population
Jungbauer 2012[713]	Inappropriate study design
Kelder 2011[748]	Inappropriate index test (included clinical model)
Kelder 2011[747]	Inappropriate study design
Knebel 2008[771]	Inappropriate reference standard
Knudsen 2005[772]	Inappropriate population
Ledwidge 2015[847]	Inappropriate population
Ledwidge 2014[846]	Inappropriate population and study design (conference abstract)
Ledwidge 2014[845]	Inappropriate population and study design (conference abstract)
Ledwidge 2013[844]	Inappropriate population and study design
Lee 2009[853]	Inappropriate population
Lepoutre 2013[863]	Inappropriate study design
Lim 2006[890]	Inappropriate study design
Lim 2006[889]	Inappropriate reference standard
Liu 2015[896]	Inappropriate population and study design
Liu 2010[895]	Inappropriate sample size
Lubien 2002[907]	Inappropriate reference standard
Luchner 2005[909]	Inappropriate population
Ma 2010[918]	Inappropriate language (not in English)
Mallamaci 2001[1320]	Inappropriate population, target condition and reference standard
Mant 2009[932]	Inappropriate study design (systematic review with broader population)
Marinho 2011[939]	Inappropriate population and study design
Mark 2006[943]	Inappropriate population
Martos 2009[946]	Inappropriate population
Mason 2013[951]	Inappropriate population
Mastandrea 2013[955]	Inappropriate study design (systematic review)
Matayoshi 2008[958]	Inappropriate population, target condition and reference standard
McCullough 2003[966]	Inappropriate population
McCullough 2003[967]	Inappropriate study design (narrative review)

Reference	Reasons for exclusion
Misuraca 2002[1002]	Not in English
Morello 2007[1015]	Inappropriate population, study design (no accuracy data)
Mueller 2005[1021]	Inappropriate study design
Mueller 2005[1024]	Inappropriate population
Mureddu 2013[1026]	Inappropriate population
Murray 2012[1027]	Inappropriate population
Murtagh 2012[1031]	Inappropriate population
Olofsson 2010[1082]	Inappropriate reference standard
Oudejans 2001[1092]	Inappropriate study design (no accuracy data)
Park 2009[1112]	Inappropriate population
Park 2010[1111]	Inappropriate population
Pichon Riviere 2011[1147]	Not in English
Porcel 2011[1166]	Inappropriate study design (narrative review)
Richards 2013[1203]	Inappropriate population
Roberts 2015[1214]	Inappropriate study design (wrong population in systematic review)
Rogers 2009[1222]	Inappropriate population
Rutten 2005[1231]	Inappropriate population
Savarese 2013[1251]	Inappropriate study design
Shelton 2006[1280]	Inappropriate target condition
Singh 2009[1294]	Inappropriate study design (conference abstract)
Sivakumar 2006[1296]	Inappropriate reference standard
Smeets 2016 [1297]	Inappropriate intervention/comparison (not BNP/NTproBNP alone)
Soleimani 2011[1309]	Excluded due to incorrect sample size
Sonoda 2012[1312]	Inappropriate population and reference standard
Spinar 2007[1320]	Inappropriate study design (no accuracy data)
Takami 2004[1355]	Inappropriate population, study design, target condition, reference standard
Tomonaga 2011[1396]	Inappropriate population and study design
Tschope 2005[1406]	Inappropriate reference standard
Vaes 2010[1418]	Inappropriate population
Valdes 2011[1422]	Inappropriate population
van Kimmenade 2006[1426]	Inappropriate population, study design (no accuracy data)
Watanabe 2008[1464]	Inappropriate population, target condition, reference standard and sample size
Wei 2005[1468]	Inappropriate reference standard
Wiley 2010[1487]	Inappropriate population and study design (no accuracy data)
Wright 2003[1496]	Inappropriate study design
Zeng 2006[1528]	Inappropriate sample size
Zhou 2010[1532]	Inappropriate study design (systematic review)

I.2 Cardiac Magnetic Resonance Imaging in heart failure

Study	Exclusion reason
Alter 2011[59]	Not relevant

Asferg 2012[96]	Inappropriate interventions
Barnett 2005[128]	Systematic review is not relevant to review question or unclear PICO
Dorosz 2012[400]	Not relevant
Health quality 2010[594]	Inappropriate outcomes
O'meara 2013[1067]	Incorrect interventions. Highlighted for relevance - trial not yet completed (study protocol).
Paterson 2013[1121]	Highlighted for potential relevance - trial not yet published (study protocol).
Pickett 2015[1148]	Systematic review is not relevant to review question or unclear PICO

I.3 Salt and fluid restriction

Study	Exclusion reason
Abshire 2015[8]	Systematic review, different PICO. Reviewed papers considered individually
Albert 2013[50]	Less than minimum duration. 8 week trial fluid restriction. Post-hospitalised decompensation
Aliti 2013[53]	Not guideline condition. Acute heart failure (decompensated)
Alvelos 2004[60]	Less than minimum duration. Follow up at 15 days
Anon 2015[595]	Systematic review: study designs inappropriate. Reviewed studies have been considered individually
Arcand 2005[91]	Less than minimum duration. Compliance with programme
Basuray 2015[133]	Incorrect study design. Compliance with programme
Bentley 2006[153]	Dissertation project
Butler 2015[226]	Less than minimum duration. Protocol only
Colin Ramirez 2004[301]	Incorrect interventions. General dietary advice including sodium and fluid restriction - impossible to separate out effects
Colin-Ramirez 2016[299]	Literature review
D'Almeida 2014[334]	Less than minimum duration. Not guideline condition. Acute heart failure (decompensated). Protocol only
Damgaard 2006[338]	Incorrect study design. Not review population. Trial of high vs low sodium diets over two weeks in HF and normal participants.
De Vecchis 2016[359]	Systematic review, different PICO. Reviewed papers considered individually
Donner Alves 2012[397]	Incorrect interventions. Wider dietary advice
Doukky 2016[402]	Incorrect study design. Observational trial of sodium intake
Dracup 1994[403]	Only available as a citation. Incorrect interventions
Dunbar 2005[415]	Intervention broader than salt restriction. Regarding compliance
Dunbar 2013[416]	Less than minimum duration. Outcomes re compliance
Dunbar 2016[417]	No extractable outcomes. Regarding compliance with low sodium diet
Holst 2003[628]	Protocol of crossover study
Holst 2008[629]	Crossover study. Less than minimum duration
Holst 2008[630]	Crossover study. Less than minimum duration
Hummel 2013[652]	Incorrect study design. Less than minimum duration. Incorrect interventions. "Dietary Approaches to Stop Hypertension" for three days

Study	Exclusion reason
Joffe 2013[700]	Not relevant. Narrative review of blood pressure control in HF
Johansson 2016[702]	Narrative review on fluid restriction
Lennie 2013[860]	Protocol only. Intervention of wider nutrition
Lennie 2013[859]	Narrative review. Sodium restriction and compliance
Li 2015[885]	Systematic review, different PICO. Reviewed studies have been considered individually
Licata 2003[887]	Randomisation during acute decompensation. Randomised to acute followed by long-term intervention - cannot disentangle
Mahtani 2014[928]	Review protocol
Parrinello 2009[109]	Retraction of related paper
Parrinello 2013[1113]	Incorrect interventions. Early follow-up to personalise diuretic dose and fluid recommendations vs Usual diuretic dose and fluid
Paterna 1999[1117]	Not guideline condition. Re acute decompensated HF
Paterna 2000[1118]	Randomised during acute decompensation. Randomised to acute followed by long-term intervention - cannot disentangle
Paterna 2008[1120]	Retraction of related paper
Paterna 2009[112]	Retraction of related paper
Paterna 2011[1119]	Randomised during acute decompensation. Randomised to acute followed by long-term intervention - cannot disentangle effects
Philipson 2010[1144]	Less than minimum duration. 12 week trial
Philipson 2013[1143]	Last outcome within scope at 12wks. Less than minimum duration. Outcome at 12 months re compliance
Rifai 2015[1210]	Incorrect interventions. "Dietary Approaches to Stop Hypertension" vs advice alone for 3 months. Less than minimum duration
Travers 2007[1399]	Not guideline condition. Acute heart failure (decompensated)
Warren 1988[1463]	Not relevant. Incorrect interventions
Welsh 2013[1472]	Less than minimum duration. Study of compliance with low salt diet
Wessler 2015[1475]	Less than minimum duration. "Dietary Approaches to Stop Hypertension" meals provided for 4 weeks, outcomes at 12 weeks

I.4 Beta-blockers in people with heart failure and atrial fibrillation

Study	Exclusion reason
Abdulla 2006[5]	Not review population
Agarwal 2001[21]	Incorrect interventions
Aggarwal 2015[22]	Not review population
Ahmed 2009[34]	Not relevant
Ahmed 2011[33]	Conference abstract
Ajami 2010[38]	Not relevant
Al suwaidi 2001[46]	Not review population
Al-gobari 2013[42]	Not review population
Ambrosio 2011[62]	Not review population
Anderson 1985[67]	Not review population
Andersson 1994[69]	Not review population

Study	Exclusion reason
Andersson 1998[68]	Not review population
Anon 1997[160]	Not relevant
Avezum 1998[105]	Not review population. Incorrect study design
Bavishi 2015[135]	Not review population
Baxter 2002[136]	Not review population
Bonet 2000[185]	Not relevant
Bouzamondo 2001[194]	Not review population
Bouzamondo 2003[195]	Not relevant
Briasoulis 2015[206]	Not review population
Bristow 1996[208]	Not review population
Bristow 2005[207]	Not relevant
Brophy 2001[211]	Not review population
Butler 2006[227]	Not review population
Cadrin-Tourigny [230]	Inappropriate comparison
Carson 2010[245]	Not relevant
Chatterjee 2013[259]	Not review population
Chatterjee 2013[258]	Not relevant
Chatterjee 2013[261]	Not relevant
Cleland 2004[285]	Not relevant
Cleland 2004[289]	Not relevant
Cleland 2006[288]	Not review population
Cleophas 2001[292]	Not review population
Colucci 1996[306]	Not review population
Colucci 1997[305]	Incorrect study design. Not review population
Contini 2013[312]	Not relevant
Cowan 2006[324]	Not relevant
De groote 2007[354]	Not review population
Deedwania 2004[364]	Not review population
Dekleva 2012[366]	Not review population
Di lenarda 2005[380]	Not review population
Di stasi 2005[381]	Not review population
Dobre 2007[387]	Not review population
Dobre 2007[389]	Not review population
Dobre 2008[388]	Not relevant
Dogan 2014[391]	Not relevant
Domanski 2003[393]	Not review population
Dulin 2005[414]	Not review population
Dyrda 2015[419]	Incorrect interventions
Edelmann 2016[424]	Not review population
Eichhorn 2001[429]	Commentary
Ekman 2001[433]	Not review population
El-refai 2013[436]	Not review population
Exner 1999[448]	Not review population

Study	Exclusion reason
Farasat 2010[451]	Not review population
Fauchier 2007[453]	Not review population
Fonarow 2007[474]	Not review population
Fonarow 2008[473]	Not review population
Fowler 2004[476]	Not review population
Frohlich 2015[489]	Not review population
Funck-brentano 2001[495]	Not relevant
Fung 2002[496]	Inappropriate comparison
Galatius 2004[498]	Not review population
Gattis 2003[510]	Not review population
Ghali 2002[514]	Not review population
Ghio 2006[517]	Not review population
Goldstein 1999[542]	Not review population
Goldstein 2000[539]	Not review population
Goldstein 2001[541]	Not review population
Goldstein 2003[540]	Not review population
Gottlieb 2002[548]	Not review population
Greenberg 2006[555]	Not relevant
Gullestad 2001[563]	Not review population
Haber 1993[570]	Not relevant
Hart 2000[583]	Not relevant
He 2012[592]	Not review population
Heidenreich 1997[596]	Not review population
Hjalmarson 2000[610]	Not review population
Hjalmarson 2000[609]	Not review population
Hori 2014[634]	Not review population
Hori 2014[635]	Not relevant
Hulkower 2015[650]	Not relevant
Joglar 2001[701]	No relevant outcomes
Kamilova 2016 [720]	Inappropriate study design
Karabacak 2015[728]	Not relevant
Kataoka 2008[738]	Not review population. Not relevant
Kennedy 1994[753]	Not review population
Khalil [759]	Inappropriate study design
Kohno 2005[779]	Not relevant
Kong 2010[782]	Not review population
Krum 1995[802]	Not review population
Krum 1995[804]	Not review population
Krum 2003[801]	Not review population
Kukin 1998[808]	Not review population. Incorrect study design
Kveiborg 2007[816]	Not relevant
Lainscak 2013[827]	Not relevant
Landray 1997[832]	Not review population. Incorrect study design

Study	Exclusion reason
Lechat 1998[841]	Not review population
Lechat 2003[842]	Commentary
Lee 2001[855]	Not review population
Leizorovicz 2002[857]	Not review population
Leonetti luparini 1999[862]	Not review population
Liu 2014[894]	Not review population
Macgregor 2009[923]	Wrong study design. Not review population
Marazzi 2011[936]	Not relevant
Massie 2007[954]	Not review population
Mcalister 2009[964]	Not review population
Metra 2005[995]	Not review population
Metra 2007[994]	Incorrect study design
Mulder 2012[1025]	Included in another study
Nasr 2007[1045]	Not relevant
Occun 2004[1070]	Not relevant
O'connor 1999[1062]	Not review population
Olsen 1995[1083]	Not review population
Packer 1996[1096]	Not review population
Packer 2001[1094]	Included in another study
Packer 2002[1097]	Not review population
Palazzuoli 2002[1101]	Not relevant
Pamboukian 1999[1102]	Not relevant
Pellicori 2015[1127]	Incorrect study design
Poole-wilson 2003[1165]	Not review population
Pousset 1995[1170]	Not relevant
Rain 2015[1180]	Not relevant
Rector 2008[1188]	Not review population
Reddy 2000[1190]	Not review population
Remme 2007[1197]	Not review population
Remme 2007[1196]	Not review population
Rickli 2004[1205]	Not review population
Rienstra 2013[1209]	Incorrect study design. Included studies already captured by another study
Roy 2008[1230]	Not relevant
Sanderson 1999[1245]	Not review population
Scherer 2013[1254]	Not review population
Schmidt 1998[1256]	Not relevant
Shelton 2009[1281]	Incorrect interventions
Shibata 2001[1285]	Not review population
Simon 2003[1290]	Not relevant
Sin 2002[1291]	Not review population. Incorrect study design
Singer 1997[1293]	Not review population
Stankovic 2012[1322]	Inappropriate comparison

Study	Exclusion reason
Swedberg 2005[1350]	Inappropriate comparison
Tate 2007[1359]	Not review population
Tepper 1996[1369]	Not relevant
Torp-pedersen 2005[1397]	Not review population
Van veldhuisen 2009[1430]	Not review population
Varney 2001[1435]	Not review population. Not relevant
Wedel 2001[1466]	Not relevant
White 2000[1480]	Not review population
Whorlow 2000[1482]	Not review population
Wikstrand 2000[1485]	Not relevant
Wikstrand 2002[1486]	Not review population
Wolf 2003[1492]	Not review population
Yamamoto 2013[1506]	Not relevant
Zebrack 2009[1526]	Not review population
Zhou 2001[1531]	Not relevant

I.5 Mineralocorticoid Receptor Antagonists

Study	Exclusion reason
Adamopoulos 2009[12]	Not review population
Agostoni 2005[25]	Incorrect sample size
Ambrosy 2011[63]	Commentary
Anon 1996[428]	Less than minimum duration
Bapoje 2013[120]	Systematic review is not relevant to review question or unclear PICO
Barr 1995[129]	Less than minimum duration
Beygui 2016[162]	Not guideline condition
Bomback 2016[184]	Narrative review
Capuano 2015[237]	Narrative review
Chami 2017[254]	Incorrect study design
Chatterjee 2012[260]	Systematic review is not relevant to review question or unclear PICO
Chen 2016[265]	Systematic review: study designs inappropriate
Chen 2015[267]	Systematic review is not relevant to review question or unclear PICO
Cicoira 2002[276]	Incorrect interventions. Incorrect outcomes

Cole 2014[298]	Narrative review
De Vecchis 2017[360]	Systematic review: methods are not adequate/unclear
Deswal 2011[376]	Incorrect sample size
Dooley 2017[398]	Incorrect study design
Emdin 2015[437]	Systematic review is not relevant to review question or unclear PICO
Ezekowitz 2009[449]	Systematic review is not relevant to review question or unclear PICO
Ferreira 2014[461]	Not guideline condition
Gandhi 2015[501]	Incorrect interventions
Gheorghiade 2009[516]	Not review population
Gu 2015[559]	Abstract only
Hu 2013[645]	Systematic review is not relevant to review question or unclear PICO
Iqbal 2014[670]	Not review population
Japp 2014[693]	Abstract only
Kasama 2002[734]	Incorrect sample size
Kimura 2011[765]	Incorrect outcomes
Kosmala 2016[788]	No extractable outcomes
Kurrelmeyer 2014[813]	Incorrect sample size
Le 2016[839]	Systematic review is not relevant to review question or unclear PICO
Li 2009[883]	Incorrect outcomes
Macdonald 2004[919]	Crossover study
Mak 2009[929]	Incorrect sample size
O'keefe 2008[1066]	Not review population
Pfeffer 2014[1138]	Commentary
Phelan 2012[1142]	Systematic review: methods are not adequate/unclear
Pitt 2003[1157]	Not review population
Pitt 2005[1158]	Not review population
Pitt 2006[1155]	Not review population

Pitt 2008[1154]	Not review population
Roongsritong 2005[1224]	Less than minimum duration
Rossignol 2012[1227]	Not review population
Rossignol 2017[1229]	Inappropriate comparison
Taheri 2009[1354]	Incorrect sample size
Taheri 2012[1353]	Incorrect sample size
Upadhya 2017[1415]	Sample size too small (<100 overall)
Vizzardi 2010[1446]	Incorrect interventions. (intervention dose above specification)
Vizzardi 2014[1447]	Incorrect interventions. (intervention doses above specification)
Waldum-grevbo 2015[1458]	Narrative review
Weir 2011[1471]	Not guideline condition. Not review population
Wu 2016[1498]	Not placebo controlled. Inappropriate comparison.
Xiang 2017[1501]	Incorrect study design
Xie 2016[1502]	Systematic review is not relevant to review question or unclear PICO
Zhang 2016[1530]	Systematic review is not relevant to review question or unclear PICO

I.6 Iron supplementation for iron deficiency in heart failure

Study	Exclusion reason
Anker 2017[80]	Meta analysis, scanned for relevant references
Bauer 2015[134]	Systematic review: methods are not adequate/unclear
Bolger 2006[181]	Incorrect study design
Harris 2009[582]	Commentary
Hayes 2014[589]	Not obtainable
Jankowska 2016[690]	Systematic review, references checked
Lewis 2016[876]	Protocol only
Lim 2014[888]	Economic evaluation
Mylonas 2014[1036]	Economic evaluation
Okonko 2008[1080]	Inappropriate comparison
Qian 2016[1177]	Systematic review, references checked
Theresa 2015[968]	Narrative review, references checked
Yeo 2016[1511]	Protocol only. Not review population
Van Veldhuisen 2017[1431]	Inappropriate comparison

I.7 Pharmacological treatment for heart failure in people with heart failure and chronic kidney disease

Study	Exclusion reason
Ahmed 2002[32]	Comment paper
Badve 2011[110]	Systematic review, studies considered individually
Bakris 2000[115]	Not guideline condition
Castagno 2009[251]	Not guideline condition. Mixture of indications for medication
Chang 2011[256]	Review, studies considered individually
Coca 2006[294]	Systematic review, studies considered individually
Damman 2014[339]	Systematic review is not relevant to review question or unclear PICO
Erdmann 2001[439]	Part of the CIBIS-2 trial but no additional data to extract
Granger 2003[552]	Relevant outcomes not reported
Hawley 2010[588]	Systematic review, studies considered individually
Kotecha 2009[790]	Conference abstract
Lam 2012[829]	Regarding prognosis not efficacy of drug. Inappropriate comparison
Peng 2015[1128]	Incorrect interventions. Medication not licenced for human use in the UK
Segall 2014[1264]	Review, studies considered individually
Shah 2013[1278]	Review, studies considered individually
Swedberg 1991[1348]	Not 100 or more patients with CKD in analysis
Taylor 2007[1361]	Not review population. Subgroup definition is "history of chronic renal insufficiency", which is not defined, and more vague than other sub-groups in the study
Terajima 2003[1371]	Not guideline condition. Looking at evidence for benefit of medication in people with CKD without heart failure
Testani 2013[1374]	Part of CIBIS-2 but no extractable data in any strata
Tobe 2011[1392]	Not guideline condition. Population did not necessarily have heart failure
Wali 2011[1459]	Not guideline condition. Population did not necessarily have heart failure
Wargo 2009[1462]	Systematic review, studies considered individually

Werner 2010[1474]	Review, references searched

I.8 Coronary revascularisation

Study	Exclusion reason
Anon 1983[318]	Study carried out before 2001
Aaberge 2002[1]	Not guideline condition. Not review population. Incorrect interventions
Ait houssa 2013[37]	Not in English
Allen 2011[54]	Conference abstract
Allman 2002[58]	Incorrect study design
Al-ruzzeh 2004[43]	Not review population. Not guideline condition. Incorrect study design
Al-ruzzeh 2005[44]	Not guideline condition. Not review population. Incorrect interventions. Incorrect study design
Anon 2014[1178]	Patient summary
Anonymous 2004[82]	Incorrect study design. Abstract
Armstrong 2006[93]	Not guideline condition. Not review population
Baker 1994[114]	Study carried out before 2001
Barsheshet 2011[130]	Incorrect interventions
Biondi zoccai 2007[171]	Incorrect study design. Systematic review
Borden 2006[188]	Not guideline condition. Not review population. Incorrect interventions
Borges-neto 2012[191]	Conference abstract
Bouchard 2015[192]	Commentary
Brener 2012[205]	Not guideline condition. Not review population
Buckberg 2012[217]	Incorrect interventions. Narrative review
Buller 2009[219]	Not review population. Not guideline condition
Buszman 2002[224]	Incorrect study design
Buszman 2005[223]	Incorrect interventions. Inappropriate comparison
Cantor 2009[234]	Not guideline condition. Not review population
Carrier 2003[242]	Not guideline condition. Not review population. Incorrect interventions
Colquitt 2014[304]	Incorrect interventions. Inappropriate comparison
Conte 2010[311]	Commentary
Cooper 2006[316]	Not guideline condition. Not review population. Incorrect interventions
Cooper 2013[314]	Not guideline condition. Not review population. Incorrect interventions
Cooper 2014[315]	Not guideline condition. Not review population
Daneault 2013[340]	Incorrect population
Deb 2013[361]	Not guideline condition. Not review population
Dzavik 2009[420]	Not review population. Not guideline condition
Eryilmaz 2002[440]	Incorrect study design
Felker 2003[457]	Incorrect study design. Incorrect interventions. Narrative review

Freixa 2011[487]	Not review population. Not guideline condition
Freixa 2012[486]	Not guideline condition. Not review population
Gimple 2008[519]	Not review population. Not guideline condition
Goel 2013[528]	Incorrect interventions
Guleserian 2003[562]	Not guideline condition. Not review population. Incorrect study design. Incorrect interventions
Guyton 2016[568]	Commentary
Hillis 2006[608]	Incorrect study design
Hochman 2005[616]	Not review population. Not guideline condition
Hochman 2006[615]	Not review population. Not guideline condition
Hochman 2011[617]	Not review population. Not guideline condition
Hofsten 2015[622]	Not guideline condition. Not review population. Incorrect interventions
Holly 2014[625]	Not review population. Not guideline condition
Holmes 2007[626]	Not guideline condition. Not review population. Incorrect interventions
Holzmann 2013[632]	Not review population. Not guideline condition
Hu 2011[646]	Incorrect interventions
Hu 2015[647]	Not guideline condition. Not review population
Ioannidis 2007[669]	Not guideline condition. Not review population. Incorrect interventions
Islamoglu 2002[671]	Incorrect study design
Jhaveri 2010[697]	Not review population. Not guideline condition
Jhaveri 2012[698]	Not review population. Not guideline condition
Jones 2009[708]	Incorrect interventions
Joyce 2003[712]	Commentary
Kawecki 2011[744]	Incorrect study design
Kelly 2011[752]	Not review population. Not guideline condition
Kruk 2008[799]	Not guideline condition. Not review population
Kukulski 2015[809]	Incorrect interventions
Kumbhani 2011[810]	Systematic review with incorrect PICO
Kunadian 2012[811]	Systematic review: incorrect study designs
Labinaz 2005[823]	Not guideline condition. Not review population
Lambert 2010[830]	Incorrect study design
Larobina 2010[836]	Commentary
Leonard 2014[861]	Incorrect interventions
Levy 2010[867]	Not review population. Not guideline condition
Libungan 2015[886]	Incorrect study design. Not guideline condition. Not review population
Ling 2013[893]	Not guideline condition. Not review population. Incorrect study design. Incorrect interventions
Macdonald 2014[920]	Incorrect interventions
Marchenko 2011[937]	Not guideline condition. Not review population
Mark 2009[941]	Incorrect interventions
Marui 2014[948]	Incorrect study design

Marui 2015[949]	Incorrect study design
Mashayekhi 2016[950]	Inappropriate comparison. conference abstract only
Mcfalls 2007[974]	Not guideline condition. Not review population. Incorrect study design
Mcgee jr 2012[975]	Incorrect study design
Mehta 2005[982]	Not review population. Incorrect interventions
Menon 2009[988]	Not guideline condition. Not review population
Menon 2013[989]	Not review population. Not guideline condition
Mentz 2013[990]	Incorrect interventions
Minai 2002[1000]	Not guideline condition. Not review population
Mitka 2011[1004]	Editorial
Moody 2013[1013]	Not review population. Not guideline condition
Nagendran 2013[1037]	Not guideline condition. Not review population
Narula 2014[1043]	Not relevant
Ng 2014[1054]	Not guideline condition. Not review population
Oh 2012[1075]	Incorrect interventions
Oh 2013[1076]	Incorrect interventions
Petrie 2016[1134]	Inappropriate comparison
Reynolds 2012[1199]	Not review population. Not guideline condition
Rizzello 2005[1213]	Incorrect study design. Incorrect interventions
Stewart 2014[1327]	Incorrect interventions
Stone 2014[1336]	Not guideline condition. Not review population
Suma 2011[1343]	Not in English
Sutton 2004[1344]	Not review population. Not guideline condition
Testa 2008[1373]	Not guideline condition. Not review population
Tsialtas 2005[1407]	Incorrect study design. Incorrect interventions
Udelson 2011[1414]	Not review population. Not guideline condition
Van diepen 2013[1425]	Not review population. Not guideline condition
Velazquez 2011[1438]	Commentary
Wagner 2011[1456]	Not guideline condition. Not review population
Wrobel 2015[1497]	Incorrect interventions
Zembala 2010[1527]	Incorrect interventions

I.9 Home-based versus centre-based rehabilitation

Reference	Reason for exclusion
Aamot 2014[2]	Inappropriate population
Aamot 2012[3]	Inappropriate population
Ades 2000[16]	Inappropriate population
Amao 2016[61]	Inappropriate comparator
Ambrosy 2017[64]	Inappropriate comparator

Reference	Reason for exclusion
Arthur 2002[95]	Inappropriate population
Austin 2005[100]	Inappropriate comparator
Austin 2009[101]	Inappropriate comparator
Austin 2008[102]	Inappropriate comparator
Babu 2016[108]	Inappropriate comparator
Belardinelli 1999[150]	Inappropriate comparator
Bell 1998[151]	Inappropriate population
Bernocchi 2018[158]	Inappropriate population
Bubnova 2014[215]	Inappropriate population
Byrnes 2015[228]	Inappropriate population
Carlson 1999[239]	Inappropriate population
Carlson 2000[240]	Inappropriate population
Carlson 2001[241]	Inappropriate population
Chan 2012[255]	Inappropriate population
Chen 2016[264]	Inappropriate population
Chien 2011[270]	Inappropriate comparator
Chow 2015[272]	Inappropriate comparator
Cinar 2016[277]	Inappropriate population
Claes 2017[280]	Inappropriate population
Corvera-Tindel 2004[320]	Inappropriate comparator
Dalal 2007[337]	Inappropriate population
Daskapan 2005[348]	Pilot study of included paper
DeBusk 1985[362]	Inappropriate population
Dracup 2007[404]	Inappropriate comparator
Donesky 2017[395]	Inappropriate comparator
Du 2017[408]	Inappropriate comparator
Du 2017[410]	Inappropriate population
Evangelista 2006[445]	Inappropriate comparator
Evangelista 2010[446]	Inappropriate comparator
Flynn 2009[471]	Inappropriate comparator
Frederix 2017[484]	Inappropriate comparator
Georgiou 2001[512]	Inappropriate comparator
Gordon 2002[545]	Inappropriate population
Grace 2016[549]	Inappropriate population
Hadadzadeh 2015[571]	Inappropriate population
Haddadzadeh 2013[572]	Inappropriate population
Haddadzadeh 2011[573]	Inappropriate population
Haddadzadeh 2011[574]	Inappropriate population
Higgins 2001[605]	Inappropriate population
Hovland-Tanneryd 2016[639]	Inappropriate intervention

Reference	Reason for exclusion
Jolly 2003[705]	Inappropriate population
Jolly 2009[706]	Inappropriate population
Jolly 2007[707]	Inappropriate population
Kassaian 2000[737]	Inappropriate population
Keteyian 2012[756]	Inappropriate comparator
Khalife-Zadeh 2015[758]	Inappropriate population
Kim 2011[764]	Inappropriate population
Kraal 2013[793]	Inappropriate population
Kraal 2014[794]	Inappropriate population
Lear 2014[840]	Inappropriate population
Lee 2013[856]	Inappropriate population
Li 2015[884]	Inappropriate population
Maddison 2015[925]	Inappropriate population
Marchionni 2003[938]	Inappropriate population
Maru 2015[947]	Inappropriate intervention
McKelvie 2002[977]	Inappropriate comparator
Midence 2016[997]	Inappropriate population
Miller 1984[998]	Inappropriate population
Miller 2017[999]	Inappropriate comparator
Moholdt 2012[1009]	Inappropriate population
Mutwalli 2012[1033]	Inappropriate population
Newton 2012[1052]	Inappropriate intervention
O'Connor 2009[1064]	Inappropriate comparator
Oerkild 2011[1072]	Inappropriate population
Oka 2000[1078]	Inappropriate comparator
Olson 2015[1084]	Inappropriate intervention
Parikh 2016[1109]	Inappropriate comparator
Pfaeffli Dale 2015[1135]	Inappropriate population
Pfaeffli Dale 2015[1136]	Inappropriate population
Piotrowicz 2015[1153]	Inappropriate comparator
Prescott 2016[1171]	Inappropriate population
Reed 2012[1192]	Inappropriate comparator
Reed 2010[1193]	Inappropriate comparator
Salavati 2015[1237]	Inappropriate population
Samayoa 2014[1239]	Inappropriate population
Senuzun 2006[1269]	Inappropriate population
Siabani 2016[1288]	Inappropriate comparator
Sinclair 2005[1292]	Inappropriate comparator
Smith 2004[1302]	Inappropriate population
Smith 2011[1303]	Inappropriate population

Reference	Reason for exclusion
Sparks 1993[1317]	Inappropriate population
Stewart 2012[1329]	Inappropriate intervention
Stewart 2012[1330]	Inappropriate intervention
Takase 2015[1356]	Inappropriate comparator
Taylor 1986[1362]	Inappropriate population
Taylor 2007[1366]	Inappropriate population
Tygesen 2001[1412]	Inappropriate comparator
Vahedian-Azimi 2016[1419]	Inappropriate population
Varnfield 2014[1436]	Inappropriate population
Verma 2017[1443]	Inappropriate comparator
Vibulchai 2016[1444]	Inappropriate population
Walters 2012[1461]	Inappropriate population
Whellan 2007[1479]	Inappropriate comparator
Whittaker 2014[1481]	Inappropriate population
Wolkanin-Bartnik 2010[1493]	Inappropriate population
Wolkanin-Bartnik 2011[1494]	Inappropriate population
Wu 2006[1499]	Inappropriate population
Xueyu 2017[1504]	Inappropriate comparator
Young 2016[1513]	Inappropriate comparator

I.10 Monitoring

Study	Exclusion reason
Anon 2013[604]	Protocol only
Anon 2016[560]	Protocol only
Anon 2016[664]	Protocol only
Beck-da-Silva 2005[141]	Less than minimum duration of follow-up
Chioncel 2016[271]	Review, references checked
Davarzani 2017[349]	Inappropriate comparison, further modelling of time-CHF data
Januzzi 2013[692]	Comment paper
Karavidas 2013[730]	Full text not available
Koshkina 2015[785]	Full-text not available
Moon 2011[1014]	Review - more recent reviews available
Oremus 2014[1087]	Protocol for review
Pufulete 2014[1173]	Protocol for review
Shah 2011[1277]	Less than minimum duration
Stienen 2014[1335]	Protocol - no results currently available
Xin 2014[1503]	Review, references checked
Yang 2017[1507]	Not review population

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I.11 Telemonitoring and self-monitoring

Reference	Reason for exclusion
Bashi 2017[132]	Systematic review scanned for references
Bekelman 2014[146]	No comparator
Brandon 2009[201]	No extractable outcomes
Cajita 2016[231]	Systematic review scanned for references
Cavusoglu 2017[253]	Inappropriate intervention
Cherofsky 2011[269]	Unable to obtain paper
Clark 2015[284]	Inappropriate intervention
Comin-Colet 2016[307]	Inappropriate intervention
Conway 2014[313]	papers previosuly included
Dang 2017[342]	Inappropriate outcomes
Dickinson 2016[384]	Inappropriate study design
Frederix 2015[483]	No extractable outcomes
Gallagher 2016[500]	Inappropriate intervention
Goldstein 2014[533]	Inappropriate intervention
Hagglund 2015[577]	Inappropriate intervention
Hameed 2014[578]	Inappropriate outcomes
Hayes 2015[590]	Unable to obtain paper
Heikkila 2016[598]	Inappropriate outcomes
Hofmann 2015[620]	Inappropriate intervention
Holthe 2015[631]	No extractable outcomes
Hsiao 2017[641]	Inappropriate study design
Hwang 2015[659]	Inappropriate population
Kalter-Leibovici 2017[719]	Inappropriate comparator
Kitsiou 2015[768]	Systematic review scanned for references
Kotb 2015[789]	Systematic review scanned for references
Kraai 2016[792]	Inappropriate comparator
Lee 2009[851]	Unable to obtain paper
Lee 2010[852]	Unable to obtain paper
Mussi 2013[1032]	Paper not in English
Piette 2015[1150]	Inappropriate comparator
Piotrowicz 2015[1152]	Inappropriate intervention
Rosen 2017[1225]	Inappropriate study design
Serrano 2015[1270]	Inappropriate study design
Sherwood 2017[1284]	Inappropriate comparator
Sousa 2014[1315]	Inappropriate study design
Tiede 2016[1387]	Inappropriate intervention
Villani 2014[1445]	Already included in the Cochrane review
Vuorinen 2014[1453]	Already included in the Cochrane review
Wagenaar 2015[1455]	No extractable outcomes
Young 2016[1513]	Inappropriate intervention
Zamanzadeh 2013[1519]	No extractable outcomes

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1 ## I.12 Multi-Disciplinary Teams

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Study	Exclusion reason
Agren 2013[26]	Incorrect interventions
Ahmed 2002[31]	Review, references checked
Albert 2016[49]	Review, references checked
Andryukhin 2010[76]	Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country)
Angermann 2012[77]	No face to face meetings outside inpatient stay. Telephone follow-up only
Anon 2005[1377]	Not in English
Anon 2009[980]	Review, references checked
Anonymous 1999[81]	Paper not available
Anonymous 2016[85]	Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country)
Ansari 2003[86]	Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country)
Auerbach 2000[99]	Incorrect study design
Austin 2009[101]	Intervention covered elsewhere in guideline
Azad 2006[107]	Primary purpose of intervention is education/information-giving
Azad 2008[106]	Primary purpose of intervention is education/information-giving
Baker 2011[113]	Primary purpose of intervention is education/information-giving
Barker 2012[125]	Not Clear description of collaborative working between professions/disciplines
Bekelman 2013[149]	Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country)
Bekelman 2015[148]	Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country)
Bekelman 2016[145]	Trial protocol only; results not published yet in full. Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country)
Bento 2009[154]	Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country)
Blue 2001[176]	Participants in trial were not stabilised from acute decompensation at the start of the intervention. Overlaps with acute heart failure interventions
Boisvert 2015[180]	Not in English
Bouvy 2003[193]	Not Clear description of collaborative working between professions/disciplines
Boxer 2013[197]	Inappropriate comparison. Trial is specifically regarding improving care in nursing homes
Bucci 2003[216]	No relevant outcomes reported
Caldwell 2005[232]	No relevant outcomes reported
Campbell 2013[233]	Incorrect interventions
Carrington 2010[243]	Aim to prevent development of heart failure. Incorrect interventions
Case 2010[248]	Review, references checked
Chen 2017[266]	Comparator (usual care) likely to differ significantly to care in NHS

Study	Exclusion reason
	(including study in US or non-OECD country)
Cockayne 2014[295]	Incorrect interventions
Coventry 2005[323]	Systematic review is not relevant to review question or unclear PICO
Danna 2014[343]	Protocol of a review
Davidson 2015[351]	Review, references checked
Davis 2014[352]	Review, references checked
De souza 2014[358]	Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country)
Drewes 2012[405]	Review, references checked
Driscoll 2015[406]	Review, references checked
Duffy 2010[413]	Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country). Setting USA
Dunbar 2005[415]	Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country)
Dunbar 2013[416]	Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country)
El-jawahri 2016[434]	Incorrect interventions
El-menyar 2009[435]	Review, different topic
Evangelista 2012[447]	Incorrect study design
Fan 2010[450]	Not in English
Feltner 2014[459]	Review, references checked
Gandhi 2017[502]	Review, references checked
Gattis 1999[509]	Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country)
Goldstein 2014[535]	Incorrect interventions. Education only
Gustafsson 2004[565]	Review, references checked
Hansen 2009[580]	Not Clear description of collaborative working between professions/disciplines
Hauptman 2008[586]	Survey
Ho 2007[612]	Incorrect study design
Hoes 2003[618]	Comment
Holland 2005[623]	Review, references checked
Holland 2007[624]	Incorrect interventions
Hua 2017[648]	Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country)
Huynh 2008[657]	Incorrect interventions
Inglis 2004[666]	Not guideline condition
Inglis 2006[668]	Less than two visit average
Isrctn 2016[673]	clinical trial webpage only; results not yet reported
Jaarsma 2008[677]	Not in English
Jaarsma 2013[676]	Review, references checked
Jerant 2003[695]	Incorrect interventions. Telecare
Kalisch 2010[715]	Review, references checked
Kalter-leibovici 2017[719]	Intervention included the delivery of fewer than two face to face meetings. Telecare

Study	Exclusion reason
Kang 2016[722]	Review, references checked
Kasper 2002[736]	Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country). Setting USA
Ke 2013[745]	Review, references checked
Koberich 2015[775]	Incorrect interventions. Education only
Kommuri 2012[781]	Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country). Setting USA
Korajkic 2011[784]	Incorrect interventions. Education only
Koshman 2007[787]	Incorrect interventions. Not guideline condition
Koshman 2008[786]	Review, references checked
Krantz 2008[797]	Incorrect interventions
Kurtz 2011[814]	Incorrect interventions. Telecare
Kutzleb 2006[815]	Incorrect study design
Kwok 2008[817]	Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country). Setting China
Lainscak 2006[828]	Incorrect study design
Lambrinou 2012[831]	Review, references checked
Laramee 2003[834]	Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country). Setting USA
Leventhal 2011[866]	Less than two visits average
Licata 2003[887]	Incorrect interventions
Lofvenmark 2011[898]	Incorrect interventions. Education only
Lopez cabezas 2006[900]	Less than one out of hospital visit average
Low 2011[903]	Review, references checked
Lowrie 2011[905]	Not Clear description of collaborative working between professions/disciplines
Lowrie 2012[904]	Not Clear description of collaborative working between professions/disciplines
Luttik 2012[915]	Insufficient information of intervention or usual care
Luttik 2014[916]	Insufficient information of intervention or usual care
Mao 2015[935]	Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country)
Masterson creber 2015[956]	Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country). Setting USA
Masterson creber 2016[957]	Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country). Setting USA
Mau 2006[959]	Paper not available
Mcalister 2001[962]	Review, references checked
Mcalister 2004[963]	Review, references checked
Mccauley 2006[965]	Review, references checked
Mcilvennan 2016[976]	Review, references checked
Mcmurray 1996[979]	Paper not available
Mehralian 2014[981]	Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country)
Mejia 2014[984]	Incorrect interventions. Delivery of psychological therapy
Mentz 2014[991]	Protocol only

Study	Exclusion reason
Mitchell 2014[1003]	Incorrect interventions
Mohan 2015[1007]	Incorrect interventions
Morrow 2007[1017]	Incorrect interventions
Murray 2004[1029]	Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country). Setting USA
Murray 2007[1028]	Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country). Setting USA
Mussi 2013[1032]	Not in English
Nahlen bose 2016[1038]	Incorrect interventions. Delivery of psychological therapy
Naylor 2004[1050]	Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country). Setting USA
Nct 2012[1051]	Protocol only
Ng 2016[1053]	Protocol only
Obieglo 2013[1069]	Review of guidelines
Odum 2012[1071]	Review, references checked
Parrinello 2013[1113]	Incorrect interventions
Pascual 2011[1115]	Protocol only
Patel 2008[1116]	Not guideline condition. Treatment of acute HF
Paterna 2011[1119]	Incorrect interventions
Paul 2000[1123]	Incorrect study design
Pearl 2003[1124]	Comment
Phillips 2005[1145]	Review, references checked
Piepoli 2006[1149]	Incorrect study design
Pressler 2011[1172]	Incorrect interventions. No relevant outcomes reported
Rainville 1999[1181]	Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country). Setting USA
Rich 1993[1202]	Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country). Setting USA
Rich 1995[1200]	Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country). Setting USA
Rich 1996[1201]	Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country). Setting USA
Riegel 2000[1206]	Incorrect study design
Robinson 2004[1215]	Incorrect interventions. Telecare
Roblek 2016[1216]	Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country)
Roccaforte 2005[1217]	Review, references checked
Rodriguez-gazquez 2012[1218]	Not in English
Rogers 2017[1220]	Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country)
Rondinini 2008[1223]	Incorrect study design
Ross 2006[1226]	Review, references checked
Sadik 2005[1234]	Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country)
Schulman 1998[1259]	Review, references checked
Sezgin 2017[1272]	Incorrect interventions. Primary purpose of intervention is

Study	Exclusion reason
	education/information-giving
Sisk 2006[1295]	Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country). Setting USA
Smeulders 2006[1299]	Incorrect interventions
Smeulders 2009[1298]	No relevant outcomes
Smith 2014[1301]	Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country). Setting USA
Smith 2015[1300]	Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country). Setting USA
Spadaro 2010[1316]	Not in English
Stewart 2011[1332]	Inappropriate comparison. Same team, different delivery model (home vs clinic)
Stewart 2012[1333]	Inappropriate comparison. Same team, different delivery model (home vs clinic)
Stewart 2014[1331]	Inappropriate comparison. Same team, different delivery model (home vs clinic)
Stromberg 2003[1341]	Less than two visits average
Sutton 2008[1345]	Incorrect study design
Takeda 2012[1357]	Cochrane review, references checked
Taylor 2005[1367]	Cochrane review, references checked
Thomas 2013[1379]	Review, references checked
Thomas 2014[1380]	Review, references checked
Thompson 2005[1382]	Not Clear description of collaborative working between professions/disciplines
Thoonsen 2011[1383]	Incorrect interventions
Thoonsen 2015[1384]	Incorrect interventions
Triller 2007[1402]	Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country). Setting USA
Trochu 2003[1403]	Paper not available
Vaillant-roussel 2014[1420]	Incorrect interventions. Education only
Valk 2015[1423]	Incorrect interventions. Education only
Van lieshout 2011[1427]	Inappropriate comparison. Same team, different delivery
Vorilhon 2016[1452]	Inappropriate comparison. This trial compared intensified protocolised care to no protocol
Whellan 2005[1478]	Review, references checked
Whellan 2014[1477]	Comment
Wierzchowiecki 2006[1483]	Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country)
Wierzchowiecki 2006[1484]	Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country)
Yallop 2006[1505]	Incorrect interventions. Telecare
Yehle 2009[1510]	Incorrect interventions
Yu 2006[1514]	Review, references checked
Yu 2015[1515]	Comparator (usual care) likely to differ significantly to care in NHS (including study in US or non-OECD country). Setting China
Zhu 2016[1533]	Incorrect study design

I.13 Transition between heart failure care settings

Reference	Reason for exclusion
Ahmad 2016[29]	Not relevant
Andreoli 2009[75]	Abstract only
Barello 2014[123]	Not relevant (acute)
Bekelman 2011[147]	US health system
Buetow 2001[218]	Not relevant
Burke 2014[220]	Not relevant
Carayon 2015[238]	Not relevant
Casida 2011[249]	Not relevant
Chow 2008[273]	Population too broad (not just CHF)
Corcoran 2013[317]	Not relevant
Costello 2004[322]	Not relevant
Crowder 2006[331]	US health system
Fuat 2003[493]	Not relevant
Gottlieb 2006[547]	Not qualitative
Gwaltney2012[569]	Not relevant
Hadjistavropoulos 2008[575]	Not relevant (acute)
Harding 2008[581]	Not relevant
Hayes 2015[591]	Not relevant (acute)
Horowitz 2004[638]	US health system
Hupcey 2011[653]	Not relevant
Jani 2013[688]	Review
Jowsey 2016[711]	Population too broad
Kaasalainen 2013[714]	Not relevant
Kansagara 2015[723]	Not qualitative
Kasje 2005[735]	Not qualitative
Khunti 2002[763]	Not relevant
LaDonna 2016[824]	Not relevant
Lewis 2014[879]	Dissertation
Li 2006[882]	Not relevant
Lough 1996[902]	Not relevant (acute)
Lowson 2013[906]	Not relevant
Mahoney 2001[927]	Not relevant
Malhotra 2016[930]	Not relevant
McDougall 2016[971]	Not relevant
McEntee 2009[972]	Review
Mendes 2010[986]	Not in English
Mirzaei 2013[1001]	Population too broad
Molloy 2004[1010]	Not relevant
Murray 2002[1030]	Not relevant
Olano-Lizarraga 2016[1081]	Review

Reference	Reason for exclusion
Ostman 2015[1089]	Not relevant
Östman 2015[1090]	Not relevant
Pattenden 2007[1122]	Not relevant
Peters-Klimm 2009[1133]	Not relevant
Phillips 2004[1146]	Not relevant
Retrum 2013[1198]	Not relevant (acute)
Riggs 2012[1211]	Not qualitative
Rogers 2000[1219]	Not relevant
Ryan 2009[1232]	Not relevant
Sanders 2010[1244]	Not relevant
Scotto 2005[1260]	Not relevant
Soares 2012[1307]	Not relevant (acute)
Sookhoo 2013[1313]	Review, not available
Steinman 2013[1324]	Not qualitative
Stevenson 2015[1325]	Not relevant
Strachan 2014[1338]	Review
Thornhill 2008[1385]	Review
Tierney 2014[1388]	Not relevant
Voils 2014[1448]	Not CHF
Waterworth 2010[1465]	Not relevant
Weierbach 2011[1469]	Not relevant (acute)
Welstand 2009[1473]	Review
Wingham 2015[1489]	Not relevant
Winters 1999[1490]	Not relevant
Young 2008[1512]	Not relevant
Zambroski 2003[1520]	Not relevant

I.14 Communication needs regarding diagnosis and prognosis

Reference	Reason for exclusion
Ahluwalia 2013[28]	US study
Andersson 2012[72]	Swedish study
Banerjee 2010[118]	survey, no qualitative analysis of responses
Barclay 2011[122]	systematic literature view of qualitative studies
Boyd 2004[198]	the main purpose of the paper does not meet the review protocol /// no findings relevant to the review protocol
Clark 2012[283]	systematic literature view of qualitative studies
Close 2013[293]	the main purpose of the paper does not meet the review protocol /// no findings relevant to the review protocol
Cortis 2007[319]	the main purpose of the paper does not meet the review protocol /// no findings relevant to the review protocol
Currie 2015[332]	systematic literature view of qualitative studies
Etkind 2017[443]	Secondary analysis of multiple studies with mixed population. Results not separated by illness.

Reference	Reason for exclusion
Fuat 2003[493]	the main purpose of the paper does not meet the review protocol /// no findings relevant to the review protocol
Glogowska 2016[524]	Communication specific to end-of-life not prognosis and diagnosis
Green 2011[553]	Communication of transitioning from active care to palliative care not prognosis and diagnosis
Greer 2006[556]	Abstract only and Canadian study
Imes 2011[663]	US study
Khunti 2002[763]	the main purpose of the paper does not meet the review protocol /// no findings relevant to the review protocol
Lord 2015[901]	Pertains to changes in heart failure services, expectations of responsibilities of care, communication between and trusts, specialties and HCP involved in HF patients care
Low 2011[903]	systematic literature view of qualitative studies
May 2016[960]	systematic literature view of qualitative studies
Momen 2011[1011]	systematic review of qualitative and concerning end-of-life conversations specifically
Pattenden 2007[1122]	the main purpose of the paper does not meet the review protocol /// no findings relevant to the review protocol
Sander 2005[1240]	Brief summary of Aldred 2005[51]
Tayler 2005[1360]	No qualitative component
Thornhill 2008[1385]	the main purpose of the paper does not meet the review protocol /// no findings relevant to the review protocol
Yu 2016[1516]	Chinese study

I.15 Diuretics in advanced heart failure

Study	Exclusion reason
Banerjee 2012[119]	Wrong study design (uncontrolled study, not RCT)
Biadi 1981[166]	Wrong population. Wrong comparison.
Faris 2012[452]	Review, references checked
Kapelios 2017[727]	Review, references checked
Meyel 1993[996]	Wrong comparison. Crossover trial. Abstract only.
Felker 2010[456]	Review, references checked

I.16 Domiciliary oxygen therapy in people with advanced heart failure

Study	Exclusion reason
Andreas 1995[74]	Not in English. Abstract only
Andreas 1996[73]	Not in English. Abstract only
Blackshear 2012[174]	Not review population. Crossover study

Bordier 2015[190]	Not review population
Bordier 2016[189]	Systematic review is not relevant to review question or unclear PICO. References checked
Clark 2011[282]	Narrative review. References checked
Diaz lobato 2015[383]	Narrative review. Wrong population
Nakao 2016[1041]	Not review population. Inappropriate study design
Sasayama 2006[1250]	Not review population
Sasayama 2009[1249]	Not review population
Seino 2007[1265]	Not review population
Staniforth 1997[1321]	Crossover study. Abstract only
Toyama 2009[1398]	Not review population
Wiseman 2013[1491]	Narrative review. References checked

I.17 Discussing Implantable Cardioverter Defibrillator (ICD) deactivation

Reference	Reason for exclusion
Abbasi 2016[4]	No relevant themes
Agard 2007[20]	No relevant themes
Bekelman 2011[147]	No relevant themes
Bolse 2012[183]	No relevant themes
Bradley 2017[200]	No qualitative analysis
Carroll 2011[244]	No relevant themes
Cinar 2013[278]	No relevant themes
Daeschler 2015[335]	No qualitative analysis
Daeschler 2017[336]	No qualitative analysis
Flanagan 2010[466]	Literature review
Goldstein 2004[536]	No qualitative analysis
Goldstein 2004[534]	No qualitative analysis
Goldstein 2014[535]	Protocol
Groarke 2012[558]	No qualitative analysis
Hauptman 2008[586]	No qualitative analysis
Hauptman 2013[585]	No relevant themes
Herman 2013[600]	No qualitative analysis
Hill 2015[607]	Systematic review: references checked
Kamphuis 2004[721]	No relevant themes
Kapa 2010[726]	No qualitative analysis

Reference	Reason for exclusion
Kelley 2009[751]	No qualitative analysis
Kelley 2009[750]	No qualitative analysis
Kirkpatrick 2012[767]	No qualitative analysis
Kobe 2012[774]	Not article
Kramer 2011[795]	No qualitative analysis
Lewis 2014[878]	Systematic review: references checked
Locsin 2010[897]	No relevant themes
Lucas 2012[908]	Abstract
Marinksis 2010[940]	No qualitative analysis
McEvedy 2017[973]	No qualitative analysis
Melon 2014[877]	No relevant themes
Mert 2012[993]	No relevant themes
Mueller 2008[1022]	No qualitative analysis
Ooi 2016[1086]	Systematic review: references checked
Ottenberg 2013[1091]	No relevant themes
Palacios-Cena 2010[1100]	No relevant themes
Palacios-Cena 2011[1099]	No relevant themes
Pederson 2013[1125]	No qualitative analysis
Pederson 2017[1126]	No qualitative analysis
Raphael 2011[1187]	No qualitative analysis
Sherazi 2008[1282]	No qualitative analysis
Sherazi 2010[1283]	No qualitative analysis
Stewart 2010[1326]	No qualitative analysis
Strachan 2012[1339]	No relevant themes
Stromberg 2014[1340]	No qualitative analysis
Svanholm 2016[1347]	Incorrect study design
Thylen 2013[1386]	No qualitative analysis

I.18 Identifying patients with an increased risk of mortality

Reference	Reason for exclusion
AbouEzzeddine 2016[7]	Composite outcome (death not >90%)
Adabag 2014[9]	Wrong outcome and time point > 1 year. Derivation only.
Adamo 2015[10]	Sample size too low
Adamo 2016[11]	Validation of HMRS in INTERMACS cohort. Larger study in same cohort already included.
Adejumo 2015[13]	Sample size too low
Adlam 2005[17]	Outcome time point > 1 year. Derivation only.
Adlbrecht 2013[19]	Outcome time point unclear. Sample size too low.

Reference	Reason for exclusion
Agha 2009[23]	Outcome > 1 year.
Agostoni 2013[24]	Wrong outcome.
Ahmad 2015[30]	No risk tool. Study design.
Aissaoui 2015[36]	Sample size too low
Akiyama 2012[40]	Sample size too low
Akoudad 2017[41]	CRT-D population (only population we know has 100% symptomatic HF n<500)
Alba 2013[47]	Review, screened for references
Alba 2009[48]	Sample size too low
Allen 2011[55]	Derivation only. Wrong outcome.
Allen 2008[57]	Sample size too low
Anand 2012[66]	Sample size too low
Andersson 2014[70]	Wrong outcome. Derivation only.
Aramburu-Bodas 2015[90]	No risk tool. Derivation only.
Arenja 2011[92]	No discrimination data. Derivation only.
Austin 2010[103]	Wrong outcome
Avery 2010[104]	Wrong outcome. Derivation only.
Barge-Caballero 2011[124]	Not in English
Barlera 2013[126]	Derivation only. No discrimination data. Time point > 1 year. Other risk tools time point unclear.
Bayes-Genis 2012[137]	Outcome time point > 1 year. Derivation only.
Bayes-Genis 2014[138]	No risk tool. Derivation only.
Bayes-Genis 2015[139]	Review, screened for references
Behnes 2016[144]	Sample size too low
Benbarkat 2012[152]	No discrimination data. Study design.
Bhandari 2016[163]	Wrong outcome
Bilchick 2012[168]	Reports outcome at >1 year, does show a nomogram for 1 year mortality but no extractable calibration or discrimination data at 1 year
Bilchick 2017[169]	Outcome > 1 year. Study design.
Bjurman 2015[172]	Outcome > 1 year.
Bjurman 2013[173]	Derivation only. Outcome > 1 year.
Bobbio 2004[178]	Sample size too low
Brophy 2004[210]	No discrimination data.
Butler 2004[225]	No discrimination data
Cabassi 2013[229]	Outcome time point unclear. Discrimination data unclear.
Castel 2009[252]	Wrong outcome
Charlson 1987[257]	ordered as background info for the aCCI tool
Cheng 2012[268]	Sample size too low
Chyu 2014[275]	Outcome > 1 year.
Cioffi 2014[279]	Composite outcome (% death not reported). Derivation only. No risk tool.
Clemens 2012[291]	Sample size too low
Cowger 2016[326]	Validation of HMRS in INTERMACS cohort. Larger

Reference	Reason for exclusion
	study in same cohort already included.
Cowger 2013[325]	Outcome time point too short. No discrimination data for validation cohort.
Dardas 2015[344]	Composite outcome (death not >90%)
de Antonio 2012[353]	Derivation only. Outcome > 1 year.
Delgado 2016[369]	Wrong outcome. Derivation only.
Dunlay 2010[418]	Outcome time point unclear. Derivation only. No risk tool.
Eapen 2013[421]	Outcome time point too short (30 days)
Echouffo-Tcheugui 2015[422]	Review, screened for references
Escobar 2017[442]	No external validation cohort
Ferreira 2016[460]	Sample size too low
Ferrero-Gregori 2016[462]	Sample size too low
Filippatos 2007[465]	Sample size too low
Fonarow 2012[472]	Review, screened for references
Forman 2012[475]	Derivation only. No risk tool.
Fox 1999[477]	No discrimination data in relevant population.
Franke 2015[478]	Outcome > 1 year.
Frankel 2006[479]	Sample size too low
Frea 2015[482]	Composite outcome (death not >90%)
Frea 2016[481]	Wrong outcome
Freitas 2017[485]	Sample size too low
Freudenberger 2016[488]	Derivation only.
Fu 2015[492]	sample size too low
Garcia-Gutierrez 2016[503]	Wrong outcome
Garcia-Olmos 2017[504]	Protocol only.
Gardin 2012[505]	Wrong outcome. Timepoint unclear. Derivation only. No risk tool.
Gardner 2003[506]	Outcome time point unclear. Sample size too low.
Gasparini 2015[507]	Outcome time point > 1 year
Gelow 2015[511]	No discrimination data. Wrong outcome.
Giamouzis 2009[518]	Composite outcome (death not >90%)
Giolo 2012[520]	No discrimination data. Study design.
Goda 2011[527]	Composite outcome (death not >90%)
Goda 2011[525]	Composite outcome (death not >90%)
Goda 2010[526]	Composite outcome (death not >90%)
Goldenberg 2008[531]	ordered as background info for the MADIT-II tool
Goldraich 2009[532]	Review, screened for references
Gorodeski 2010[546]	Sample size too low
Gracin 1998[550]	No discrimination data
Gradaus 2002[551]	No discrimination data. Study design.
Green 2007[554]	No discrimination data
Griva 2015[557]	Review, screened for references
Gula 2014[561]	Wrong outcome

Reference	Reason for exclusion
Haga 2012[576]	Sample size too low
Heidenreich 2015[597]	No external validation cohort
Heitz 2017[599]	Wrong outcome
Ho 2016[611]	Wrong population. Wrong outcome.
Hoffmann 2015[619]	Sample size too low
Holmstrom 2013[627]	Outcome > 1 year. Derivation only.
Honold 2013[633]	Outcome > 1 year.
Horne 2010[636]	Wrong population
Howlett 2013[640]	Review, screened for references
Hsiao 2012[642]	Sample size too low
Hsieh 2008[643]	Wrong outcome or outcome time point too short.
Hsu 2017[644]	Outcome and time point unclear.
Hudson 2016[649]	No discrimination data.
Hummel 2013[651]	Sample size too low
Hussain 2014[654]	Sample size too low
Huynh 2008[657]	sample size too low
Huynh 2006[656]	Derivation only.
Huynh 2015[658]	Wrong outcome
Imamura 2012[662]	Sample size too low
Ingle 2014[665]	Sample size too low
Ivanov 2017[674]	Outcome time point unclear.
Iwakami 2017[675]	Tool as derived does not predict 1 year mortality, no re-calibration in this cohort.
Jabbour 2014[682]	Sample size too low
Jacob 2016[683]	Wrong outcome
Jacobs 2017[684]	Wrong population
Jacobson 2010[685]	ordered for cohort dates for Ketchum 2012 [754]
Jankowska 2011[689]	No risk tool. Derivation only. Wrong outcome.
Jhund 2015[699]	Wrong study design (no discrimination data, no validation cohort, time point unclear).
Kalogeropoulos 2009[717]	Sample size too low
Kalogeropoulos 2010[716]	Wrong population. Wrong outcome.
Kalogeropoulos 2015[718]	Sample size too low
Kato 2015[739]	Sample size too low
Kato 2013[740]	Sample size too low
Kavsak 2011[742]	Derivation only. Wrong outcome and time point > 1 year. No risk tool.
Kawase 2015[743]	Wrong outcome
Kearney 2003[746]	Outcome > 1 year. Derivation only.
Kelder 2011[747]	not prognostic
Ketchum 2010[755]	No discrimination data. Study design.
Keteyian 2016[757]	Derivation only
Khan 2016[760]	Wrong population
Khazanie 2015[761]	No discrimination data for validation cohort.

Reference	Reason for exclusion
Kheirbek 2015[762]	Tool as derived does not predict 1 year mortality, no re-calibration in this cohort.
Kinugasa 2009[766]	Sample size too low
Kleber 2015[769]	Sample size too low
Ko 2008[773]	No discrimination data
Koelling 2004[777]	Composite outcome (death not >90%)
Koglin 2001[778]	No discrimination data (ROC curve only).
Komajda 2011[780]	Outcome > 1 year. Derivation only.
Kristensen 2015[798]	Wrong outcome
Krumholz 2016[805]	Wrong outcome
Kuramoto 2011[812]	No discrimination data
Ky 2011[819]	Composite outcome (death not >90%)
La Rovere 2017[821]	No discrimination data on risk tool.
La Rovere 2015[820]	Sample size too low
La Rovere 2003[822]	Sample size too low
Lanfear 2017[833]	Sample size too low
Lassus 2013[837]	No risk tool. Derivation only.
Laszczynska 2016[838]	Unobtainable
Lee 2012[850]	Outcome time point too short.
Lemesle 2015[858]	Sample size too low
Levenson 2000[865]	No discrimination data
Levy 2012[868]	Composite outcome (death not >90%)
Levy 2012[869]	Sample size too low
Levy 2009[872]	Sample size too low
Levy 2008[871]	Review, screened for references
Levy 2017[870]	Wrong outcome
Leyva 2009[880]	Sample size too low
Li 2008[881]	Tool as derived does not predict 1 year mortality, no re-calibration in this cohort.
Lin 2016[891]	Review, screened for references
Ling 2015[892]	Sample size too low. No discrimination data. No risk tool.
Loghmanpour 2015[899]	Validation of HMRS in INTERMACS cohort. Larger study in same cohort already included.
Lund 2005[911]	No discrimination data
Lund 2003[910]	No discrimination data
Lupon 2013[912]	Derivation only. Outcome > 1 year.
Lupon 2014[913]	Derivation only. Outcome time point unclear for other tools.
Lupon 2015[914]	Outcome > 1 year.
Manzano 2011[934]	Outcome time point > 1 year
Melin 2016[985]	Outcome time point unclear (> 1 year).
Menon 2016[987]	Sample size too low
Mohamedali 2017[1006]	Sample size too low

Reference	Reason for exclusion
Mortazavi 2016[1019]	Wrong outcome. Derivation only.
Mozaffarian 2007[1020]	Wrong outcome
Myers 2008[1034]	Wrong outcome. Derivation only.
Myers 2013[1035]	Wrong outcome
Nakada 2016[1039]	Sample size too low
Nakagomi 2016[1040]	Sample size too low
Nakayama 2011[1042]	Population >60% NYHA class I (not symptomatic)
Narumi 2013[1044]	Sample size too low
Nishi 2017[1058]	Sample size too low
Nymo 2017[1060]	No discrimination data for validated risk tools (supplementary online tables unobtainable).
O'Connor 2008[1061]	Outcome timepoint too short. No discrimination data in validation cohorts.
O'Connor 2012[1065]	Derivation only
O'Connor 2010[1063]	Sample size too low
Oh 2012[1074]	Sample size too low
Okazaki 2014[1079]	Outcome time point unclear
Packer 1996[1098]	Ordered for ref for PRAISE trial. Levy 2006 original derivation cohort.
Pamboukian 2012[1103]	No discrimination data. Study design.
Panahiazar 2015[1104]	No risk tool.
Parenica 2016[1108]	Wrong population
Parikh 2009[1110]	Composite outcome (death not >90%)
Pascual-Figal 2011[1114]	Derivation only.
Perrotta 2012[1129]	Composite outcome (death not >90%)
Pfister 2008[1140]	Wrong outcome
Pocock 2013[1160]	No discrimination data.
Pocock 2006[1161]	Outcome time point > 1 year. Derivation only.
Poses 2000[1167]	No discrimination data for relevant outcome
Postmus 2012[1169]	Outcome time point > 1 year
Pulignano 2016[1175]	Sample size too low
Rahimi 2014[1179]	Review, screened for references
Rangel 2014[1185]	No discrimination dat for relevant outcome. Study design.
Richter 2013[1204]	Derivation only. Outcome > 1 year.
Ritt 2012[1212]	No discrimination data.
Salah 2014[1236]	Sample size too low. Unclear whether discrimination data relates to validation cohort.
Sartipy 2014[1248]	Composite outcome (death not >90%)
Sartipy 2014[1247]	Sample size too low
Schaffer 2009[1253]	No discrimination data
Scrutinio 2014[1261]	sample size too low
Scrutinio 2012[1263]	sample size too low
Scrutinio 2013[1262]	sample size too low

Reference	Reason for exclusion
Senni 2006[1268]	Composite outcome (% death not reported)
Shiraishi 2016[1286]	Sample size too low
Smith 2012[1304]	Sample size too low
Smits 2013[1305]	Sample size too low.
Snow 2016[1306]	not 12 month mortality
Spiess 2017[1318]	review screened for refs
Stiell 2013[1334]	Wrong outcome. Derivation only.
Szabo 2014[1351]	Unable to obtain paper
Sze 2017[1352]	Sample size too low
Tang 2009[1358]	No discrimination data
Tentzeris 2011[1368]	No risk tool. Wrong outcome. Outcome time point unclear.
Terzi 2006[1372]	Outcome time point unclear (in hospital mortality).
Teuteberg 2012[1375]	Wrong outcome and timepoint too short
Thomas 2014[1381]	Sample size too low
Timmons 2013[1390]	sample size too low
Tjam 2012[1391]	Derivation only.
Tokatli 2015[1395]	Derivation only. Outcome timepoint > 1 year.
Treece 2017[1400]	Review, screened for references
Trejo-Velasco 2016[1401]	Not in English
Upshaw 2016[1416]	No discrimination data for relevant outcome time point.
Uszko-Lencer 2017[1417]	Outcome > 1 year.
Vakil 2014[1421]	Validation of SHFM in original validation cohorts, data on which already included.
Van Der Heijden 2016[1424]	Outcome > 1 year.
Van Spall 2011[1428]	Outcome timepoint too short
Vazquez 2009[1437]	Outcome time point > 1 year. Validation unclear.
von Haehling 2010[1449]	Derivation only.
Voors 2017[1450]	No discrimination data for risk tool. Outcome > 1 year.
Wedel 2009[1467]	Not validated in an external cohort
Whellan 2012[1476]	Tool as derived does not predict 1 year mortality, no re-calibration in this cohort.
Win 2017[1488]	No discrimination data available.
Xanthopoulos 2017[1500]	Sample size too low
Zafrir 2012[1517]	Outcome > 1 year.
Zahn 2010[1518]	No discrimination data
Zhang 2013[1529]	Derivation only.
Zielinski 2009[1534]	Composite outcome (death not >90%)
Zilinski 2012[1535]	Sample size too low
Zugck 2001[1537]	Sample size too low

Appendix J: Excluded health economic studies

J.1 BNP and NT-proBNP in diagnosing heart failure

None.

J.2 Cardiac Magnetic Resonance Imaging in heart failure

None.

J.3 Salt and fluid restriction

None.

J.4 Beta-blockers in people with heart failure and atrial fibrillation

None.

J.5 Mineralocorticoid Receptor Antagonists

Reference	Reason for exclusion
Ademi 2014[14]	This study was selectively excluded due to the availability of more applicable evidence. This study analysed the same trial as other available evidence but from a non-UK perspective, therefore the committee judged that other available evidence was of greater applicability, and therefore this study was selectively excluded.
Ademi 2016[15]	This study was selectively excluded due to the availability of more applicable evidence. This study analysed the same trial as other available evidence but from a non-UK perspective, therefore the committee judged that other available evidence was of greater applicability, and therefore this study was selectively excluded.
Athanasakis 2016[97]	This study was selectively excluded due to the availability of more applicable evidence. This study analysed the same trial as other available evidence but from a non-UK perspective, therefore the committee judged that other available evidence was of greater applicability, and therefore this study was selectively excluded.
Thanh 2016[1376]	This study was selectively excluded due to the availability of more applicable evidence. This study analysed the same trial as other available evidence but from a non-UK perspective, therefore the committee judged that other available evidence was of greater applicability, and therefore this study was selectively excluded.

J.6 Iron supplementation for iron deficiency in heart failure

Reference	Reason for exclusion
Comin-Colet 2014 [309]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was available, this study was selectively excluded.
Hofmarcher 2015 [621]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was

Reference	Reason for exclusion
	available, this study was selectively excluded.
Lim 2014 [888]	This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis was available, this study was selectively excluded.

J.7 Pharmacological treatment for heart failure in people with heart failure and chronic kidney disease

None.

J.8 Coronary revascularisation

None.

J.9 Home-based versus centre-based rehabilitation

None.

J.10 Monitoring

None.

J.11 Telemonitoring and self-monitoring

Reference	Reason for exclusion
Dendale 2012[370]	This study was assessed as partially applicable with very serious limitations due to a non-UK perspective, no health outcome estimates, and the analysis did not consider potentially important cost components (e.g. drug, intervention, and outpatient visits). This study was therefore excluded from the review.
Scalvini 2005[1252]	This study was assessed as partially applicable with very serious limitations due to a short time horizon, no quality of life estimates, source of cost not reported, the analysis did not consider potentially important cost components (e.g. drug, intervention, outpatient visit, emergency visit) and the usual care intervention was not described. This study was therefore excluded from the review.
Sohn 2012[1308]	This study was assessed as partially applicable with very serious limitations due to a short time horizon, it is not clear if the analysis considered potentially important cost components (outpatient visits, emergency visits). This study was therefore excluded from the review.
Villani 2014 [1445]	This study was assessed as partially applicable with potentially serious limitations due to a non-UK perspective, no quality of life estimates and source of cost not reported. However, given that a more applicable UK analysis was available, this study was selectively excluded.

J.12 Multi-Disciplinary Teams

Reference	Reason for exclusion

Reference	Reason for exclusion
Adlbrecht 2011 [18]	This study was assessed as partially applicable with potentially serious limitations due to a non-UK payer perspective (charges used as proxy for costs), QALYs were not used as the health outcome measure. It is a within-trial analysis and so does not reflect the full body of available evidence available for this intervention, and there were very large standard deviations were reported around the costs, with limited exploration of uncertainty.

J.13 Transition between heart failure care settings

None.

J.14 Communication needs regarding diagnosis and prognosis

None.

J.15 Diuretics in advanced heart failure

None.

J.16 Domiciliary oxygen therapy in people with advanced heart failure

None.

J.17 Discussing Implantable Cardioverter Defibrillator (ICD) deactivation

None.

J.18 Identifying patients with an increased risk of mortality

None.

Appendix K: Unit costs

K.1 Coronary revascularisation

Table 77: Relevant NHS reference costs for CABG without ventricular reconstruction (Elective inpatient) [Source: NHS Reference Costs 2014/15[1056]]

Reference cost HRG (a)	National average unit cost	Lower Quartile Unit Cost	Upper Quartile Unit Cost	Average cost of excess bed day	Lower Quartile Unit Cost	Upper Quartile Unit Cost	Average length of stay (days)(b)	NOTES (c)
Complex Coronary Artery Bypass Graft with CC score 10+ [ED26A]	£17,714	£12,594	£20,151	£277	£126	£275	9	The number of data submissions for this code was 23, with 90 units of activity
Complex Coronary Artery Bypass Graft with CC score 5-9 [ED26B]	£12,224	£9,454	£14,224	£372	£282	£383	8	The number of data submissions for this code was 28, with 182 units of activity
Complex Coronary Artery Bypass Graft with CC score 0-4 [ED26C]	£9,876	£8,832	£9,838	£473	£322	£659	5	The number of data submissions for this code was 29, with 349 units of activity
Major Coronary Artery Bypass Graft with CC score 10+ [ED27A]	£12,508	£11,011	£14,042	£328	£328	£328	8	The number of data submissions for this code was 24, with 100 units of activity
Major Coronary Artery Bypass Graft with CC score 5-9 [ED27B]	£11,093	£9,524	£12,913	£613	£287	£622	7	The number of data submissions for this code was 29, with 414 units of activity
Major Coronary Artery Bypass Graft with CC score 0-4 [ED27C]	£9,650	£8,110	£11,490	£188	£142	£279	5	The number of data submissions for this code was 29, with 956 units of activity

Reference cost HRG (a)	National average unit cost	Lower Quartile Unit Cost	Upper Quartile Unit Cost	Average cost of excess bed day	Lower Quartile Unit Cost	Upper Quartile Unit Cost	Average length of stay (days)(b)	NOTES (c)
Standard Coronary Artery Bypass Graft with CC score 10+ [ED28A]	£12,706	£11,384	£13,044	£265	£72	£389	8	The number of data submissions for this code was 28, with 331 units of activity
Standard Coronary Artery Bypass Graft with CC score 5-9 [ED28B]	£10,106	£8,431	£11,161	£571	£218	£357	6	The number of data submissions for this code was 30, with 1,461 units of activity
Standard Coronary Artery Bypass Graft with CC score 0-4 [ED28C]	£8,952	£7,332	£10,389	£618	£257	£601	5	The number of data submissions for this code was 34, with 3,838 units of activity

(a) The HRG code was not split by age and/or co morbidities and complications. Therefore the unit cost was thought to be an underestimate of that which would be incurred by the population under consideration.
(b) The average length of stay was thought to be reflective of that which would be incurred by the population under consideration.
(c) Note that the number of data submissions for the activity level recorded indicated that the unit cost may not be reflective of the national average.

Table 78: Relevant NHS reference costs for Percutaneous Transluminal Coronary Angioplasty (Elective inpatient) [Source: NHS Reference Costs 2014/15[1056]]

Reference cost HRG (a)	National average unit cost	Lower Quartile Unit Cost	Upper Quartile Unit Cost	Average cost of excess bed day	Lower Quartile Unit Cost	Upper Quartile Unit Cost	Average length of stay (days)(b)	NOTES (c)
Complex Percutaneous Transluminal Coronary Angioplasty with CC Score 12+ [EY40A]	£7,302	£3,684	£11,339	-	-	-	7	The number of data submissions for this code was 10, with 13 units of activity
Complex Percutaneous	£4,585	£2,349	£5,754	£468	£468	£468	3	The number of data submissions for

Reference cost HRG (a)	National average unit cost	Lower Quartile Unit Cost	Upper Quartile Unit Cost	Average cost of excess bed day	Lower Quartile Unit Cost	Upper Quartile Unit Cost	Average length of stay (days)(b)	NOTES (c)
Transluminal Coronary Angioplasty with CC Score 8-11 [EY40B]								this code was 36, with 90 units of activity
Complex Percutaneous Transluminal Coronary Angioplasty with CC Score 4-7 [EY40C]	£3,917	£2,411	£4,528	£469	£267	£713	2	The number of data submissions for this code was 76, with 945 units of activity
Complex Percutaneous Transluminal Coronary Angioplasty with CC Score 0-3 [EY40D]	£2,961	£1,971	£3,584	£326	£222	£430	1	The number of data submissions for this code was 79, with 3,065 units of activity
Standard Percutaneous Transluminal Coronary Angioplasty with CC Score 12+ [EY41A]	£7,684	£2,257	£8,864	-	-	-	9	The number of data submissions for this code was 19, with 24 units of activity
Standard Percutaneous Transluminal Coronary Angioplasty with CC Score 8-11 [EY41B]	£4,290	£2,284	£6,756	£437	£180	£699	3	The number of data submissions for this code was 60, with 189 units of activity
Standard Percutaneous Transluminal Coronary Angioplasty with CC Score 4-7 [EY41C]	£3,020	£2,039	£3,520	£298	£226	£404	2	The number of data submissions for this code was 83, with 1,790 units of activity
Standard Percutaneous Transluminal Coronary Angioplasty with CC Score 0-3 [EY41D]	£2,351	£1,557	£2,669	£263	£187	£331	1	The number of data submissions for this code was 82, with 7,134 units of activity

(a) The HRG code was not split by age and/or co morbidities and complications. Therefore the unit cost was thought to be an underestimate of that which would be incurred by the population under consideration.
(b) The average length of stay was thought to be reflective of that which would be incurred by the population under consideration

(c) Note that the number of data submissions for the activity level recorded indicated that the unit cost may not be reflective of the national average.

Appendix L: Scope

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Guideline scope

Chronic heart failure in adults: diagnosis and management

Topic

This guideline will update the NICE guideline on chronic heart failure (CG108) as set out in the surveillance review decision.

The guideline will be developed using the methods and processes outlined in Developing NICE guidelines: the manual.

For more information about why this guideline is being developed, and how the guideline will fit into current practice, see the context section.

Who the guideline is for

- People using services, families and carers, and the public.
- Healthcare professionals in primary and secondary care.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive.

Equality considerations

NICE has carried out an equality impact assessment during scoping. The assessment:

- lists equality issues identified, and how they have been addressed
- explains why any groups are excluded from the scope.

The guideline will look at inequalities relating to people who are older and frail, and people living in rural areas with limited access to services.

1 What the guideline is about

1.1 Who is the focus?

Groups that will be covered

- Adults (18 and older) with symptoms or a diagnosis of chronic heart failure (including heart failure with reduced ejection fraction and heart failure with preserved ejection fraction).

Groups that will not be covered

- Diagnostic screening for heart failure in people who are asymptomatic.
- People with isolated right heart failure.
- Heart failure in people having chemotherapy.
- Heart failure in people having treatment for HIV.
- Heart failure in women who are pregnant.

1.2 Settings

Settings that will be covered

- Primary and secondary NHS-commissioned care including referral to tertiary care.

1.3 Activities, services or aspects of care

Areas from the published guideline that will not be updated

1. Symptoms and signs in diagnosing heart failure.
2. Clinical review and monitoring of serum digoxin.
3. Lifestyle.
   - Sexual activity, vaccination and air travel.

Recommendations in areas that are not being updated may be edited to ensure that they meet current editorial standards, and reflect the current policy and practice context.

Areas from the published guideline that will be updated

1 Diagnosing heart failure.
- Role of circulating biomarkers (including natriuretic peptides).
- Echocardiography and cardiac MRI.

2 Managing chronic heart failure.
- Initiation and sequencing of pharmacological therapies including:
  - ◊ Isosorbide/hydralazine.
  - ◊ Angiotensin-II receptor antagonists (ARBs).
  - ◊ Mineralocorticoid receptor antagonists
- Fluid balance (optimum fluid and salt intake).

3 Rehabilitation (including Home-based rehabilitation packages that include an exercise element).

4 Monitoring heart failure.
- Role of biomarkers (including natriuretic peptides).
- Role of echocardiography.
- Distance monitoring including telemonitoring.
- Self-monitoring.

- Referral for invasive procedures:
  - Coronary revascularisation (including coronary artery bypass graft and angioplasty).
- Referral and approach to care.
  - Heart failure multidisciplinary team.
  - Transfer of care between secondary and primary care services.
- Information and support.
  - Information and support on diagnosis and prognosis for people with chronic heart failure, their families and carers.
- Supportive and palliative care.
  - Domiciliary oxygen therapy.
  - Parenteral and intravenous diuretics.
  - Criteria for withdrawing treatment and device inactivation.

Areas not in the published guideline that will be included in the update

1 How to manage chronic heart failure in different subgroups:

- People with iron deficiency.
- People with chronic kidney disease (estimated glomerular filtration rate [eGFR] less than 60 ml/min/1.73m^2 with or without markers of kidney damage).
- People with chronic heart failure and secondary atrial fibrillation.
- People aged over 75.

2 Pharmacological therapies.

- Beta-blockers in people with chronic heart failure and secondary atrial fibrillation.

3 Palliative care.

- Referral to palliative care.
- Delivery of diuretics

4 Monitoring heart failure.

- Role of cardiac MRI.

Areas from the published guideline that will be removed

1 General.

- Age.
- Gender.

2 Pharmacological agents.

- Aspirin.
- Statins.

3 Heart failure caused by valve disease.

4 Management of depression and anxiety.

5 Benefit of other therapies such as homeopathy, reflexology, hydrotherapy, crystal therapy and acupuncture.

6 Referral for invasive procedures.

- Implantable cardiac defibrillators.

7 Valve surgery.

8 Non-NHS agencies.

9 Lifestyle.

- Smoking and alcohol.

1.4 Economic aspects

We will take economic aspects into account when making recommendations. We will develop an economic plan that states for each review question (or key area in the scope) whether economic considerations are relevant, and if so whether this is an area that should be prioritised for economic modelling and analysis. We will review the economic evidence and carry out economic analyses, using an NHS and personal social services (PSS) perspective, as appropriate.

1.5 Key issues and questions

While writing this scope, we have identified the following key issues, and key questions related to them:

1 Diagnosing heart failure.
   1.1 What is the diagnostic accuracy of N-terminal pro-B-type natriuretic peptide (NTproBNP) versus B-type natriuretic peptide (BNP) for heart failure?
   1.2 What should the diagnostic thresholds for BNPs in people with heart failure and chronic kidney disease be?
   1.3 What should the diagnostic thresholds for BNPs in people with heart failure and atrial fibrillation be?
   1.4 What is the diagnostic accuracy of echocardiography and cardiac MRI versus echocardiography for heart failure?
   1.5 What is the role of secondary imaging investigations in diagnosing suspected amyloidosis?

2 Managing chronic heart failure.
   2.1 In people with chronic heart failure who have received 1 pharmacological treatment, what is the next most clinically and cost-effective option?
   2.2 What is the clinical and cost effectiveness of pharmacological interventions (erythropoietin and intravenous iron) in people with chronic heart failure and iron deficiency?

2.3 How will the use of pharmacological interventions for people with chronic heart failure be different in people who also have chronic kidney disease?

2.4 What is the clinical and cost effectiveness of beta-blockers in people with chronic heart failure and secondary atrial fibrillation?

2.5 What is the clinical and cost effectiveness of mineralocorticoid receptor antagonists compared with ARBs in people with symptomatic chronic heart failure who are having treatment with:

- a beta-blocker and an ACE Inhibitor or
- a beta-blocker alone because of intolerance to ACE inhibitors?

2.6 Is there a role for coronary revascularisation with coronary artery bypass grafting or angioplasty in people with chronic heart failure?

3 Rehabilitation in chronic heart failure.

3.1 What is the clinical and cost effectiveness of home-based rehabilitation (that includes an exercise element) for people with chronic heart failure?

4 Monitoring heart failure.

4.1 What is the clinical and cost effectiveness of biomarker-based monitoring compared with standard care?

4.2 What is the clinical and cost effectiveness of repeated echocardiography compared with standard care for monitoring chronic heart failure?

4.3 What is the clinical and cost effectiveness of cardiac MRI compared with standard care for monitoring chronic heart failure?

4.4 What is the clinical effectiveness of salt and fluid restriction for people with chronic heart failure?

4.5 What is the clinical and cost effectiveness of distance monitoring (including telemonitoring) compared with outpatient monitoring in people with chronic heart failure?

4.6 What is the clinical and cost effectiveness of self-monitoring compared with outpatient monitoring in people with chronic heart failure?

5 Information and support.

5.1 What are the specific needs to be considered when communicating a diagnosis and consequent prognosis to people with chronic heart failure, their families and carers?

6 Referral and approach to care.

6.1 Which members of the multidisciplinary team should be involved in the care of people with chronic heart failure?

6.2 How should the transition between secondary and primary care be managed in people with chronic heart failure?

7. Palliative care.

7.1 What criteria should be used to refer people with chronic heart failure to palliative care and when should they be referred?

7.2 What is the clinical and cost effectiveness of domiciliary oxygen therapy in people with chronic heart failure who are having palliative care?

7.3 What is the clinical and cost effectiveness of intravenously delivered diuretics compared with diuretics delivered subcutaneously in people with chronic heart failure who are having palliative care?

7.4 What criteria should be taken into account when deciding on the timing of the discussion about the deactivation of a defibrillator?

The key questions may be used to develop more detailed review questions, which guide the systematic review of the literature.

1.6 Main outcomes

The main outcomes that will be considered when searching for and assessing the evidence are:

1. Mortality.
2. Hospitalisation.
3. Re-admission to hospital.
4. Quality of life.
5. Adverse events.

2 Links with other NICE guidance, NICE quality standards, and NICE Pathways

2.1 NICE guidance

NICE guidance that will be updated by this guideline

- Chronic heart failure in adults: management (2010) NICE guideline CG108.

NICE guidance that will be incorporated by this guideline

- Ivabradine for treating chronic heart failure (2012) NICE technology appraisal guidance 267. It is proposed that this guideline will incorporate and contextualise recommendations from TA267, subject to a review proposal by the technology appraisals programme.

NICE guidance about the experience of people using NHS services

NICE has produced the following guidance on the experience of people using the NHS. This guideline will not include additional recommendations on these topics unless there are specific issues related to chronic heart failure:

- Medicines optimisation (2015) NICE guideline NG5
- Patient experience in adult NHS services (2012) NICE guideline CG138
- Medicines adherence (2009) NICE guideline CG76

NICE guidance that is closely related to this guideline

Published

NICE has published the following guidance that is closely related to this guideline:

- Acute heart failure: diagnosis and management (2014) Nice guideline [CG187]
- Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure (2014) NICE technology appraisal guidance [TA314]

In development

NICE is currently developing the following guidance that is closely related to this guideline:

- Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction. NICE technology appraisal. Publication expected April 2016. It is proposed that this guideline will incorporate and contextualise recommendations for this topic, subject to a review proposal by the technology appraisals programme.

2.2 NICE quality standards

NICE quality standards that may need to be revised or updated when this guideline is published

- Chronic heart failure in adults (2011) NICE quality standard 9

2.3 NICE Pathways

When this guideline is published, the recommendations will update the current NICE Pathway on chronic heart failure. NICE Pathways bring together all related NICE guidance and associated products on a topic in an interactive topic-based flow chart.

Other relevant NICE guidance will also be added to the NICE Pathway, including:

- Implantation of a left ventricular assist device for destination therapy in people ineligible for heart transplantation (2015) NICE interventional procedure guidance 516
- Insertion and use of implantable pulmonary artery pressure monitors in chronic heart failure (2013) NICE interventional procedure guidance 463
- Short-term circulatory support with left ventricular assist devices as a bridge to cardiac transplantation or recovery (2006) NICE interventional procedure guidance 177

3 Context

3.1 Key facts and figures

Chronic heart failure is a complex clinical syndrome of symptoms and signs that suggest the efficiency of the heart as a pump is impaired. It is caused by structural or functional abnormalities of the heart. The British Heart Foundation's 2014 report Cardiovascular disease statistics reported that about 550,000 people in the UK were living with heart failure in 2013. Both the incidence and the prevalence of heart failure increase with age, with an average age at first diagnosis of 76 years.

The prevalence of heart failure is expected to rise in future as a result of an ageing population, improved survival of people with ischaemic heart disease and more effective treatments for heart failure.

3.2 Current practice

This guideline will update NICE's current guidance on chronic heart failure in adults (2010). Uptake of that guidance appears to be good (see the NICE website for uptake information). The Department of Health's Cardiovascular disease outcomes strategy (2013) noted that prescribing of ACE inhibitors, ARBs and beta-blockers remains suboptimal, and that improved use of these drugs has the potential to prevent around 190 deaths per year. This update will review evidence on the clinical and cost effectiveness of these therapies.

The Cardiovascular disease outcomes strategy also aims to increase the provision of cardiac rehabilitation from 4% to 33% of people with chronic heart failure. This update will address specific evidence on the content and delivery of cardiac rehabilitation in heart failure.

4 Further information

This is the final scope, incorporating comments from registered stakeholders during consultation.

The guideline is expected to be published in March 2018.

You can follow progress of the guideline.

Our website has information about how NICE guidelines are developed.

Appendix M: Declarations of interest

Anthony Wierzbicki (GC Chair)

Date	Item declared	Classification	Action taken
Initial declaration	Clinical investigator for Trust hospital on studies of lipid-lowering compounds for Merck, Pfizer and Amgen.	Non-personal, financial, non-specific	Declare and participate
	Commercially funded registry (GENIALL) for lipoprotein lipase deficiency (Chiesi).	Non-personal, financial, non-specific	Declare and participate
28/04/16	GC1: No new declarations.	-	-
29/04/16	GC2: No new declarations.	-	-
03/06/16	GC3: No new declarations.	-	-
06/07/16	GC4: No new declarations.	-	-
01/09/16	GC5: No new declarations.	-	-
02/09/16	GC6: No new declarations.	-	-
26/10/16	GC7: No new declarations.	-	-
05/12/16	GC8: No new declarations	-	-
26/01/17	GC9: No new declarations.	-	-
08/03/17	GC10: A member of the PCSK9 forum and have given talks at that meeting. Not relevant to this guideline.	Non-personal, financial, non-specific	Declare and participate
20/04/17	GC11: No new declarations.	-	-
31/05/17	GC12: No new declarations.	-	-
06/07/17	GC13: No new declarations.	-	-
05/09/17	GC14: No new declarations.	-	-
06/09/17	GC15: No new declarations.	-	-
19/10/17	GC16: No new declarations	-	-

Date	Item declared	Classification	Action taken
29/11/17	GC17: No new declarations	-	-
30/11/17	GC18: No new declarations	-	-

Rajai Ahmad

Date	Item declared	Classification	Action taken
Initial declaration	Honoraria received for invited educational talks/lectures: • Stroke prevention in atrial fibrillation – Pfizer 15/1/16 • Lipid modification and CVD prevention – Merck Sharp & Dohme 23/3/16 • Lipid modification and role of primary care – Merck Sharp & Dohme 12/4/16 • Anticoagulation guidelines in AF – Boehringer Ingelheim 16/6/16 • Lipid modification in primary care – PULSE magazine CVD symposium 21/9/16 • Novel oral anticoagulants – Bristol-Myers Squibb 16/11/16 • Lipid management workshop – RCGP Midlands Faculty 25/11/16 • Lipid management in the ACS patient – Merck Sharp & Dohme 26/11/16	Personal, financial, non-specific	Declare and participate
08/03/17	GC10: No new declarations	Non-personal, financial, non-specific	Declare and participate
20/04/17	GC11: No new declarations.	-	-
31/05/17	GC12: No new declarations.	-	-
06/07/17	GC13: No new declarations.	-	-
05/09/17	GC14: Attended the European Society of Cardiology congress 26-30 August 2017 as guest of Daiichi Sankyo (registration, travel and accommodation).	Personal, financial, non-specific	Declare and participate
06/09/17	GC15: No new declarations.	-	-
19/10/17	GC16: No new declarations	-	-
29/11/17	GC17: No new declarations	-	-

Date	Item declared	Classification	Action taken
30/11/17	GC18: No new declarations	-	-

Abdallah Al-Mohammad

Date	Item declared	Classification	Action taken
Initial declaration	Accepted travel and accommodation to attend the ESC-Heart Failure Meeting in Athens 2014 and in Seville 2015 from Servier.	Regular expenses only	None
	Holder of a grant for Sheffield Teaching Hospitals Charitable Trust for partial funding of the Sheffield Contribution to the International Study of Sildenafil in the treatment of patients with heart failure due to left ventricular systolic dysfunction and raised pulmonary artery hypertension (SilHF trial).	Non-personal, financial, non-specific	Declare and participate
	Currently the principal investigator in Sheffield for SilHF on the following trials: • PARAGON: a trial sponsored by Novartis of LCZ696 in patients with heart failure with preserved left ventricular ejection fraction. • LIVE:LIFE: a trial sponsored by Servier on the quality of life of patients with heart failure with impaired left ventricular systolic function who are in sinus rhythm, over 70 years of age. Completed the recruitment into this study. Involvement with this stopped over a year ago. Co-principal investigator in Sheffield for REVIVED trial: • REVIVED: is a trial of percutaneous coronary intervention or medical therapy in patients with severe left ventricular systolic impairment and coronary artery disease with evidence on cardiac MRI of sufficient hibernating myocardium. The funding is from NIHR.	Personal, financial, non-specific	Declare and participate
28/04/16	GC1: No new declarations.	-	-
29/04/16	GC2: No new declarations.	-	-
03/06/16	GC3: Co-principle investigator for a Phase II trial of a new agent to be given for patients with severe heart failure complicated by pulmonary hypertension.	Personal, financial, non-specific	Declare and participate
06/07/16	GC4: No new declarations.	-	-
01/09/16	GC5: No new declarations.	-	-
02/09/16	GC6: No new declarations.	-	-

Date	Item declared	Classification	Action taken
26/10/16	GC7: No new declarations.	-	-
05/12/16	GC8: PI to ongoing IRONMAN study in Sheffield	Personal, financial, non-specific	Declare and participate
26/01/17	GC9: No new declarations.	-	-
08/03/17	GC10: No new declarations.	-	-
20/04/17	GC11: No new declarations.	-	-
31/05/17	GC12: No new declarations.	-	-
06/07/17	GC13: No new declarations.	-	-
05/09/17	GC14: Co-author on Pandor et al 2013 and Thankola et al 2013 which are discussed in tele-monitoring and self-monitoring clinical evidence review papers.	Personal, non-financial, specific	Declare and withdraw from discussion of the telemonitoring evidence review
06/09/17	GC15: No new declarations.	-	-
19/10/17	GC16: No new declarations	-	-
29/11/17	GC17: No new declarations	-	-
30/11/17	GC18: No new declarations	-	-

Martin Cowie

Date	Item declared	Classification	Action taken
Initial declaration	Research grants to Imperial College from: • ResMed (Sleep apnoea in heart failure), Boston Scientific (sleep apnoea algorithm in pacemakers) • Bayer (prevalence of atrial fibrillation in people with a defibrillator/pacemaker – epidemiological study)	Non-personal, financial, non-specific	Declare and participate
	Consultancy agreements/speaker fees for specific input from: • ResMed (sleep apnoea in heart failure) • Boston Scientific, Medtronic, St Jude Medical, (all three relate to funding of a randomised trial of remote monitoring of implanted devices (Rem-	Personal, financial, non-specific	Declare and participate

Date	Item declared	Classification	Action taken
	HF) that is due to complete in next month and thereafter support stops - not relevant to this guideline) • Bayer (manufactures rivaroxaban, which is not a specific drug for heart failure and is not in scope of this guideline)		
	Consultancy agreements/speaker fees for specific input from: • Servier (manufactures ivabradine) • Novartis (lecture on use of this drug in clinical practice and worked with their cost-effectiveness team on preparing the dossier for NICE).	Personal, financial, specific	Declare and participate. No review of evidence to be undertaken. Recommendations from TA267 to be incorporated into guideline.
28/04/16	GC1: No new declarations.	-	-
29/04/16	GC2: No new declarations.	-	-
03/06/16	GC3: Apologies sent.	-	-
06/07/16	GC4: No new declarations.	-	-
01/09/16	GC5: No new declarations.	-	-
02/09/16	GC6: No new declarations.	-	-
26/10/16	GC7: No new declarations.	-	-
05/12/16	GC8: Resigned from GC	-	-

Suzanna Hardman

Date	Item declared	Classification	Action taken
Initial declaration	None declared.	-	-
28/04/16	GC1: Board member of the British Society for Heart Failure (Past Chair 2013-15)	Personal, non-financial, non-specific	Declare and participate
	GC1: Committee member of the National HF Audit Board, and RSM Cardiology	Personal, non-financial, non-	Declare and

Date	Item declared	Classification	Action taken
	Council	specific	participate
29/04/16	GC2: No new declarations.	-	-
03/06/16	GC3: No new declarations.	-	-
06/07/16	GC4: No new declarations.	-	-
01/09/16	GC5: No new declarations.	-	-
02/09/16	GC6: No new declarations.	-	-
26/10/16	GC7: No new declarations.	-	-
05/12/16	GC8: Apologies sent	-	-
26/01/17	GC9: No new declarations.	-	-
08/03/17	GC10: Apologies sent.	-	-
20/04/17	GC11: Apologies sent.	-	-
31/05/17	GC12: Apologies sent.	-	-
06/07/17	GC13: No new declarations.	-	-
05/09/17	GC14: No new declarations.	-	-
06/09/17	GC15: No new declarations.	-	-
19/10/17	GC16: Worked on NICE Acute Heart Failure GC HE Model	Personal, non-financial, non-specific	Declare and participate
29/11/17	GC17: No new declarations	-	-
30/11/17	GC18: No new declarations	-	-

Nick Hartshorne-Evans

Date	Item declared	Classification	Action taken
Initial declaration	Remunerated by the Pumping Marvellous Foundation as the CEO. In the past 12 months The Pumping Marvellous Foundation have been grant funded by the following companies: Novartis, St Jude Medical, Servier.	Personal, financial, specific	Declare and participate . No review of evidence to be undertaken. Recommendations

Date	Item declared	Classification	Action taken
			from TA267 Ivabradine (Servier) and TA388 Sacubitril valsartan (Novartis) to be incorporated into guideline
28/04/16	GC1: No new declarations.	-	-
29/04/16	GC2: No new declarations.	-	-
03/06/16	GC3: No new declarations.	-	-
06/07/16	GC4: No new declarations.	-	-
01/09/16	GC5: No new declarations.	-	-
02/09/16	GC6: No new declarations.	-	-
26/10/16	GC7: No new declarations.	-	-
05/12/16	GC8: Stepped down as President of the Global cardiac trustee group (charity) iHHub Global heart Failure Alliance (www.inhub.org)	Personal, non-financial, non-specific	Declare and participate
26/01/17	GC9: No new declarations.	-	-
08/03/17	GC10: Grant from Vifor Pharma (manufacturer of iron supplement) as part of a multi stakeholder funded activity to fund a heart failure summit that Pumping Marvellous are organising in May 2017. There are two other funders who aren't relevant to the guidelines – St Jude Medical and Bostin Scientific.	Non-personal financial specific	Declare and participate
20/04/17	GC11: No new declarations.	-	-
31/05/17	GC12: Educational grant funding by Vifor Pharma to create two videos – 1 Cardiac Rehab 2 Iron Deficiency in HF Educational grant funding from Vifor Pharma for HF awareness day in association with the British Society of Heart Failure to –	Non-personal financial specific	Declare and participate

Date	Item declared	Classification	Action taken
	1 Develop materials to build awareness of HF and it's causes for Euro HF day 5th May 2017 (posters and leaflets) 2 Distribution to 150 NHS HF Teams for awareness day The benefactor in both cases was the Pumping Marvellous Foundation with 100% of funding directed to the organisation.		
06/07/17	GC13: No new declarations.	-	-
05/09/17	GC14: Speaker fee – title 'Heart failure through the patients lens' to Roche Diagnostics Global in Switzerland – 20 minute presentation with honorarium Educational Grant Funding – Novartis UK – to reprint 40,000 more Symptom Trackers for distribution to patients across UK. Grant money paid direct to Pumping Marvellous Foundation. http://pumpingmarvellous.org.uk/wp-content/uploads/2016/05/Heart-Failure-in-Lights-RAG-Sheet.pdf	Personal, financial, specific Non-personal, financial, specific	Declare and withdraw from discussion of the health economic model Declare and participate No review of evidence to be undertaken. Recommendations from TA388 Sacubitril valsartan (Novartis) to be incorporated into guideline
06/09/17	GC15: No new declarations.	-	-
19/10/17	GC16: Apologies sent	-	-
29/11/17	GC17:No new declarations	-	-
30/11/17	GC18: Apologies sent	-	-

Rani Khatib

Date	Item declared	Classification	Action taken
Initial declaration	Novartis: Educational Grant covering travel, accommodation and conference fees to attend the HF SUMMIT 2015 – PACE. Consultancy fee for attending "Implementation of a new HF treatment" advisory meeting in November 2015.	Personal, financial, specific	Declare and participate. No review of evidence to be undertaken. Recommendations from TA388 Sacubitril valsartan (Novartis) to be incorporated into guideline
	Servier: Educational Grant covering travel, accommodation and conference fees to attend the ESC Congress 2015.	Personal, financial, specific	Declare and participate. No review of evidence to be undertaken. Recommendations from TA267 Ivabradine (Servier) to be incorporated into guideline
	AstraZeneca: Service Development / Research grant as part of a joint working partnership with Leeds Teaching Hospitals on Post MI Medicines Optimisation Clinic (January – December 2016). Sponsorship of the Yorkshire and North-east Cardiovascular Pharmacy Network (YNCPN) educational meeting in February 2016 titled "ACS management update" – sponsorship included venue, equipment, food and speakers' fees.	Personal, financial, non-specific	Declare and participate
	Daiichi Sankyo: Sponsorship of Yorkshire and North-east Cardiovascular Pharmacy Network (YNCPN) Sept 2015 educational meeting "antiplatelets update". Sponsorship included venue, equipment, food and speakers' fees.	Personal, financial, non-specific	Declare and participate
28/04/16	GC1: Committee member of the UKCPA national cardiology pharmacists group and of the European Society of Cardiology Science Committee of the CCNAP.	Personal, non-financial, non-specific	Declare and participate
	GC1: Co-author of the updated national educational material about Heart Failure.	Personal, financial, non-specific	Declare and participate

Date	Item declared	Classification	Action taken
	GC1: Member of “Pumping Marvellous” Charity clinical board.	Personal, non-financial, non-specific	Declare and participate
29/04/16	GC2: No new declarations.	-	-
03/06/16	GC3: No new declarations.	-	-
06/07/16	GC4: Apologies sent.	-	-
01/09/16	GC5: No new declarations.	-	-
02/09/16	GC6: No new declarations.	-	-
26/10/16	GC7: Agreed to work on a project on research and analysis into the variance of emergency hospitalisation across CCGs, in relation to iron deficiency in heart failure patients (based on NHS Hospital Episode Statistics). This report will be peer reviewed and presented at the British Cardiology Society meeting in June 2017. The project is managed by Firstlight (a research, business and management consultancy company) with funding from Vifor Pharma UK.	Personal, financial, specific	Declare and withdraw when the IV and oral iron evidence review is being considered.
05/12/16	GC8: Apologies sent	-	-
26/01/17	GC9: Agreed to participate as a consultant and partner in the ISCOMAT (Improving the Safety and Continuity of Medicines management at Transitions of care) e-learning to support medicines optimisation. The e-learning is being developed by the Centre for Pharmacy Postgraduate Education, Manchester Pharmacy School, University of Manchester. The ISCOMAT project is an NIHR funded project led by the University of Leeds and the University of Bradford. Funding including expenses and consultancy fees paid for by the University of Manchester. Project started 31st January 2017.	Personal, financial non-specific	Declare and participate
08/03/17	GC10: No new declarations.	-	-
20/04/17	GC11: No new declarations.	-	-
31/05/17	GC12: Apologies sent.	-	-

Date	Item declared	Classification	Action taken
06/07/17	GC13: Speaker fee for a presentation to heart failure nurses and cardiologists in the SE of England at an event sponsored by Novartis UK. The presentation was titled "Capturing heart failure through the patient lens" focussing on insights of HF through the patient's eyes and how HCP's could help patients better. The benefactor was the Pumping Marvellous Foundation with payment directed to the organisation.	Non-personal, financial, specific	Declare and participate No review of evidence to be undertaken. Recommendations from TA388 Sacubitril valsartan (Novartis) to be incorporated into guideline
05/09/17	GC14: Attended ESC congress in Barcelona 26 – 29 August 2017 which was funded by Pharmacy management. The funding included travel and accommodation expenses and registration fee. The funding was made available to Pharmacy Management by Mylan.	Personal, financial, non-specific	Declare and participate
06/09/17	GC15: No new declarations.	-	-
19/10/17	GC16: No new declarations	-	-
29/11/17	GC17: No new declarations	-	-
30/11/17	GC18: No new declarations	-	-

Richard Mindham

Date	Item declared	Classification	Action taken
Initial declaration	Member of the: • National Heart Failure Audit • Royal Brompton & Harefield Trust's Patient Advisory Group for Heart Failure Research • Ironman Trial Steering Committee.	Personal, non-financial, specific	Declare and participate
28/04/16	GC1: No new declarations	-	-
29/04/16	GC2: No new declarations.	-	-
03/06/16	GC3: No new declarations.	-	-

Date	Item declared	Classification	Action taken
06/07/16	GC4: No new declarations.	-	-
01/09/16	GC5: No new declarations.	-	-
02/09/16	GC6: No new declarations.	-	-
26/10/16	GC7: No new declarations.	-	-
05/12/16	GC8: No new declarations.	-	-
26/01/17	GC9: No new declarations.	-	-
08/03/17	GC10: No new declarations.	-	-
20/04/17	GC11: No new declarations.	-	-
31/05/17	GC12: No new declarations.	-	-
06/07/17	GC13: No new declarations.	-	-
05/09/17	GC14: No new declarations.	-	-
06/09/17	GC15: No new declarations.	-	-
19/10/17	GC16: No new declarations	-	-
29/11/17	GC17: No new declarations	-	-
30/11/17	GC18: No new declarations	-	-

Jim Moore

Date	Item declared	Classification	Action taken
Initial declaration	Novartis: Received honoraria, travel and accommodation for Advance Heart Failure steering committee and Heart Failure Speaker Faculty meetings.	Personal, financial, specific	Declare and participate. No review of evidence to be undertaken. Recommendations from TA388 Sacubitril valsartan (Novartis) to be incorporated into guideline
	Bayer: Received honoraria and travel expenses from for participating in Advisory	Personal, financial, non-specific	Declare and

Date	Item declared	Classification	Action taken
	boards related to novel oral anticosgulants and in particular Rivaroxaban. Received honoraria for participating in educational activities related to stroke prevention in atrial fibrillation. Received travel and accommodation to attend an international cardiology meeting. Clinical lead for the West of England Academic Health Science Network "Don't wait to anticoagulate" project promoting stroke prevention in atrial fibrillation partly funded by Bayer.		participate
	Has recruited patients to the CLARIFY registry (stable CAD), sponsored by Servier. Patient follow-up was completed in the past year.	Personal, financial, specific	Declare and participate. No review of evidence to be undertaken. Recommendations from TA267 Ivabradine (Servier) to be incorporated into guideline
28/04/16	GC1: No new declarations.	-	-
29/04/16	GC2: No new declarations.	-	-
03/06/16	GC3: No new declarations.	-	-
06/07/16	GC4: • Attended a NOVARTIS sponsored meeting in June 2016 related to a presentation on ENTRESTO to cardiology clinicians working in Gloucestershire. This drug had been added to the local formulary and attended as an 'interest' clinician (delegate) working as a GPSI and in the GLOS Heart Failure service. Was not involved in the presentation and attendance was not sponsored by the company. Received no remuneration for attending this meeting and declined any hospitality associated with it. • Received from BAYER Pharmaceutical company. Honoraria/ travel expenses/accommodation for participating in advisory boards related to NOAC's and in particular RIVAROXABAN. This included an advisory board where BAYER were working with the company Smartpatient in	Personal, non financial, specific Personal, financial, non-specific	Declare and participate. No review of evidence to be undertaken. Recommendations from TA388 Sacubitril valsartan (Novartis) to be incorporated into guideline Declare and participate

Date	Item declared	Classification	Action taken
	developing an adherence app. Also, an honoraria for participating in educational activities (chairing/lecturing) related to stroke prevention in AF. Also, accommodation/travel expenses to attend an international cardiology meeting. • Sits on the steering group for the Alliance for Heart Failure and has participated in oral evidence sessions at the Houses of Parliament related to the All Party Parliamentary group for heart disease 'Living with Heart Failure' inquiry. The AHF is a coalition of charities, patient groups, professional bodies and healthcare companies working together to raise the profile of heart failure in government, the NHS and media. The AHF is supported and funded by Abbott Laboratories, Medtronic UK and Novartis Pharmaceuticals UK Ltd. Has received no funding/remuneration/hospitality of any sort related to involvement with the AHF.	Personal non-financial non specific	Declare and participate
01/09/16	GC5: No new declarations.	-	-
02/09/16	GC6: No new declarations.	-	-
26/10/16	GC7: No new declarations.	-	-
05/12/16	GC8: No new declarations.	-	-
26/01/17	GC9: No new declarations.	-	-
08/03/17	GC10: No new declarations	-	-
20/04/17	GC11: No new declarations.	-	-
31/05/17	GC12: No new declarations.	-	-
06/07/17	GC13: No new declarations.	-	-
05/09/17	GC14: No new declarations.	-	-
06/09/17	GC15: No new declarations.	-	-
19/10/17	GC16: No new declarations	-	-
29/11/17	GC17: No new declarations	-	-
30/11/17	GC18: No new declarations	-	-

Rebecca Schiff

Date	Item declared	Classification	Action taken
Initial declaration	None declared.	-	-
28/04/16	GC1: No new declaration.	-	-
29/04/16	GC2: Apologies sent.	-	-
03/06/16	GC3: No new declarations.	-	-
06/07/16	GC4: No new declarations.	-	-
01/09/16	GC5: No new declarations.	-	-
02/09/16	GC6: No new declarations.	-	-
26/10/16	GC7: No new declarations.	-	-
05/12/16	GC8: Apologies sent.	-	-
26/01/17	GC9: No new declarations.	-	-
08/03/17	GC10: No new declarations.	-	-
20/04/17	GC11: No new declarations.	-	-
31/05/17	GC12: No new declarations.	-	-
06/07/17	GC13: No new declarations.	-	-
05/09/17	GC14: No new declarations.	-	-
06/09/17	GC15: No new declarations.	-	-
19/10/17	GC16: No new declarations	-	-
29/11/17	GC17: No new declarations	-	-
30/11/17	GC18: No new declarations	-	-

Sue Simpson

Date	Item declared	Classification	Action taken
Initial declaration	None declared.	-	-

Date	Item declared	Classification	Action taken
28/04/16	GC1: Travel expenses paid by Servier to attend a heart failure conference in November 2015.	Regular expenses only	Declare and participate
29/04/16	GC2: No new declarations.	-	-
03/06/16	GC3: No new declarations.	-	-
06/07/16	GC4: No new declarations.	-	-
01/09/16	GC5: No new declarations.	-	-
02/09/16	GC6: No new declarations.	-	-
26/10/16	GC7: No new declarations.	-	-
05/12/16	GC8: No new declarations.	-	-
26/01/17	GC9: Apologies sent.	-	-
08/03/17	GC10: No new declarations.	-	-
20/04/17	GC11: No new declarations.	-	-
31/05/17	GC12: No new declarations.	-	-
06/07/17	GC13: No new declarations.	-	-
05/09/17	GC14: No new declarations.	-	-
06/09/17	GC15: No new declarations.	-	-
19/10/17	GC16: Apologies sent	-	-
29/11/17	GC17: No new declarations	-	-
30/11/17	GC18: Apologies sent	-	-

Clare Taylor

Date	Item declared	Classification	Action taken
Initial declaration	Starts an NIHR-funded Academic Clinical Lecturer post at the University of Oxford on 31st March 2016.	Personal, financial, non-specific	Declare and participate
	Has been involved in an NIHR-funded diagnostic accuracy study (the 'REFER' study) examining the effectiveness of a clinical decision rule in identifying patients with heart failure. As well as a heart failure screening study (ECHOES-X)	Non-personal, financial, specific	Declare and withdraw from discussion of the Health Economic

Date	Item declared	Classification	Action taken
	that followed up patients screened for heart failure in the late 1990s to see who had developed the disease over time.		model.
	Is a module lead for the Heart Failure Masters module – part of the Masters in 'Primary and Community Care' at the University of Birmingham. Does not get paid for lecturing (the teaching forms part of university contract of employment).	Personal, non-financial, non-specific	Declare and participate
28/04/16	GC1: No new declarations.	-	-
29/04/16	GC2: No new declarations.	-	-
03/06/16	GC3: Went to the University of Sydney for a research visit in October 2015 which was funded by NIHR Doctoral Research Fellowship and £1,000 from a prize (Yvonne Carter Award for Outstanding New Researcher). I was attached to the Bettering the Evaluation of Care and Health (BEACH) team - a continuous, national, cross-sectional survey of Australian general practice activity. We used data from the Supplementary Analysis of Nominated Data sub-studies of the BEACH dataset to write a paper on the management of heart failure in general practice in Australia which is currently under consideration by the Australian Family Physician journal. No payment from any of the companies was received directly.	Personal, non-financial, specific	Declare and participate
06/07/16	GC4: No new declarations.	-	-
01/09/16	GC5: No new declarations.	-	-
02/09/16	GC6: No new declarations.	-	-
26/10/16	GC7: No new declarations.	-	-
05/12/16	GC8: No new declarations.	-	-
26/01/17	GC9: No new declarations.	-	-
08/03/17	GC10: No new declarations.	-	-
20/04/17	GC11: No new declarations.	-	-
31/05/17	GC12: Apologies sent.	-	-
06/07/17	GC13: No new declarations.	-	-
05/09/17	GC14: No new declarations.	-	-
06/09/17	GC15: No new declarations.	-	-

Date	Item declared	Classification	Action taken
19/10/17	GC16: No new declarations	-	-
29/11/17	GC17: No new declarations	-	-
30/11/17	GC18: No new declarations	-	-

Simon Corbett (co-optee)

Date	Item declared	Classification	Action taken
Initial declaration	Director of Clinical Effectiveness, University Hospital Southampton NHS Foundation Trust (2014 onwards) – this role forms part of my supporting professional activities (SPA) as a consultant cardiologist at UHSFT. The role involves implementing NICE guidance in the trust.	Personal, financial, non-specific	Declare and participate
	Member of Guidelines and Practice Committee, British Cardiovascular Society (BCS) (June 2016 onwards) – the committee reviews relevant cardiology practice guidelines (including those from NICE) and advises the BCS membership on their implementation and applicability. Non-pecuniary. Travel expenses paid by BCS as required.	Personal, non-financial, non-specific	Declare and participate
	BCS/Royal College of Physicians (RCP) Regional Service Advisor (since 2010) – a liaison role between cardiologists and the BCS and RCP in the South Central region. Non-pecuniary. Travel expenses paid by BCS/RCP as required.	Personal, non-financial, non-specific	Declare and participate
	Independent Cardiologist member of Trial Steering Committee for the ongoing AVATAR trial sponsored by Imperial College London and funded by the British Heart Foundation and Medtronic (2015 onwards). This is a randomised controlled trial of different ablation techniques in atrial fibrillation. Non-pecuniary. Travel expenses paid by Imperial College as required.	Personal, non-financial, non-specific	Declare and participate
	Member of NICE Standing Committee B for Guidelines Updates (2014 onwards).	Personal, non-financial, non-specific	Declare and participate
	Condition-specific member of NICE Standing Committee C for Guidelines Updates (2016 onwards).	Personal, non-financial, non-specific	Declare and participate

Date	Item declared	Classification	Action taken
02/09/16	GC6: Local co-investigator at University Hospital Southampton for the NIHR HTA CET funded REVIVED randomised clinical trial. This is an ongoing randomised comparison of coronary stenting vs medical therapy in patients with ischaemic cardiomyopathy. My role is screening and recruiting potentially suitable patients under my care for the trial.	Non-personal, financial, specific	Declare and participate

Hayes Dalal (co-optee)

Date	Item declared	Classification	Action taken
Initial declaration	None declared.	-	-
26/01/17	GC9: No new declarations.	-	-

Darren Green (co-optee)

Date	Item declared	Classification	Action taken
Initial declaration	Local investigator in 2 BHF funded heart failure trials: IRON-MAN, and Peritoneal Dialysis for Heart Failure	Non-personal, financial, specific Non-personal, financial, non-specific	Declare and participate
	Member of Kidney Research UK Cardiorenal Clinical Study Group	Personal, non-financial, non-specific	Declare and participate
01/09/16	GC5: No new declarations.	-	-

Suzanne Kite (co-optee)

Date	Item declared	Classification	Action taken
Initial declaration	None declared.	-	-
08/03/17	GC10: No new declarations.	-	-

Date	Item declared	Classification	Action taken
19/10/17	GC16: NICE End of life care GC member	Personal, non-financial, specific	Declare and participate

Kathryn Measures (co-optee)

Date	Item declared	Classification	Action taken
Initial declaration	None declared.	-	-
26/01/17	GC9: No new declarations.	-	-

Rod Taylor (co-optee)

Date	Item declared	Classification	Action taken
Initial declaration	None declared.	-	-
26/01/17	GC9: No new declarations.	-	-

NCGC team

Date	Item declared	Classification	Action taken
Initial declaration	In receipt of NICE commissions	-	-

Appendix N: Literature search strategies

N.1 Contents

Search strategies used for the chronic heart failure guideline are outlined below and were run in accordance with the methodology in the NICE guidelines manual 2014, available from https://www.nice.org.uk/article/pmg20/. All searches were run up to 6 December 2017 unless otherwise stated. Any studies added to the databases after this date (even those published prior to this date) were not included unless specifically stated in the text. Where possible searches were limited to retrieve material published in English.

Searches for the **clinical reviews** were run in Medline (OVID), Embase (OVID) and the Cochrane Library (Wiley). Additional searches were run in CINAHL, Current Nursing and Allied Health Literature (EBSCO), PsycINFO (Ovid & ProQuest] and AMED, Allied and Complementary Medicine (Ovid), see Table 2.

Searches for **intervention and diagnostic studies** were usually constructed using a PICO format where population (P) terms were combined with Intervention (I) and sometimes Comparison (C) terms. An intervention can be a drug, a procedure or a diagnostic test. Outcomes (O) are rarely used in search strategies for interventions. Search filters were also added to the search where appropriate.

Table 2: Databases searched

Question	Question number	Databases
Beta Blockers	N.4.1	Medline, Embase, The Cochrane Library
BNP Diagnosis	N.4.2	Medline, Embase, The Cochrane Library
Cardiac MRI	N.4.3	Medline, Embase, The Cochrane Library
Communications, diagnosis and prognosis	N.4.4	Medline, Embase, CINAHL PsycINFO
Coronary revascularisation	N.4.5	Medline, Embase, The Cochrane Library
Diuretics	N.4.6	Medline, Embase, The Cochrane Library
Domiciliary Oxygen	N.4.7	Medline, Embase, The Cochrane Library
Implantable cardiac defibrillators	N.4.8	Medline, Embase, CINAHL PsycINFO
Iron	N.4.9	Medline, Embase, The Cochrane Library
Multi-disciplinary teams	N.4.10	Medline, Embase, The Cochrane Library
Monitoring	N.4.11	Medline, Embase, The Cochrane Library
Mineralcorticoid receptor antagonists	N.4.12	Medline, Embase, The Cochrane Library
Pharma in CKD	N.4.13	Medline, Embase, The Cochrane Library
Referral risk tools	N.4.14	Medline, Embase, The Cochrane Library
Salf and fluid	N.4.15	Medline, Embase, The Cochrane Library

Question	Question number	Databases
Telemonitoring	N.4.16	Medline, Embase, The Cochrane Library, AMED
Transition	N.4.17	Medline, Embase, CINAHL PsycINFO

Searches for the health economic reviews were run in Medline, Embase, the NHS Economic Evaluations Database (NHS EED) and the Health Technology Assessment (HTA). NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). The NHS EED database has not been updated since 2015.

For Medline and Embase an economic filter (instead of a study type filter) was added to the same clinical search strategy. Searches in CRD were constructed using population terms only.

N.2 Population search strategies

N.2.1 Standard Chronic heart failure population

The standard population was not used in questions N.4.11 and N.4.16.

The standard population was use in combination with added population terms in questions N.4.1, N.4.2, N.4.8 and N.4.13.

Medline search terms

1.	exp heart failure/
2.	cardiomyopathy, dilated/
3.	shock, cardiogenic/
4.	exp ventricular dysfunction/
5.	cardiac output, low/
6.	((heart or cardiac or myocardial) adj2 (failure or decompensation)).ti.
7.	((congestive or acute or decompensat* or chronic) adj2 "heart failure").ti,ab.
8.	((dilated or congestive) adj2 cardiomyopath*).ti.
9.	"cardiogenic shock".ti.
10.	((ventricular or ventricle*) adj2 (failure or insufficien* or dysfunction*)).ti.
11.	(("left ventricular" or "left ventricle") adj2 (failure or insufficien* or dysfunction*)).ti,ab.
12.	lvsd.ti,ab.
13.	or/1-12

Embase search terms

1.	*heart failure/ or acute heart failure/ or *cardiogenic shock/ or *diastolic dysfunction/ or *forward heart failure/ or *high output heart failure/ or *systolic dysfunction/
2.	*congestive cardiomyopathy/ or exp *congestive heart failure/
3.	exp *heart ventricle failure/
4.	((heart or cardiac or myocardial) adj2 (failure or decompensation)).ti.
5.	((congestive or acute or decompensat* or chronic) adj2 "heart failure").ti,ab.
6.	((dilated or congestive) adj2 cardiomyopath*).ti.
7.	"cardiogenic shock".ti.
8.	((ventricular or ventricle*) adj2 (failure or insufficien* or dysfunction*)).ti.
9.	(("left ventricular" or "left ventricle") adj2 (failure or insufficien* or dysfunction*)).ti,ab.

10.	lvsd.ti,ab.
11.	or/1-10

Cochrane search terms

#1.	MeSH descriptor: [heart failure] explode all trees
#2.	MeSH descriptor: [cardiomyopathy, dilated] this term only
#3.	MeSH descriptor: [shock, cardiogenic] this term only
#4.	MeSH descriptor: [ventricular dysfunction] explode all trees
#5.	MeSH descriptor: [cardiac output, low] this term only
#6.	(heart or cardiac or myocardial) next (failure or decompensation):ti
#7.	((congestive or chronic) next ("heart failure")):ti,ab
#8.	((dilated or congestive) next cardiomyopath*):ti
#9.	("cardiogenic shock"):ti
#10.	((ventricular or ventricle) next (failure or insufficienc* or dysfunction*)):ti
#11.	lvsd:ti,ab
#12.	(("left ventricular" or "left ventricle") next (failure or insufficienc* or dysfunction*)):ti,ab
#13.	(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12)

CINAHL search terms

S1	(MH "heart failure+")
S2	(MH "cardiac output, decreased")
S3	(MH "shock, cardiogenic")
S4	(MH "ventricular dysfunction+")
S5	ti heart n2 failure or ti heart n2 decompensation or ti cardiac n2 failure or ti cardiac n2 decompensation or ti myocardial n2 decompensation or ti myocardial n2 failure or tx congestive n2 "heart failure" or tx chronic n2 "heart failure" or ti dilated n2 cardiomyopath* or ti congestive n2 cardiomyopath* or ti cardiogenic n2 shock or tx lvsd
S6	tx ventricular n2 failure or tx ventricular n2 dysfunction or tx ventricular n2 insufficiency or tx ventricle n2 failure or tx ventricle n2 dysfunction or tx ventricle n2 insufficiency
S7	S1 or S2 or S3 or S4 or S5 or S6

CRD search terms

1	MeSH descriptor heart failure explode all trees
2	MeSH descriptor cardiomyopathy, dilated
3	MeSH descriptor shock, cardiogenic
4	MeSH descriptor ventricular dysfunction explode all trees
5	MeSH descriptor cardiac output, low
6	(((heart or cardiac or myocardial) adj2 (failure or decompensation))):ti
7	(((congestive or acute or decompensat* or chronic) adj2 "heart failure"))
8	(((dilated or congestive) adj2 cardiomyopath*)):ti
9	("cardiogenic shock"):ti
10	(((ventricular or ventricle*) adj2 (failure or insufficien* or dysfunction*))):ti
11	((("left ventricular" or "left ventricle") adj2 (failure or insufficien* or dysfunction*)))
12	(lvsd)
13	(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12)

N.3 Study filter search terms

N.3.1 Excluded study designs and publication types

The following study designs and publication types were removed from retrieved results using the NOT operator.

Medline search terms

1.	letter/
2.	editorial/
3.	news/
4.	exp historical article/
5.	anecdotes as topic/
6.	comment/
7.	case report/
8.	(letter or comment*).ti.
9.	or/1-8
10.	randomized controlled trial/ or random*.ti,ab.
11.	9 not 10
12.	animals/ not humans/
13.	exp animals, laboratory/
14.	exp animal experimentation/
15.	exp models, animal/
16.	exp rodentia/
17.	(rat or rats or mouse or mice).ti.
18.	or/11-17

Embase search terms

1.	letter.pt. or letter/
2.	note.pt.
3.	editorial.pt.
4.	case report/ or case study/
5.	(letter or comment*).ti.
6.	or/1-5
7.	randomized controlled trial/ or random*.ti,ab.
8.	6 not 7
9.	animal/ not human/
10.	nonhuman/
11.	exp animal experiment/
12.	exp experimental animal/
13.	animal model/
14.	exp rodent/
15.	(rat or rats or mouse or mice).ti.
16.	or/8-15

AMED search terms

1.	case report/

2.	(letter or comment*).ti.
3.	or/1-2
4.	randomized controlled trials/ or random*.ti,ab.
5.	3 not 4
6.	animals/ not humans/
7.	(rat or rats or mouse or mice).ti.
8.	or/5-7

CINAHL search terms

S1.	pt anecdote or pt audiovisual or pt bibliography or pt biography or pt book or pt book review or pt brief item or pt cartoon or pt commentary or pt computer program or pt editorial or pt games or pt glossary or pt historical material or pt interview or pt letter or pt listservs or pt masters thesis or pt obituary or pt pamphlet or pt pamphlet chapter or pt pictorial or pt poetry or pt proceedings or pt “questions and answers” or pt response or pt software or pt teaching materials or pt website

N.3.2 Randomised controlled trials (RCT)

Medline search terms

(Based on the sensitivity and precision maximising version reported in the Cochrane Handbook (http://handbook.cochrane.org/)).

1.	randomized controlled trial.pt.
2.	controlled clinical trial.pt.
3.	randomi#ed.ti,ab.
4.	placebo.ab.
5.	randomly.ab.ti
6.	clinical trials as topic.sh.
7.	trial.ti.
8.	or/1-7

Embase search terms

1.	random*.ti,ab.
2.	factorial*.ti,ab.
3.	(crossover* or cross over*).ti,ab.
4.	((doubl* or singl*) adj blind*).ti,ab.
5.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
6.	crossover procedure/
7.	double blind procedure/
8.	single blind procedure/
9.	randomized controlled trial/
10.	or/1-9

N.3.3 Systematic reviews (SR)

Medline search terms

1.	meta-analysis/
2.	meta-analysis as topic/

3.	(meta analy* or metanaly* or metaanaly*).ti,ab.
4.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
5.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7.	(search* adj4 literature).ab.
8.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9.	cochrane.jw.
10.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
11.	or/1-10

Embase search terms

1.	systematic review/
2.	meta-analysis/
3.	(meta analy* or metanaly* or metaanaly*).ti,ab.
4.	((systematic or evidence) adj3 (review* or overview*)).ti,ab.
5.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7.	(search* adj4 literature).ab.
8.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9.	cochrane.jw.
10.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
11.	or/1-10

N.3.4 Health economic studies (HE)

Medline search terms

1.	economics/
2.	value of life/
3.	exp "costs and cost analysis"/
4.	exp economics, hospital/
5.	exp economics, medical/
6.	economics, nursing/
7.	economics, pharmaceutical/
8.	exp "fees and charges"/
9.	exp budgets/
10.	budget*.ti,ab.
11.	cost*.ti.
12.	(economic* or pharmaco?economic*).ti.
13.	(price* or pricing*).ti,ab.
14.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
15.	(financ* or fee or fees).ti,ab.
16.	(value adj2 (money or monetary)).ti,ab.
17.	or/1-16

Embase search terms

1.	health economics/
2.	exp economic evaluation/
3.	exp health care cost/
4.	exp fee/
5.	budget/
6.	funding/
7.	budget*.ti,ab.
8.	cost*.ti.
9.	(economic* or pharmaco?economic*).ti.
10.	(price* or pricing*).ti,ab.
11.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
12.	(financ* or fee or fees).ti,ab.
13.	(value adj2 (money or monetary)).ti,ab.
14.	or/1-13

N.3.5 Quality of life studies (QoL)

Medline search terms

1.	quality-adjusted life years/
2.	sickness impact profile/
3.	(quality adj2 (wellbeing or well-being)).ti,ab.
4.	sickness impact profile.ti,ab.
5.	disability adjusted life.ti,ab.
6.	(qal* or qtime* or qwb* or daly*).ti,ab.
7.	(euroqol* or eq5d* or eq 5d*).ti,ab.
8.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
9.	(health utility* or utility score* or disutilit*).ti,ab.
10.	(hui or hui1 or hui2 or hui3).ti,ab.
11.	health* year* equivalent*.ti,ab.
12.	(hye or hyes).ti,ab.
13.	rosser.ti,ab.
14.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
15.	(sf36 or sf 36 or short form 36 or shortform 36 or shortform36).ti,ab.
16.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
17.	(sf12 or sf 12 or short form 12 or shortform 12 or shortform12).ti,ab.
18.	(sf8 or sf 8 or short form 8 or shortform 8 or shortform8).ti,ab.
19.	(sf6 or sf 6 or short form 6 or shortform 6 or shortform6).ti,ab.
20.	or/1-19

Embase search terms

1.	quality adjusted life year/
2.	"quality of life index"/
3.	short form 12/ or short form 20/ or short form 36/ or short form 8/
4.	sickness impact profile/
5.	(quality adj2 (wellbeing or well-being)).ti,ab.
6.	sickness impact profile.ti,ab.

7.	disability adjusted life.ti,ab.
8.	(qal* or qtime* or qwb* or daly*).ti,ab.
9.	(euroqol* or eq5d* or eq 5d*).ti,ab.
10.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
11.	(health utility* or utility score* or disutilit*).ti,ab.
12.	(hui or hui1 or hui2 or hui3).ti,ab.
13.	health* year* equivalent*.ti,ab.
14.	(hye or hyes).ti,ab.
15.	rosser.ti,ab.
16.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
17.	(sf36 or sf 36 or short form 36 or shortform 36 or shortform36).ti,ab.
18.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
19.	(sf12 or sf 12 or short form 12 or shortform 12 or shortform12).ti,ab.
20.	(sf8 or sf 8 or short form 8 or shortform 8 or shortform8).ti,ab.
21.	(sf6 or sf 6 or short form 6 or shortform 6 or shortform6).ti,ab.
22.	or/1-21

N.3.6 Diagnostic test accuracy studies (DIAG)

Medline search terms

1.	exp "sensitivity and specificity"/
2.	(sensitivity or specificity).ti,ab.
3.	((pre test or pretest or post test) adj probability).ti,ab.
4.	(predictive value* or ppv or npv).ti,ab.
5.	likelihood ratio*.ti,ab.
6.	likelihood function/
7.	(roc curve* or auc).ti,ab.
8.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
9.	gold standard.ab.
10.	or/1-9

Embase search terms

1.	exp "sensitivity and specificity"/
2.	(sensitivity or specificity).ti,ab.
3.	((pre test or pretest or post test) adj probability).ti,ab.
4.	(predictive value* or ppv or npv).ti,ab.
5.	likelihood ratio*.ti,ab.
6.	(roc curve* or auc).ti,ab.
7.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness)).ti,ab.
8.	diagnostic accuracy/
9.	diagnostic test accuracy study/
10.	gold standard.ab.
11.	or/1-10

N.3.7 Observational studies (OBS)

Medline search terms

1.	epidemiologic studies/
2.	exp case control studies/
3.	exp cohort studies/
4.	cross-sectional studies/
5.	case control.ti,ab.
6.	(cohort adj (study or studies or analys*)).ti,ab.
7.	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
8.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.
9.	or/1-8

Embase search terms

1.	clinical study/
2.	exp case control study/
3.	family study/
4.	longitudinal study/
5.	retrospective study/
6.	prospective study/
7.	cross-sectional study/
8.	cohort analysis/
9.	follow-up/
10.	cohort*.ti,ab.
11.	9 and 10
12.	case control.ti,ab.
13.	(cohort adj (study or studies or analys*)).ti,ab.
14.	((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)).ti,ab.
15.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)).ti,ab.
16.	or/1-8,11-15

N.3.8 Qualitative reviews (QUAL)

Medline search terms

1.	qualitative research/ or narration/ or exp interviews as topic/ or exp questionnaires/ or health care surveys/
2.	(qualitative or interview* or focus group* or theme* or questionnaire* or survey*).ti,ab.
3.	(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* adj3 analys*) or theoretical sampl* or purposive sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*).ti,ab.
4.	or/1-3

Embase search terms

1.	health survey/ or exp questionnaire/ or exp interview/ or qualitative research/ or narrative/
2.	(qualitative or interview* or focus group* or theme* or questionnaire* or survey*).ti,ab.
3.	(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* adj3 analys*) or theoretical sampl* or purposive sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*).ti,ab.
4.	or/1-3

CINAHL search terms

S1.	(MH "qualitative studies+")
S2.	(MH "qualitative validity+")
S3.	(MH "interviews+") or (MH "focus groups") or (MH "surveys") or (MH "questionnaires+")
S4.	TI ((qualitative or interview* or focus group* or theme* or questionnaire* or survey*)) or AB ((qualitative or interview* or focus group* or theme* or questionnaire* or survey*))
S5.	TI ((metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* n3 analys*) or theoretical sampl* or purposive sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*)) or AB ((metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* n3 analys*) or theoretical sampl* or purposive sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*))
S6.	S1 or S2 or S3 or S4 or S5

N.4 Searches for specific questions

N.4.1 Beta Blockers

- What is the clinical and cost effectiveness of beta-blockers in the management of chronic heart failure in people with heart failure with reduced ejection fraction (HFREF) and atrial fibrillation?

Medline search terms

1.	Standard population [N.2.1]
2.	exp atrial fibrillation/
3.	(atrial adj3 fibrillat*).ti,ab.
4.	((auricular adj3 fibrillat*) or (supraventricul* adj3 arrhythmi*)).ti,ab.
5.	or/2-4
6.	Excluded study designs and publication types [N.3.1]
7.	1 not 6
8.	5 not 6
9.	adrenergic beta-antagonists/ or adrenergic beta-1 receptor antagonists/
10.	bisoprolol/
11.	metoprolol/
12.	nebivolol/
13.	(carvedilol or metoprolol or bisoprolol or nebivolol).mp.
14.	(beta* adj3 (blockade or blocker* or blocking or antagonist*)).ti,ab.
15.	((beta-adrenoceptor or b-adrenoceptor or beta-adrenergic) adj3 (blockade or blocker* or

	blocking or antagonist*)).ti,ab.
16.	or/25-31
17.	7 and 16
18.	8 and 16
19.	Study filters RCT [N.3.2] or SR [N.3.3]
20.	17 and 19 (Inception – 6 December 2017)
21.	18 and 19 (2013 – 6 December 2017)
22.	20 or 21
23.	Limit 22 to English language

Embase search terms

1.	Standard population [N.2.1]
2.	heart atrium fibrillation/
3.	(atrial adj3 fibrillat*).ti,ab.
4.	((auricular adj3 fibrillat*) or (supraventricul* adj3 arrhythmi*)).ti,ab.
5.	or/2-4
6.	Excluded study designs and publication types [N.3.1]
7.	1 not 6
8.	5 not 6
9.	*beta adrenergic receptor blocking agent/ or *beta 1 adrenergic receptor blocking agent/
10.	*bisoprolol/ or *bisoprolol fumarate/ or *bisoprolol fumarate plus hydrochlorothiazide/ or *carvedilol/ or *metoprolol/ or *metoprolol fumarate/ or *metoprolol succinate/ or *metoprolol tartrate/ or *nebivolol/
11.	(carvedilol or metoprolol or bisoprolol or nebivolol).mp.
12.	(beta* adj3 (blockade or blocker* or blocking or antagonist*)).ti,ab.
13.	((beta-adrenoceptor or b-adrenoceptor or beta-adrenergic) adj3 (blockade or blocker* or blocking or antagonist*)).ti,ab.
14.	or/9-13
15.	Study filters RCT [N.3.2] or SR [N.3.3]
16.	7 and 14
17.	8 and 14
18.	16 and 15 (Inception – 6 December 2017)
19.	17 and 15 (2013 – 6 December 2017)
20.	18 or 19
21.	Limit 20 to English language

Cochrane search terms

#1.	Standard population [N.2.1]
#2.	MeSH descriptor: [atrial fibrillation] this term only
#3.	(atrial near/3 fibrillat*):ti,ab
#4.	(auricular near/3 fibrillat*):ti,ab
#5.	(supraventricular near/3 *arrhythmia*):ti,ab
#6.	(or #2-#5)
#7.	#1 or #6
#8.	MeSH descriptor: [adrenergic beta-antagonists] this term only
#9.	MeSH descriptor: [adrenergic beta-1 receptor antagonists] this term only
#10.	MeSH descriptor: [bisoprolol] this term only

#11.	MeSH descriptor: [metoprolol] this term only
#12.	(carvedilol or metoprolol or bisoprolol or nebivolol):ti,ab
#13.	(beta* next/3 (blockade or blocker* or blocking or antagonist*)):ti,ab
#14. (	((beta-adrenoceptor or b-adrenoceptor or beta-adrenergic) next/3 (blockade or blocker* or blocking or antagonist*)):ti,ab
#15.	(or #8-#14)
#16.	#6 and #15 Year from 2013
#17.	#1 and #15 Year from Inception

N.4.2 BNP Diagnosis

N.4.2.1 Chronic heart failure population only

Searches for the following 2 questions were run as one search:

- In people with suspected heart failure, what thresholds of pro B type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP) are most accurate in identifying heart failure (as indicated by the reference standard)?
- In people with suspected heart failure, what is the clinical and cost effectiveness of N-terminus pro-B-type natriuretic peptide (NT-proBNP) compared to B-type natriuretic peptide (BNP), when each is followed by the appropriate patient pathway, in order to improve patient outcomes?

Medline search terms

1.	Standard population [N.2.1]
2.	Excluded study designs and publication types [N.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	natriuretic peptide, brain/
6.	(natriuretic adj2 peptide*).ti,ab.
7.	(bnp or nt-probnp or nt-pro bnp or nt-bnp).ti,ab.
8.	natriuretic peptides/
9.	or/5-8
10.	4 and 9
11.	Study filters RCT [N.3.2] or SR [N.3.3] or OBS [N.3.7] or DIAG [N.3.6]
12.	10 and 11
	Date limits: 2009 – 6 December 2017

Embase search terms

1.	Standard population [N.2.1]
2.	Excluded study designs and publication types [N.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	*natriuretic factor/
6.	*amino terminal pro brain natriuretic peptide/
7.	*brain natriuretic peptide/
8.	(bnp or nt-probnp or nt-pro bnp or nt-bnp).ti,ab.
9.	(natriuretic adj2 peptide*).ti,ab.
10.	or/5-9
11.	4 and 10

12.	Study filters RCT [N.3.2] or SR [N.3.3] or OBS [N.3.7] or DIAG [N.3.6]
13.	11 and 12
	Date limits: 2009 – 6 December 2017

Cochrane search terms

#1.	Standard population [N.2.1]
#2.	MeSH descriptor: [natriuretic peptide, brain] this term only
#3.	(natriuretic near/2 peptide*):ti,ab
#4.	(bnp or nt-probnp or nt-pro bnp or nt-bnp):ti,ab
#5.	MeSH descriptor: [natriuretic peptides] this term only
#6.	#2 or #3 or #4 or #5
#7.	#1 and #6
	Date limits: 2009 – 6 December 2017

N.4.2.2 Chronic heart failure with either atrial fibrillation or chronic kidney disease

Searches for the following 4 questions were run as one search:

- In people with suspected heart failure who also have atrial fibrillation, what thresholds of N-terminus pro-B-type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP) are most accurate in identifying heart failure (as indicated by the reference standard)?
- In people with suspected heart failure who also have atrial fibrillation, what is the clinical and cost effectiveness of N-terminus pro-B-type natriuretic peptide (NT-proBNP) compared to B-type natriuretic peptide (BNP), when each is followed by the appropriate patient pathway, in order to improve patient outcomes?
- In people with suspected heart failure who also have chronic kidney disease, what thresholds of N-terminus pro-B-type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP) are most accurate in identifying heart failure (as indicated by the reference standard)?
- In people with suspected heart failure who also have chronic kidney disease, what is the clinical and cost effectiveness of N-terminus pro-B-type natriuretic peptide (NT-proBNP) compared to B-type natriuretic peptide (BNP), when each is followed by the appropriate patient pathway, in order to improve patient outcomes?

Medline search terms

1.	Standard population [N.2.1]
2.	atrial fibrillation/
3.	(atrial adj3 fibrillat*).ti,ab.
4.	((auricular adj3 fibrillat*) or (supraventricul* adj3 arrhythmi*)).ti,ab.
5.	or/2-4
6.	renal insufficiency, chronic/ or exp kidney failure, chronic/
7.	kidney diseases/ and chronic.ti,ab.
8.	((chronic or progressive) adj3 (renal or kidney)).ti,ab.
9.	ckd.ti,ab.
10.	((renal or kidney) adj3 (insufficienc* or disease*)).ti,ab.
11.	((renal or kidney) adj3 (function* or failure* or dysfunction*)).ti,ab.
12.	glomerular filtration rate/
13.	(glomerul* filtration rate* or gfr).ti,ab.
14.	diabetic neuropathies/
15.	exp glomerulonephritis/

16.	exp proteinuria/
17.	(glomerulosclerosis or glomerulonephritis or nephropath* or proteinuria* or albuminuria or microalbuminuria).ti,ab.
18.	(glomerular adj (sclerosis or nephritis)).ti,ab.
19.	acidosis, renal tubular/
20.	((renal or kidney* or distal or proximal or tubul*) adj3 acidos*).ti,ab.
21.	exp hypertension, renal/
22.	((renal or kidney* or renovascular) adj3 hypertensi*).ti,ab.
23.	exp hyperparathyroidism, secondary/
24.	((renal or kidney* or secondary) adj3 hyperparathyroidism).ti,ab.
25.	hyperuricemia/
26.	hyperuric?emi*.ti,ab.
27.	((renal or kidney*) adj3 osteo*).ti,ab.
28.	or/6-27
29.	1 or 5 or 28
30.	Excluded study designs and publication types [N.3.1]
31.	29 not 30
32.	Limit 31 to English language
33.	natriuretic peptide, brain/
34.	(natriuretic adj2 peptide*).ti,ab.
35.	(bnp or nt-probnp or nt-pro bnp or nt-bnp).ti,ab.
36.	natriuretic peptides/
37.	or/33-36
38.	32 and 37
	Date limits: Inception - 2008

Embase search terms

1.	Standard population [N.2.1]
2.	exp atrial fibrillation/
3.	(atrial adj3 fibrillat*).ti,ab.
4.	((auricular adj3 fibrillat*) or (supraventricul* adj3 arrhythmi*)).ti,ab.
5.	or/2-4
6.	chronic kidney failure/
7.	chronic kidney disease/
8.	(kidney failure/ or kidney disease/) and chronic.ti,ab.
9.	((chronic or progressive) adj3 (renal or kidney*)).ti,ab.
10.	ckd.ti,ab.
11.	((renal or kidney*) adj3 (insufficienc* or disease*)).ti,ab.
12.	((renal or kidney*) adj3 (function* or failure* or dysfunction*)).ti,ab.
13.	glomerulus filtration rate/
14.	(glomerul* filtration rate* or gfr).ti,ab.
15.	diabetic neuropathy/
16.	exp glomerulonephritis/
17.	exp proteinuria/
18.	(glomerulosclerosis or glomerulonephritis or nephropath* or proteinuria* or albuminuria or microalbuminuria).ti,ab.

19.	(glomerular adj (sclerosis or nephritis)).ti,ab.
20.	kidney tubule acidosis/
21.	((renal or kidney* or distal or proximal or tubul*) adj3 acidos*).ti,ab.
22.	exp renovascular hypertension/
23.	((renal or kidney* or renovascular) adj3 hypertensi*).ti,ab.
24.	hyperuricemia/
25.	hyperuric?emi*.ti,ab.
26.	secondary hyperparathyroidism/
27.	((renal or kidney* or secondary) adj3 hyperparathyroidism).ti,ab.
28.	renal osteodystrophy/
29.	((renal or kidney*) adj3 osteo*).ti,ab.
30.	or/6-29
31.	1 or 5 or 30
32.	Excluded study designs and publication types [N.3.1]
33.	31 not 32
34.	Limit 33 to English language
35.	*natriuretic factor/
36.	*amino terminal pro brain natriuretic peptide/
37.	*brain natriuretic peptide/
38.	(bnp or nt-probnp or nt-pro bnp or nt-bnp).ti,ab.
39.	(natriuretic adj2 peptide*).ti,ab.
40.	or/35-39
41.	34 and 40
	Date limits: Inception - 2008

Cochrane search terms

#1.	Standard population [N.2.1]
#2.	MeSH descriptor: [atrial fibrillation] this term only
#3.	(atrial near/3 fibrillat*):ti,ab
#4.	(auricular near/3 fibrillat*):ti,ab
#5.	(supraventricular near/3 *arrhythmia*):ti,ab
#6.	#2 or #3 or #4 or #5
#7.	MeSH descriptor: [renal insufficiency, chronic] this term only
#8.	MeSH descriptor: [kidney failure, chronic] explode all trees
#9.	MeSH descriptor: [kidney diseases] this term only
#10.	chronic:ti,ab
#11.	#9 and #10
#12.	((chronic or progressive) near/3 (renal or kidney)):ti,ab
#13.	ckd:ti,ab
#14.	((renal or kidney*) near/3 (insufficienc* or disease*)):ti,ab
#15.	((renal or kidney*) near/3 (function* or failure* or dysfunction*)):ti,ab
#16.	(glomerul* filtration rate* or gfr):ti,ab
#17.	MeSH descriptor: [glomerular filtration rate] this term only
#18.	MeSH descriptor: [diabetic neuropathies] this term only
#19.	MeSH descriptor: [glomerulonephritis] explode all trees

#20.	MeSH descriptor: [proteinuria] explode all trees
#21.	(glomerulosclerosis or glomerulonephritis or nephropath* or proteinuria* or albuminuria or microalbuminuria):ti,ab
#22.	(glomerular next (sclerosis or nephritis)):ti,ab
#23.	[mh ^"acidosis, renal tubular"]
#24.	((renal or kidney* or distal or proximal or tubul*) near/3 acidos*):ti,ab
#25.	[mh "hypertension, renal"]
#26.	((renal or kidney* or renovascular) near/3 hypertensi*):ti,ab
#27.	[mh "hyperparathyroidism, secondary"]
#28.	((renal or kidney* or renovascular) near/3 hypertensi*):ti,ab
#29.	[mh "hyperparathyroidism, secondary"]
#30.	((renal or kidney* or secondary) near/3 hyperparathyroidism):ti,ab
#31.	[mh ^hyperuricemia]
#32.	hyperuric?emi*:ti,ab
#33.	((renal or kidney*) near/3 osteo*):ti,ab
#34.	(or #7-#9, #11, #12-#33)
#35.	#1 or #6 or #34
#36.	MeSH descriptor: [natriuretic peptide, brain] this term only
#37.	(natriuretic near/2 peptide*):ti,ab
#38.	(bnp or nt-probnp or nt-pro bnp or nt-bnp):ti,ab
#39.	MeSH descriptor: [natriuretic peptides] this term only
#40.	(or #36-#39)
#41.	#35 and #40
	Date limits: 1900 - 2008

N.4.3 Cardiac MRI

- In people with heart failure what is the clinical and cost effectiveness of cardiac MRI followed by the appropriate patient pathway?

Medline search terms

1.	Standard population [N.2.1]
2.	Excluded study designs and publication types [N.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	magnetic resonance imaging/
6.	(mri* or nmr* or magnetic resonance).ti,ab.
7.	(cmr or ((cardiac or cardiovascular) adj mr)).ti,ab.
8.	or/5-7
9.	4 and 8
10.	Study filters RCT [N.3.2] or SR [N.3.3]
11.	9 and 10
	Date limits: Inception – 6 December 2017

Embase search terms

1.	Standard population [N.2.1]
2.	Excluded study designs and publication types [N.3.1]

3.	1 not 2
4.	Limit 3 to English language
5.	nuclear magnetic resonance imaging/ or cardiovascular magnetic resonance/
6.	(mri* or nmr* or magnetic resonance).ti,ab.
7.	(cmr or ((cardiac or cardiovascular) adj mr)).ti,ab.
8.	or/5-7
9.	4 and 8
10.	Study filters RCT [N.3.2] or SR [N.3.3]
11.	9 and 10
	Date limits: Inception – 6 December 2017

Cochrane search terms

#1.	Standard population [N.2.1]
#2.	MeSH descriptor: [magnetic resonance imaging] this term only
#3.	(mri* or nmr* or magnetic resonance):ti,ab
#4.	(cmr or ((cardiac or cardiovascular) next mr)):ti,ab
#5.	#2 or #3 or #4
#6.	#1 and #5
	Date limits: Inception – 6 December 2017

N.4.4 Communication, Diagnosis and Prognosis

- What are the information and support needs to be considered when communication a diagnosis and consequent prognosis, to people with heart failure, their families and carers?

Medline search terms

1.	Standard population [N.2.1]
2.	Excluded study designs and publication types [N.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	communication/
6.	patient education as topic/
7.	consumer health information/
8.	patient satisfaction/
9.	"attitude of health personnel"/
10.	physician-patient relations/
11.	nurse-patient relations/
12.	professional-family relations/ or professional-patient relations/
13.	patient participation/
14.	decision making/
15.	popular-works-publication-type/ or exp information-services/ or publications/ or books/ or pamphlets/ or counseling/ or directive-counseling/
16.	or/5-15
17.	caregivers/ or exp family/ or exp parents/ or exp legal-guardians/
18.	patients/ or inpatients/ or outpatients/
19.	((patient* or carer* or famil* or parent* or father* or mother* or caregiver* or next of kin) adj6 (attitude* or perspective* or view* or interpret* or understand* or misunderstand* or opinion* or decision* or decid* or belief* or believe* or feeling* or priorit* or perception* or

	choic* or preferen*)).ti,ab.
20.	((patient* or carer* or famil* or parent* or father* or mother* or caregiver* or next of kin) adj6 (inform* or educat* or learn* or advi?e or knowledge or involve* or support* or counsel* or communicat* or discuss* or convers*)).ti,ab.
21.	((information* or support* or advi?e* or counsel* or knowledge or educat* or psycholog*) adj6 (provision* or provide* or deliver* or facilitat* or establish* or arrang* or offer* or need* or access*)).ti,ab.
22.	((patient* or carer* or famil* or parent* or father* or mother* or caregiver* or next of kin) adj6 (resource* or pamphlet* or leaflet* or booklet* or manual* or brochure* or publication* or handout* or website* or web site* or web page* or webpage* or video* or dvd* or internet or computer* or program* or interactive* or email* or e-mail* or wireless or bluetooth or telephone or phone or sms or text*)).ti,ab.
23.	or/17-22
24.	diagnosis/ or prognosis/
25.	advance care planning/ or palliative care/ or terminal care/
26.	(diagnos* or prognos*).ti,ab.
27.	(advance* adj2 (plan* or decision* or directive*)).ti,ab.
28.	((advance* or patient*) adj3 (care or caring) adj3 (continu* or plan*)).ti,ab.
29.	(end of life or terminal* or palliativ*).ti,ab.
30.	or/24-30
31.	17 and 30
32.	16 or 31
33.	Study filter QUAL (N.3.8)
34.	4 and 32 and 33
35.	exp great britain/
36.	(national health service* or nhs*).ti,ab,in.
37.	(english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab.
38.	(gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*).ti,ab,jw,in.
39.	(bath or "bath's" or ((birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachusetts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not

	("new york*" or ny or ontario* or ont or toronto*))))).ti,ab,in.
40.	(bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's" or st asaph or "st asaph's" or st davids or swansea or "swansea's").ti,ab,in.
41.	(aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's").ti,ab,in.
42.	(armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or "londonderry's" or derry or "derry's" or newry or "newry's").ti,ab,in.
43.	or/35-42
44.	(exp africa/ or exp americas/ or exp antarctic regions/ or exp arctic regions/ or exp asia/ or exp australia/ or exp oceania/) not (exp great britain/ or europe/)
45.	43 not 44
46.	34 and 45
47.	34 not 46
	Date limits: 2002 – 13 April 2017

1 **Embase search terms**

1.	Standard population [N.2.1]
2.	Excluded study designs and publication types [N.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	interpersonal communication/
6.	patient education/
7.	consumer health information/
8.	patient satisfaction/
9.	health personnel attitude/
10.	doctor patient relation/
11.	nurse patient relationship/
12.	human relation/
13.	patient participation/
14.	decision making/
15.	patient preference/
16.	patient attitude/
17.	patient satisfaction/
18.	patient information/
19.	information service/ or information center/ or publication/ or book/ or counseling/ or directive counseling/
20.	or/5-19
21.	patient/ or hospital patient/ or outpatient/
22.	caregiver/ or exp family/ or exp parent/
23.	((patient* or carer* or famil* or parent* or father* or mother* or caregiver* or next of kin) adj6 (attitude* or perspective* or view* or interpret* or understand* or misunderstand* or opinion* or decision* or decid* or belief* or believe* or feeling* or priorit* or perception* or choic* or preferen*)).ti,ab.
24.	((patient* or carer* or famil* or parent* or father* or mother* or caregiver* or next of kin) adj6 (inform* or educat* or learn* or advi?e or knowledge or involve* or support* or counsel* or communicat* or discuss* or convers*)).ti,ab.
25.	((information* or support* or advi?e* or counsel* or knowledge or educat* or psycholog*)

	adj6 (provision* or provide* or deliver* or facilitat* or establish* or arrang* or offer* or need* or access*)).ti,ab.
26.	((patient* or carer* or famil* or parent* or father* or mother* or caregiver* or next of kin) adj6 (resource* or pamphlet* or leaflet* or booklet* or manual* or brochure* or publication* or handout* or website* or web site* or web page* or webpage* or video* or dvd* or internet or computer* or program* or interactive* or email* or e-mail* or wireless or bluetooth or telephone or phone or sms or text*)).ti,ab.
27.	or/21-26
28.	diagnosis/
29.	prognosis/
30.	patient care planning/
31.	palliative therapy/ or terminal care/
32.	(diagnos* or prognos*).ti,ab.
33.	(advance* adj2 (plan* or decision* or directive*)).ti,ab.
34.	((advance* or patient*) adj3 (care or caring) adj3 (continu* or plan*)).ti,ab.
35.	(end of life or terminal* or palliativ*).ti,ab.
36.	or/28-35
37.	27 and 36
38.	20 or 37
39.	Study filter QUAL [N.3.8]
40.	4 and 38 and 39
41.	united kingdom/
42.	(national health service* or nhs*).ti,ab,in,ad.
43.	(english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab.
44.	(gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*).ti,ab,jw,in,ad.
45.	(bath or "bath's" or ((birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachusetts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*))))).ti,ab,in,ad.
46.	(bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's" or st asaph or "st asaph's" or st davids or swansea or "swansea's").ti,ab,in,ad.

47.	(aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's").ti,ab,in,ad.
48.	(armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or "londonderry's" or derry or "derry's" or newry or "newry's").ti,ab,in,ad.
49.	or/41-48
50.	(exp "arctic and antarctic"/ or exp oceanic regions/ or exp western hemisphere/ or exp africa/ or exp asia/ or exp "australia and new zealand"/) not (united kingdom/ or europe/)
51.	49 not 50
52.	40 and 51
53.	40 not 52
	Date limits: 2002 – 13 April 2017

CINAHL search terms

S1.	Standard population [N.2.1]
S2.	Excluded study designs and publication types [N.3.1] or (MH “case studies”)
S3.	1 not 2
S4.	Limit S3 to English language
S5.	MH communication
S6.	MH patient education
S7.	MH consumer health information
S8.	MH patient satisfaction
S9.	MH attitude of health personnel
S10.	MH physician-patient relations
S11.	(MH "nurse-patient relations") or (MH "professional-patient relations")
S12.	(MH "professional-family relations")
S13.	(MH "consumer participation")
S14.	MH decision making
S15.	(MH "pamphlets")
S16.	MH information Services+
S17.	MH books+
S18.	MH counseling
S19.	S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18
S20.	MH patients or MH inpatients or MH outpatients or MH caregivers or MH family+ or MH parents+ or MH guardianship, legal
S21.	ti (((patient* or carer* or famil* or parent* or father* or mother* or caregiver* or next of kin) n6 (attitude* or perspective* or view* or interpret* or understand* or misunderstand* or opinion* or decision* or decid* or belief* or believe* or feeling* or priorit* or perception* or choic* or preferen*))) or ab (((patient* or carer* or famil* or parent* or father* or mother* or caregiver* or next of kin) n6 (attitude* or perspective* or view* or interpret* or understand* or misunderstand* or opinion* or decision* or decid* or belief* or believe* or feeling* or priorit* or perception* or choic* or preferen*)))
S22.	ti (((patient* or carer* or famil* or parent* or father* or mother* or caregiver* or next of kin) n6 (inform* or educat* or learn* or advi?e or knowledge or involve* or support* or counsel* or communicat* or discuss* or convers*))) or AB (((patient* or carer* or famil* or parent* or father* or mother* or caregiver* or next of kin) n6 (inform* or educat* or learn* or advi?e or knowledge or involve* or support* or counsel* or communicat* or discuss* or convers*)))
S23.	ti (((information* or support* or advi?e* or counsel* or knowledge or educat* or psycholog*) n6 (provision* or provide* or deliver* or facilitat* or establish* or arrang* or offer* or need*

	or access*))) or ab (((information* or support* or advi?e* or counsel* or knowledge or educat* or psycholog*) n6 (provision* or provide* or deliver* or facilitat* or establish* or arrang* or offer* or need* or access*)))
S24.	ti (((patient* or carer* or famil* or parent* or father* or mother* or caregiver* or next of kin) n6 (resource* or pamphlet* or leaflet* or booklet* or manual* or brochure* or publication* or handout* or website* or web site* or web page* or webpage* or video* or dvd* or internet or computer* or program* or interactive* or email* or e-mail* or wireless or bluetooth or telephone or phone or sms or text*))) or ab (((patient* or carer* or famil* or parent* or father* or mother* or caregiver* or next of kin) n6 (resource* or pamphlet* or leaflet* or booklet* or manual* or brochure* or publication* or handout* or website* or web site* or web page* or webpage* or video* or dvd* or internet or computer* or program* or interactive* or email* or e-mail* or wireless or bluetooth or telephone or phone or sms or text*)))
S25.	S20 or S21 or S22 or S23 or S24
S26.	(MH "diagnosis+")
S27.	(MH "prognosis+")
S28.	(MH "advance care planning")
S29.	(MH "palliative care")
S30.	(MH "terminal care+")
S31.	ti ((diagnos* or prognos*)) or ab ((diagnos* or prognos*))
S32.	ti ((advance* n2 (plan* or decision* or directive*))) or ab ((advance* n2 (plan* or decision* or directive*)))
S33.	ti (((advance* or patient*) n3 (care or caring) n3 (continu* or plan*))) or ab (((advance* or patient*) n3 (care or caring) n3 (continu* or plan*)))
S34.	ti ((end of life or terminal* or palliativ*)) or ab ((end of life or terminal* or palliativ*))
S35.	S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34
S36.	S25 and S35
S37.	S19 or S36
S38.	S4 and S37
S39.	Study filter QUAL [N.3.8]
S40.	S38 and S39
	Date limits: 2002 – 13 April 2017

PyscINFO search terms

1.	((if(("heart failure" or "cardiomyopathy, dilated" or "shock, carcinogenic" or "ventricular dysfunction" or "cardiac output, low")) or (su.exact.explode("heart") and su.exact.explode("failure")) or ti(((heart or cardiac or myocardial) near/2 (failure or decompensation))) or ti("carcinogenic shock") or ti(((dilated or congestive) near/2 cardiomyopath*)) or ti(((ventricular or ventricle*) near/2 (failure or insufficien* or dysfunction*))) or ti,ab((congestive or acute or decompensat* or chronic) near/2 "heart failure") or ti,ab(("left ventricular" or "left ventricle") near/2 (failure or insufficien* or dysfunction*)) or ti(lsvd) or ab(lsvd)) and ((su.exact.explode("qualitative research") or su.exact("narratives") or su.exact.explode("questionnaires") or su.exact.explode("interviews") or su.exact.explode("health care services") or ti,ab(qualitative or interview* or focus group* or theme* or questionnaire* or survey*) or ti,ab(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or hemic or ethic or phenomenolog* or grounded theory or constant compar* or (thematic* near/3 analys*) or theorethical-sampl* or purposive-sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*))) and su.exact("books" or "communication barriers" or "patient education as topic" or "communication" or "professional-patient relations" or "nurse-patient relations" or "directive counseling" or "decision making" or "consumer health information" or "patient satisfaction" or "pamphlets" or "publications" or

	"physician-patient relations" or "professional-family relations" or "information services" or "attitude of health personnel" or "counseling")) and (su.exact("terminal care" or "diagnosis" or "palliative care" or "advance care planning" or "prognosis") or ti,ab(diagnos* or prognos*) or ti,ab(advance* near/2 (plan* or decision* or directive*)) or ((advance* or patient*) near/3 (care or caring) near/3 (continu* or plan*)) or ("end of life" or terminal* or palliativ*)) and (su.exact("parents" or "patients" or "caregivers" or "family" or "inpatients" or "legal guardians" or "outpatients") or ti,ab((patient* or carer* or famil* or parent* or father* or mother* or caregiver* or "next of kin") near/6 (attitude* or perspective* or view* or interpret* or understand* or misunderstand* or opinion* or decision* or decid* or belief* or believe* or feeling* or priorit* or perception* or choic* or preferen*)) or ti,ab((patient* or carer* or famil* or parent* or father* or mother* or caregiver* or "next of kin") near/6 (inform* or educat* or learn* or advi?e or knowledge or involve* or support* or counsel* or communicat* or discuss* or convers*)) or ti,ab((information* or support* or advi?e* or counsel* or knowledge or educat* or psycholog*) near/6 (provision* or provide* or deliver* or facilitat* or establish* or arrang* or offer* or need* or access*)) or ((patient* or carer* or famil* or parent* or father* or mother* or caregiver* or "next of kin") near/6 (resource* or pamphlet* or leaflet* or booklet* or manual* or brochure* or publication* or handout* or website* or webpage* or video* or dvd* or internet or computer* or program* or interactive* or email* or e-mail* or wireless or bluetooth or telephone or phone or isms or text*)) or ti,ab((patient* or carer* or famil* or parent* or father* or mother* or caregiver* or "next of kin") near/6 (web near/1 page*)) or ti,ab((patient* or carer* or famil* or parent* or father* or mother* or caregiver* or "next of kin") near/6 (web near/1 site*))))
2.	Date limits: 2002 – 13 April 2017

N.4.5 Coronary revascularisation

- What is the clinical and cost effectiveness of coronary revascularisation with coronary artery bypass grafting or angioplasty in people with heart failure?

Medline search terms

1.	Standard population [N.2.1]
2.	Excluded study designs and publication types [N.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	revascular*.ti,ab.
6.	myocardial revascularization/
7.	exp angioplasty/
8.	angioplast*.ti,ab.
9.	exp percutaneous coronary intervention/
10.	(percutaneous adj5 (coronary or intervention)).ti,ab.
11.	(ptca or pci).ti,ab.
12.	exp coronary artery bypass/
13.	(bypass adj5 (surg* or graft* or coronary or arter*)).ti,ab.
14.	(cabg or cab or acb).ti,ab.
15.	or/5-14
16.	Study filters RCT [N.3.2] or SR [N.3.3]
17.	4 and 15 and 16
	Date limits: 2002 – 6 December 2017

Embase search terms

1.	Standard population [N.2.1]
2.	Excluded study designs and publication types [N.3.1]

3.	1 not 2
4.	Limit 3 to English language
5.	revascular*.ti,ab.
6.	heart muscle revascularization/
7.	exp angioplasty/
8.	angioplast*.ti,ab.
9.	exp percutaneous coronary intervention/
10.	(percutaneous adj5 (coronary or intervention)).ti,ab.
11.	(ptca or pci).ti,ab.
12.	coronary artery bypass graft/
13.	(bypass adj5 (surg* or graft* or coronary or arter*)).ti,ab.
14.	(cabg or cab or acb).ti,ab.
15.	or/5-14
16.	Study filters RCT [N.3.2] or SR [N.3.3]
17.	4 and 15 and 16
	Date limits: 2002 – 6 December 2017

Cochrane search terms

#1.	Standard population [N.2.1]
#2.	revascular*:ti,ab,kw
#3.	MeSH descriptor: [myocardial revascularization] explode all trees
#4.	MeSH descriptor: [angioplasty] explode all trees
#5.	angioplast*:ti,ab
#6.	MeSH descriptor: [percutaneous coronary intervention] explode all trees
#7.	(percutaneous near/5 (coronary or intervention)):ti,ab
#8.	(ptca or pci):ti,ab
#9.	MeSH descriptor: [coronary artery bypass] this term only
#10.	(bypass near/5 (surg* or graft* or coronary or arter*)):ti,ab
#11.	(cabg or cab or acb):ti,ab
#12.	(or #2-#11)
#13.	#1 and #12
	Date limits: 2002 – 6 December 2017

N.4.6 Diuretics

- Which route of administration of diuretics (intravenous (IV), subcutaneous or oral) is most clinically and cost effective in people with advanced heart failure who are in the community, including patients receiving palliative care?

Medline search terms

1.	Standard population [N.2.1]
2.	Excluded study designs and publication types [N.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	((oral* or subcut* or IV or intravenous* or iv or infusion* or drip or drips or augment* or sequential* or loop or "high ceiling") adj6 diuretic*).ti,ab.
6.	(augment* adj diuresis).ti,ab.
7.	*diuretics/

8.	sodium potassium chloride symporter inhibitors/
9.	furosemide/
10.	(furosemid* or frusemid* or diuresal or frusolerrolon or furanthril or furantral or fursemide or fusid or lasix).ti,ab.
11.	bumetanide/
12.	(bumetanide or bumethanide or bumex or burinex or bumedyl or drenural or fordiuran or miccil).ti,ab.
13.	(torsemide or torasemide or torem or demadex).ti,ab.
14.	metolazone/
15.	(metolazone or microx or mykrox or zaroxolyn or diulo).ti,ab.
16.	thiazides/
17.	thiazide*.ti,ab.
18.	bendroflumethiazide/
19.	(bendroflumethiazide or aprinox or neo-naclex or bendrofluazide or benzide or benzidem or berkozide or esberizid or centyl or naturetin or naturine or neo-naclex or neonaclex or pluryl or urizid).ti,ab.
20.	chlorthalidone/
21.	(chlortalidone or chlorphthalidolone or chlorthalidone or hygroton or oxodoline or phthalamudine or thalitone).ti,ab.
22.	cyclopenthiazide/
23.	(cyclopenthiazide or cyclomethiazide or navidrex or navispare).ti,ab.
24.	indapamide/
25.	(indapamide or metindamide or cardide or indipam or natrilix or rawel or tensaid).ti,ab.
26.	xipamide/
27.	(xipamide or xipamid or diurexan).ti,ab.
28.	or/5-27
29.	Study filters RCT [N.3.2] or SR [N.3.3]
30.	4 and 28 and 29
	Date limits: 1946– 1 September 2017

1 **Embase search terms**

1.	Standard population [N.2.1]
2.	Excluded study designs and publication types [N.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	((oral* or subcut* or IV or intravenous* or iv or infusion* or drip or drips or augment* or sequential* or loop or "high ceiling") adj6 diuretic*).ti,ab.
6.	(augment* adj diuresis).ti,ab.
7.	*diuretic agent/
8.	loop diuretic agent/ or bumetanide/ or furosemide/ or furosemide plus spironolactone/ or furosemide plus triamterene/ or torasemide/
9.	(furosemid* or frusemid* or diuresal or frusolerrolon or furanthril or furantral or fursemide or fusid or lasix).ti,ab.
10.	(bumetanide or bumethanide or bumex or burinex or bumedyl or drenural or fordiuran or miccil).ti,ab.
11.	(torsemide or torasemide or torem or demadex).ti,ab.
12.	metolazone/

13.	(metolazone or microx or mykrox or zaroxolyn or diulo).ti,ab.
14.	thiazide diuretic agent/
15.	thiazide*.ti,ab.
16.	bendroflumethiazide/
17.	(bendroflumethiazide or aprinox or neo-naclex or bendrofluazide or benzide or benzidem or berkozide or esberizid or centyl or naturetin or naturine or neo-naclex or neonaclex or pluryl or urizid).ti,ab.
18.	chlortalidone/
19.	(chlortalidone or chlorphthalidolone or chlorthalidone or hygroton or oxodoline or phthalamudine or thalitone).ti,ab.
20.	cyclopenthiazide/
21.	(cyclopenthiazide or cyclomethiazide or navidrex or navispare).ti,ab.
22.	indapamide/
23.	(indapamide or metindamide or cardide or indipam or natrilix or rawel or tensaid).ti,ab.
24.	xipamide/
25.	(xipamide or xipamid or diurexan).ti,ab.
26.	or/5-25
27.	Study filters RCT [N.3.2] or SR [N.3.3]
28.	4 and 26 and 27
	Date limits: 1974 – 1 September 2017

1 **Cochrane search terms**

#1.	Standard population [N.2.1]
#2.	((oral* or subcut* or IV or intravenous* or iv or infusion* or drip or drips or augment* or sequential* or loop or "high ceiling") near/6 diuretic*):ti,ab
#3.	(augment* next diuresis):ti,ab
#4.	MeSH descriptor: [diuretics] explode all trees
#5.	MeSH descriptor: [sodium potassium chloride symporter inhibitors] this term only
#6.	MeSH descriptor: [furosemide] this term only
#7.	(furosemid* or frusemid* or diuresal or frusolerrolon or furanthril or furantral or fursemide or fusid or lasix):ti,ab
#8.	MeSH descriptor: [bumetanide] this term only
#9.	(bumetanide or bumethanide or bumex or burinex or bumedyl or drenural or fordiuran or miccil):ti,ab
#10.	(torsemide or torasemide or torem or demadex):ti,ab
#11.	MeSH descriptor: [metolazone] this term only
#12.	(metolazone or microx or mykrox or zaroxolyn or diulo):ti,ab
#13.	MeSH descriptor: [thiazides] this term only
#14.	thiazide*:ti,ab
#15.	MeSH descriptor: [bendroflumethiazide] this term only
#16.	(bendroflumethiazide or aprinox or neo-naclex or bendrofluazide or benzide or benzidem or berkozide or esberizid or centyl or naturetin or naturine or neo-naclex or neonaclex or pluryl or urizid):ti,ab
#17.	MeSH descriptor: [chlorthalidone] this term only
#18.	(chlortalidone or chlorphthalidolone or chlorthalidone or hygroton or oxodoline or phthalamudine or thalitone):ti,ab
#19.	MeSH descriptor: [cyclopenthiazide] this term only

#20.	(cyclopenthiazide or cyclomethiazide or navidrex or navispare):ti,ab
#21.	MeSH descriptor: [indapamide] this term only
#22.	(indapamide or metindamide or cardide or indipam or natrilix or rawel or tensaid):ti,ab
#23.	MeSH descriptor: [xipamide] this term only
#24.	(xipamide or xipamid or diurexan):ti,ab
#25.	(or #2-#24)
#26.	#1 and #25
	Date limits: Inception - 1 September 2017

N.4.7 Domiciliary Oxygen

- What is the effectiveness of domiciliary oxygen therapy in people with advanced heart failure?

Medline search terms

1.	Standard population [N.2.1]
2.	Excluded study designs and publication types [N.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	oxygen inhalation therapy/
6.	((home or therapy) adj3 respirat*).ti,ab.
7.	((domiciliary or home or nocturnal* or long-term or palliativ*) adj3 oxygen).ti,ab.
8.	(oxygen adj3 therap*).ti,ab.
9.	(hot or ltot).ti,ab.
10.	or/5-9
11.	Study filters RCT [N.3.2] or SR (N.3.3)
12.	4 and 10 and 11
	Date limits: 1946 – 21 April 2017

Embase search terms

1.	Standard population [N.2.1]
2.	Excluded study designs and publication types [N.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	oxygen therapy/
6.	((home or therapy) adj3 respirat*).ti,ab.
7.	((domiciliary or home or nocturnal* or long-term or palliativ*) adj3 oxygen).ti,ab.
8.	(oxygen adj3 therap*).ti,ab.
9.	(hot or ltot).ti,ab.
10.	or/5-9
11.	Study filters RCT [N.3.2] or SR [N.3.3]
12.	4 and 10 and 11
13.	Date limits: 1974 – 21 April 2017

Cochrane search terms

#1.	Standard population [N.2.1]
#2.	MeSH descriptor: [oxygen inhalation therapy] this term only
#3.	((home or therapy) near/3 respirat*):ti,ab
#4.	((domiciliary or home or nocturnal* or long-term or palliativ*) near/3 oxygen):ti,ab

#5.	(oxygen near/3 therap*):ti,ab
#6.	(hot or ltot):ti,ab
#7.	#2 or #3 or #4 or #5 or #6
#8.	#1 and #7
	Date limits: Inception – 21 April 2017

N.4.8 Implantable cardiac defibrillators

- What criteria should determine when to discuss defibrillator deactivation?

Medline search terms

1.	Standard population [N.2.1]
2.	(palliat* or terminal* or dying* or eolc or death).ti,ab.
3.	(end adj2 life).ti,ab.
4.	((long term or longterm) adj2 (care* or caring or ill*)).ti,ab.
5.	(advance* adj2 (plan* or decision* or directive*)).ti,ab.
6.	terminal care/ or palliative care/ or exp advance care planning/ or long-term care/ or *patient care planning/
7.	death, sudden cardiac/
8.	or/2-7
9.	"attitude of health personnel"/ or decision making/ or patient preference/ or health knowledge, attitudes, practice/ or informed consent/ or patient participation/ or patient satisfaction/ or attitude to health/ or patient education as topic/ or consumer health information/
10.	communication/
11.	nurse-patient relations/ or professional-family relations/ or professional-patient relations/ or physician-patient relations/
12.	((consumer* or client* or resident* or patient* or spouse* or wife or wives or husband* or carer* or caregiver* or care giver* or significant other* or family or families or individual* or next of kin or partner* or sibling* or brother* or sister* or relative or relatives or mother* or daughter* or father* or son or sons) adj4 (participat* or satisf* or educat* or attitude* or preference* or decision* or deciding or decide* or consent* or communicat* or empower* or perspective* or view* or interpret* or wish* or need* or understand* or misunderstand* or opinion* or belief* or believe* or feeling* or perception* or choice* or inform* or learn* or advi?e or knowledge or involve* or support* or expectation* or experience* or counsel* or facilitat* or barrier*)).ti,ab.
13.	((personnel or doctor* or nurse* or professional* or physician* or practitioner* or GP* or psychologist* or consultant* or cardiologist* or health worker* or geriatrician* or psychologist* or counselor* or counsellor*) adj4 (participat* or satisf* or educat* or attitude* or preference* or decision* or deciding or decide* or consent* or communicat* or empower* or perspective* or view* or interpret* or wish* or need* or understand* or misunderstand* or opinion* or belief* or believe* or feeling* or perception* or choice* or inform* or learn* or advi?e or knowledge or involve* or support* or expectation* or experience* or counsel* or facilitat* or barrier*)).ti,ab.
14.	((interdisciplin* or inter-disciplin* or interprofession* or inter-profession* or multidisciplin* or multi-disciplin* or multi-profession* or multiprofession* or transprofession* or trans-profession* or combin* or integrat* or network*) adj2 (work* or team* or care or ward or wards) adj4 (participat* or satisf* or educat* or attitude* or preference* or decision* or deciding or decide* or consent* or communicat* or empower* or perspective* or view* or interpret* or wish* or need* or understand* or misunderstand* or opinion* or belief* or believe* or feeling* or perception* or choice* or inform* or learn* or advi?e or knowledge or involve* or support* or expectation* or experience* or counsel* or facilitat* or barrier*)).ti,ab.

15.	((share* or sharing or make* or making* or made or agree* or participat* or support* or collaborat* or joint or inform*) adj2 decision*).ti,ab.
16.	informed consent.ti,ab.
17.	(information* adj2 support*).ti,ab.
18.	or/9-17
19.	1 or 8 or 18
20.	Excluded study designs and publication types [N.3.1]
21.	19 not 20
22.	Limit 21 to English language
23.	(defibrillat* or icd*).ti,ab.
24.	defibrillators/ or defibrillators, implantable/
25.	((cardiovascular or cardiac or cardio) adj2 implant* adj3 device*).ti,ab.
26.	cied*.ti,ab.
27.	or/23-26
28.	Study filter QUAL [N.3.8]
29.	22 and 27 and 28
30.	exp great britain/
31.	(national health service* or nhs*).ti,ab,in.
32.	(english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab.
33.	(gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*).ti,ab,jw,in.
34.	(bath or "bath's" or ((birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachusetts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*))))).ti,ab,in.
35.	(bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's" or st asaph or "st asaph's" or st davids or swansea or "swansea's").ti,ab,in.
36.	(aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's").ti,ab,in.
37.	(armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or

	"londonderry's" or derry or "derry's" or newry or "newry's").ti,ab,in.
38.	or/30-37
39.	(exp africa/ or exp americas/ or exp antarctic regions/ or exp arctic regions/ or exp asia/ or exp australia/ or exp oceania/) not (exp great britain/ or europe/)
40.	38 not 39
41.	29 and 40
42.	29 not 41
	Date limits: 2002 – 21 July 2017

1 **Embase search terms**

1.	Standard population [N.2.1]
2.	(palliat* or terminal* or dying or eolc or death).ti,ab.
3.	(end adj2 life).ti,ab.
4.	((long term or longterm) adj2 (care* or caring or ill*)).ti,ab.
5.	(advance* adj2 (plan* or decision* or directive*)).ti,ab.
6.	terminal care/ or advance care planning/ or palliative therapy/ or long term care/ or *patient care planning/
7.	sudden cardiac death/
8.	or/2-7
9.	interpersonal communication/ or patient education/ or consumer health information/ or patient satisfaction/ or health personnel attitude/ or patient participation/ or decision making/ or patient preference/ or patient attitude/ or patient information/ or attitude to health/ or informed consent/
10.	doctor patient relation/ or nurse patient relationship/
11.	((consumer* or client* or resident* or patient* or spouse* or wife or wives or husband* or carer* or caregiver* or care giver* or significant other* or family or families or individual* or next of kin or partner* or sibling* or brother* or sister* or relative or relatives or mother* or daughter* or father* or son or sons) adj4 (participat* or satisf* or educat* or attitude* or preference* or decision* or deciding or decide* or consent* or communicat* or empower* or perspective* or view* or interpret* or wish* or need* or understand* or misunderstand* or opinion* or belief* or believe* or feeling* or perception* or choice* or inform* or learn* or advi?e or knowledge or involve* or support* or expectation* or experience* or counsel* or facilitat* or barrier*)).ti,ab.
12.	((personnel or doctor* or nurse* or professional* or physician* or practitioner* or GP* or psychologist* or consultant* or cardiologist* or health worker* or geriatrician* or psychologist* or counselor* or counsellor*) adj4 (participat* or satisf* or educat* or attitude* or preference* or decision* or deciding or decide* or consent* or communicat* or empower* or perspective* or view* or interpret* or wish* or need* or understand* or misunderstand* or opinion* or belief* or believe* or feeling* or perception* or choice* or inform* or learn* or advi?e or knowledge or involve* or support* or expectation* or experience* or counsel* or facilitat* or barrier*)).ti,ab.
13.	((interdisciplin* or inter-disciplin* or interprofession* or inter-profession* or multidisciplin* or multi-disciplin* or multi-profession* or multiprofession* or transprofession* or trans-profession* or combin* or integrat* or network*) adj2 (work* or team* or care or ward or wards) adj4 (participat* or satisf* or educat* or attitude* or preference* or decision* or deciding or decide* or consent* or communicat* or empower* or perspective* or view* or interpret* or wish* or need* or understand* or misunderstand* or opinion* or belief* or believe* or feeling* or perception* or choice* or inform* or learn* or advi?e or knowledge or involve* or support* or expectation* or experience* or counsel* or facilitat* or barrier*)).ti,ab.
14.	((share* or sharing or make* or making* or made or agree* or participat* or support* or collaborat* or joint or inform*) adj2 decision*).ti,ab.

15.	informed consent.ti,ab.
16.	(information* adj2 support*).ti,ab.
17.	or/9-16
18.	1 or 8 or 17
19.	Excluded study designs and publication types [N.3.1]
20.	18 not 19
21.	Limit 20 to English language
22.	(defibrillat* or ICD*).ti,ab.
23.	defibrillator/ or implantable cardioverter defibrillator/ or internal defibrillator/
24.	((cardiovascular or cardiac or cardio) adj2 implant* adj3 device*).ti,ab.
25.	cied*.ti,ab.
26.	or/22-25
27.	Study filter QUAL [N.3.8]
28.	21 and 26 and 27
29.	united kingdom/
30.	(national health service* or nhs*).ti,ab,in,ad.
31.	(english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab.
32.	(gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*).ti,ab,jw,in,ad.
33.	(bath or "bath's" or ((birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachusetts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*))))).ti,ab,in,ad.
34.	(bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's" or st asaph or "st asaph's" or st davids or swansea or "swansea's").ti,ab,in,ad.
35.	(aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's").ti,ab,in,ad.
36.	(armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or "londonderry's" or derry or "derry's" or newry or "newry's").ti,ab,in,ad.
37.	or/29-36

38.	(exp "arctic and antarctic"/ or exp oceanic regions/ or exp western hemisphere/ or exp africa/ or exp asia/ or exp "australia and new zealand"/) not (united kingdom/ or europe/)
39.	37 not 38
40.	28 and 39
41.	28 not 40
	Date limits: 2002 – 21 July 2017

PyscINFO search terms

1.	(((((su.exact.explode("qualitative research") or su.exact("narratives") or su.exact.explode("questionnaires") or su.exact.explode("interviews") or su.exact.explode("health care services") or ti,ab(qualitative or interview* or focus group* or theme* or questionnaire* or survey*) or ti,ab(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* near/3 analys*) or theoretical-sampl* or purposive-sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*))) and la.exact("eng")) and ((ti,ab((cardiovascular or cardiac or cardio) near/2 implant* near/3 device*) or ti,ab(defibrillat* or icd* or cied*) or su.exact("defibrillators" or "defibrillators, implantable")) and la.exact("eng"))) not ((su.exact.explode("rodents") or su.exact.explode("mice") or (su.exact("animals") not (su.exact("human males") or su.exact("human females"))) or ti(rat or rats or mouse or mice)) and la.exact("eng"))) and la.exact("English")
	Date limits: 2002- 21 July 2017

CINAHL search terms

S1.	Standard population [N.2.1]
S2.	ti ((eolc or terminal* or palliativ* or dying or death)) or ab ((eolc or terminal* or palliativ* or eolc or dying or death))
S3.	ti ((end n2 life) or ab (end n2 life))
S4.	ti ((long term or longterm) n2 (care* or caring or ill*)) or ab ((long term or longterm) n2 (care* or caring or ill*))
S5.	ti ((advance* n2 (plan* or decision* or directive*))) or ab ((advance* n2 (plan* or decision* or directive*)))
S6.	(MH "terminal care")
S7.	(MH "palliative care")
S8.	(MH "advance care planning")
S9.	(MH "long term care")
S10.	(MH "patient care plans")
S11.	(MH "death, sudden, cardiac")
S12.	S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11
S13.	(MH "attitude of health personnel+")
S14.	(MH "consent")
S15.	(MH "attitude of health personnel") or (MH "health knowledge")
S16.	(MH "decision making, patient") or (MH "decision making, family") or (MH "decision making, clinical")
S17.	(MH "consumer participation")
S18.	(MH "patient satisfaction")
S19.	(MH "attitude to health+")
S20.	(MH "patient education")
S21.	(MH "consumer health information") or (MH "health information")

S22.	(MH "communication")
S23.	(MH "nurse-patient relations") or (MH "professional-patient relations") or (MH "physician-patient relations")
S24.	(MH "professional-family relations")
S25.	(MH "decision making")
S26.	ti ((consumer* or client* or resident* or patient* or spouse* or wife or wives or husband* or carer* or caregiver* or care giver* or significant other* or family or families or individual* or next of kin or partner* or sibling* or brother* or sister* or relative or relatives or mother* or daughter* or father* or son or sons) n4 (participat* or satisf* or educat* or attitude* or preference* or decision* or deciding or decide* or consent* or communicat* or empower* or perspective* or view* or interpret* or wish* or need* or understand* or misunderstand* or opinion* or belief* or believe* or feeling* or perception* or choice* or inform* or learn* or advi?e or knowledge or involve* or support* or expectation* or experience* or counsel* or facilitat* or barrier*)) or ab ((consumer* or client* or resident* or patient* or spouse* or wife or wives or husband* or carer* or caregiver* or care giver* or significant other* or family or families or individual* or next of kin or partner* or sibling* or brother* or sister* or relative or relatives or mother* or daughter* or father* or son or sons) n4 (participat* or satisf* or educat* or attitude* or preference* or decision* or deciding or decide* or consent* or communicat* or empower* or perspective* or view* or interpret* or wish* or need* or understand* or misunderstand* or opinion* or belief* or believe* or feeling* or perception* or choice* or inform* or learn* or advi?e or knowledge or involve* or support* or expectation* or experience* or counsel* or facilitat* or barrier*))
S27.	ti ((personnel or doctor* or nurse* or professional* or physician* or practitioner* or gp* or psychologist* or consultant* or cardiologist* or health worker* or geriatrician* or psychologist* or counselor* or counsellor*) n4 (participat* or satisf* or educat* or attitude* or preference* or decision* or deciding or decide* or consent* or communicat* or empower* or perspective* or view* or interpret* or wish* or need* or understand* or misunderstand* or opinion* or belief* or believe* or feeling* or perception* or choice* or inform* or learn* or advi?e or knowledge or involve* or support* or expectation* or experience* or counsel* or facilitat* or barrier*)) or ab ((personnel or doctor* or nurse* or professional* or physician* or practitioner* or gp* or psychologist* or consultant* or cardiologist* or health worker* or geriatrician* or psychologist* or counselor* or counsellor*) n4 (participat* or satisf* or educat* or attitude* or preference* or decision* or deciding or decide* or consent* or communicat* or empower* or perspective* or view* or interpret* or wish* or need* or understand* or misunderstand* or opinion* or belief* or believe* or feeling* or perception* or choice* or inform* or learn* or advi?e or knowledge or involve* or support* or expectation* or experience* or counsel* or facilitat* or barrier*))
S28.	ti ((interdisciplin* or inter-disciplin* or interprofession* or inter-profession* or multidisciplin* or multi-disciplin* or multi-profession* or multiprofession* or transprofession* or trans-profession* or combin* or integrat* or network*) n2 (work* or team* or care or ward or wards) n4 (participat* or satisf* or educat* or attitude* or preference* or decision* or deciding or decide* or consent* or communicat* or empower* or perspective* or view* or interpret* or wish* or need* or understand* or misunderstand* or opinion* or belief* or believe* or feeling* or perception* or choice* or inform* or learn* or advi?e or knowledge or involve* or support* or expectation* or experience* or counsel* or facilitat* or barrier*)) or ab ((interdisciplin* or inter-disciplin* or interprofession* or inter-profession* or multidisciplin* or multi-disciplin* or multi-profession* or multiprofession* or transprofession* or trans-profession* or combin* or integrat* or network*) n2 (work* or team* or care or ward#) n4 (participat* or satisf* or educat* or attitude* or preference* or decision* or deciding or decide* or consent* or communicat* or empower* or perspective* or view* or interpret* or wish* or need* or understand* or misunderstand* or opinion* or belief* or believe* or feeling* or perception* or choice* or inform* or learn* or advi?e or knowledge or involve* or support* or expectation* or experience* or counsel* or facilitat* or barrier*))
S29.	ti ((share* or sharing or make* or making* or made or agree* or participat* or support* or collaborat* or joint or inform*) n2 decision*) or ab ((share* or sharing or make* or making* or made or agree* or participat* or support* or collaborat* or joint or inform*) n2 decision*)

S30.	ti informed consent or ab informed consent
S31.	ti (information* n2 support*) or ab (information* n2 support*)
S32.	S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31
S33.	S1 or S12 or S32
S34.	Excluded study designs and publication types [N.3.1] or (”Case Studies”)
S35.	S33 not S34
S36.	Limit S35 to English language
S37.	ti (defibrillat* or icd*) or ab (defibrillat* or icd*)
S38.	(MH "defibrillators") or (MH "defibrillators, implantable")
S39.	ti ((cardiovascular or cardiac or cardio) n2 implant* n3 device*) or ab ((cardiovascular or cardiac or cardio) n2 implant* n3 device*)
S40.	ti cied* or ab cied*
S41.	S37 or S38 or S39 or S40
S42.	Study filter QUAL [N.3.8]
S43.	S36 and S41 and S42
	Date limits: 2002- 21 July 2017

N.4.9 Iron

- What is the clinical and cost effectiveness of iron supplementation in people with chronic heart failure and iron deficiency?

Medline search terms

1.	Standard population [N.2.1]
2.	Excluded study designs and publication types [N.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	exp hematinics/
6.	exp iron compounds/
7.	iron/
8.	erythropoietin/ or epoetin alfa/
9.	(iron or ferrous or ferric or ferumoxytol or ferinject* or ferritin* or magnetite or "ferriferous oxide").ti,ab.
10.	(erythropoie* or epoetin* or epoietin* or epo or epogen or eporatio or eprex or procrit or binocrit or eprex or mircera or neorecormon or recormon or retacrit or darbopoetin or darbepoetin or darbepoietin or aranesp or r-huepo or huepo or r-hepo or rhepo or glycol-epoetin).ti,ab.
11.	(h?ematinic* or h?ematopoieti*).ti,ab.
12.	(anti-an?emi* or antian?emi*).ti,ab.
13.	or/5-12
14.	Study filters RCT [N.3.2] or SR [N.3.3]
15.	4 and 13 and 14
	Date limits: 1946 – 6 December 2017

Embase search terms

1.	Standard population [N.2.1]
2.	Excluded study designs and publication types [N.3.1]
3.	1 not 2

4.	Limit 3 to English language
5.	exp *antianemic agent/
6.	*iron/
7.	*iron derivative/
8.	*iron intake/
9.	(iron or ferrous or ferric or ferumoxytol or ferinject* or ferritin* or magnetite or "ferriferous oxide").ti,ab.
10.	(erythropoie* or epoetin* or epoietin* or epo or epogen or eporatio or eprex or procrit or binocrit or eprex or mircera or neorecormon or recormon or retacrit or darbopoetin or darbepoetin or darbepoietin or aranesp or r-huepo or huepo or r-hepo or rhepo or glycol-epoetin).ti,ab.
11.	(h?ematinic* or h?ematopoieti*).ti,ab.
12.	(anti-an?emi* or antian?emi*).ti,ab.
13.	or/5-12
14.	Study filters RCT [N.3.2] or SR [N.3.3]
15.	4 and 13 and 14
	Date limits: 1974 – 6 December 2017

Cochrane search terms

#1.	Standard population [N.2.1]
#2.	MeSH descriptor: [hematinics] explode all trees
#3.	MeSH descriptor: [iron compounds] explode all trees
#4.	MeSH descriptor: [iron] this term only
#5.	MeSH descriptor: [erythropoietin] this term only
#6.	MeSH descriptor: [epoetin alfa] this term only
#7.	(iron or ferrous or ferric or ferumoxytol or ferinject* or ferritin* or magnetite or "ferriferous oxide"):ti,ab
#8.	(erythropoie* or epoetin* or epoietin* or epo or epogen or eporatio or eprex or Procrit or binocrit or eprex or mircera or neorecormon or recormon or retacrit or darbopoetin or darbepoetin or darbepoietin or aranesp or r-huepo or huepo or r-hepo or rhepo or glycol-epoetin):ti,ab
#9.	(h?ematinic* or h?ematopoieti*):ti,ab
#10.	(anti-an?emi* or antian?emi*):ti,ab
#11.	#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
#12.	#1 and #11
	Date limits: Inception – 6 December 2017

N.4.10 Multi-disciplinary teams

- What competencies should be present in the multidisciplinary teams involved in the outpatient or community-based care of people with heart failure?

Medline search terms

1.	Standard population [N.2.1]
2.	Excluded study designs and publication types [N.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	(heart failure adj2 team).ti,ab.
6.	(((interdisciplin* or inter-disciplin* or interprofession* or inter-profession* or multidisciplin*

	or multi-disciplin* or multi-profession* or multiprofession* or transprofession* or trans-profession* or integrat* or network*) adj2 (team* or staff* or meeting* or manag* or appointment* or intervention* or service* or approach* or system* or practice* or program* or advis* or advice* or caring or care or intervention* or communicat* or relation* or relate* or collaborat* or strateg* or model*)) or MDT or IDT).ti,ab.
7.	((interdisciplin* or inter-disciplin* or interprofession* or inter-profession* or multidisciplin* or multi-disciplin* or multi-profession* or multiprofession* or transprofession* or trans-profession* or integrat*) adj2 network*).ti,ab.
8.	((healthcare or care) adj2 team*).ti,ab.
9.	((team or teams or staff) adj6 (competenc* or skill* or expert* or knowledge* or composition*)).ti,ab.
10.	exp patient care team/
11.	exp interprofessional relations/
12.	exp clinical competence/
13.	interdisciplinary communication/
14.	exp cooperative behavior/
15.	((counsel* or coach* or advise* or advice or advisor* or led or co-ordinat* or coordinat* or expert* or skill* or service* or competenc* or knowledg* or team* or lead or leader or leads or intervention* or program* or therap*) adj2 (pharmacist* or physician* or practitioner* or gp* or psychologist* or consultant* or cardiologist* or community health worker* or prescriber* or physiotherap* or mental health* or nutrition* or diet* or rehab* or end of life or palliative or nurse* or nursing or pharmaceutical or geriatric* or elderly)).ti,ab.
16.	(specialis* or specializ*).ti,ab.
17.	(nurse* adj2 (heart failure or hf)).ti,ab.
18.	advance* practice nurs*.ti,ab.
19.	((person or patient) adj (centered or centred)).ti,ab.
20.	holistic care.ti,ab.
21.	practice patterns, nurses'/
22.	physician's practice patterns/
23.	pharmacists/
24.	nurses/ or nurse clinicians/ or nurse practitioners/ or nurses, community health/ or exp nursing staff/ or nursing/ or specialties, nursing/ or advanced practice nursing/
25.	community health workers/ or nutritionists/ or physical therapists/
26.	physicians/ or general practitioners/ or physicians, primary care/
27.	consultants/
28.	palliative care/
29.	geriatric assessment/
30.	nutrition assessment/
31.	mental health services/
32.	counseling/
33.	or/5-32
34.	Study filters RCT [N.3.2] or SR [N.3.3]
35.	4 and 33 and 34
	Date limits: 1946 – 6 December 2017

1 **Embase search terms**

1.	Standard population [N.2.1]
2.	Excluded study designs and publication types [N.3.1]
3.	1 not 2

4.	Limit 3 to English language
5.	(heart failure adj2 team).ti,ab.
6.	(((interdisciplin* or inter-disciplin* or interprofession* or inter-profession* or multidisciplin* or multi-disciplin* or multi-profession* or multiprofession* or transprofession* or trans-profession* or integrat* or network*) adj2 (team* or staff* or meeting* or manag* or appointment* or intervention* or service* or approach* or system* or practice* or program* or advis* or advice* or caring or care or intervention* or communicat* or relation* or relate* or collaborat* or strateg* or model*)) or mdt or idt).ti,ab.
7.	((interdisciplin* or inter-disciplin* or interprofession* or inter-profession* or multidisciplin* or multi-disciplin* or multi-profession* or multiprofession* or transprofession* or trans-profession* or integrat*) adj2 network*).ti,ab.
8.	((healthcare or care) adj2 team*).ti,ab.
9.	((team or teams or staff) adj6 (competenc* or skill* or expert* or knowledge* or composition*)).ti,ab.
10.	patient care/
11.	public relations/
12.	clinical competence/
13.	interdisciplinary communication/
14.	teamwork/
15.	cooperation/
16.	((counsel* or coach* or advise* or advice or advisor* or led or co-ordinat* or coordinat* or expert* or skill* or service* or competenc* or knowledg* or team* or lead or leader or leads or intervention* or program* or therap*) adj2 (pharmacist* or physician* or practitioner* or GP* or psychologist* or consultant* or cardiologist* or community health worker* or prescriber* or physiotherap* or mental health* or nutrition* or diet* or rehab* or end of life or palliative or nurse* or nursing or pharmaceutical or geriatric* or elderly)).ti,ab.
17.	(specialis* or specializ*).ti,ab.
18.	(nurse* adj2 (heart failure or HF)).ti,ab.
19.	advance* practice nurs*.ti,ab.
20.	((person or patient) adj (centered or centred)).ti,ab.
21.	holistic care.ti,ab.
22.	holistic care/
23.	*nurse/ or *nursing/
24.	advanced practice nurse/ or clinical nurse specialist/ or nurse practitioner/ or expert nurse/ or nurse consultant/ or holistic nursing/ or nursing competence/ or nursing intervention/ or nursing management/ or nursing role/ or nursing staff/
25.	medical specialist/
26.	pharmacist/
27.	health auxiliary/ or dietitian/ or physiotherapist/ or nutritional assessment/ or nutritional counseling/
28.	geriatrician/ or gerontologist/
29.	consultation/
30.	palliative nursing/ or palliative therapy/
31.	geriatric assessment/ or geriatric care/ or elderly care/ or geriatric nursing/
32.	mental health/ or psychiatrist/ or counseling/ or psychologist/
33.	cardiologist/
34.	general practitioner/
35.	*physician/
36.	or/5-35

37.	Study filters RCT [N.3.2] or SR [N.3.3]
38.	4 and 36 and 37
	Date limits: 1974 – 6 December 2017

Cochrane search terms

#1.	Standard population [N.2.1]
#2.	(heart failure next/2 team):ti,ab
#3.	(((interdisciplin* or inter-disciplin* or interprofession* or inter-profession* or multidisciplin* or multi-disciplin* or multi-profession* or multiprofession* or transprofession* or trans-profession* or integrat* or network*) next/2 (team* or staff* or meeting* or manag* or appointment* or intervention* or service* or approach* or system* or practice* or program* or advis* or advice* or caring or care or intervention* or communicat* or relation* or relate* or collaborat* or strateg* or model*)) or mdt or idt):ti,ab
#4.	((interdisciplin* or inter-disciplin* or interprofession* or inter-profession* or multidisciplin* or multi-disciplin* or multi-profession* or multiprofession* or transprofession* or trans-profession* or integrat*) next/2 network*):ti,ab
#5.	((healthcare or care) next/2 team*):ti,ab
#6.	((team or teams or staff) next/6 (competenc* or skill* or expert* or knowledge* or composition*)):ti,ab
#7.	MeSH descriptor: [patient care team] explode all trees
#8.	MeSH descriptor: [interprofessional relations] explode all trees
#9.	MeSH descriptor: [clinical competence] explode all trees
#10.	MeSH descriptor: [interdisciplinary communication] this term only
#11.	MeSH descriptor: [cooperative behavior] explode all trees
#12.	((counsel* or coach* or advise* or advice or advisor* or led or co-ordinat* or coordinat* or expert* or skill* or service* or competenc* or knowledg* or team* or lead or leader or leads or intervention* or program* or therap*) next/2 (pharmacist* or physician* or practitioner* or GP* or psychologist* or consultant* or cardiologist* or community next health next worker* or prescriber* or physiotherap* or mental next health* or nutrition* or diet* or rehab* or end next of next life or palliative or nurse* or nursing or pharmaceutical or geriatric* or elderly)):ti,ab
#13.	(specialis* or specializ*):ti,ab
#14.	(nurse* next/2 (heart failure or HF)):ti,ab
#15.	advance* next practice next nurs*:ti,ab
#16.	((person or patient) next (centered or centred)):ti,ab
#17.	"holistic care":ti,ab
#18.	MeSH descriptor: [practice patterns, nurses'] this term only
#19.	MeSH descriptor: [practice patterns, physicians'] this term only
#20.	MeSH descriptor: [pharmacists] this term only
#21.	MeSH descriptor: [nurses] this term only
#22.	MeSH descriptor: [nurse clinicians] this term only
#23.	MeSH descriptor: [nurse practitioners] this term only
#24.	MeSH descriptor: [nurses, community health] this term only
#25.	MeSH descriptor: [nursing staff] explode all trees
#26.	MeSH descriptor: [nursing] this term only
#27.	MeSH descriptor: [specialties, nursing] this term only
#28.	MeSH descriptor: [advanced practice nursing] this term only
#29.	MeSH descriptor: [community health workers] this term only
#30.	MeSH descriptor: [nutritionists] this term only

#31.	MeSH descriptor: [physical therapists] this term only
#32.	MeSH descriptor: [physicians] this term only
#33.	MeSH descriptor: [general practitioners] this term only
#34.	MeSH descriptor: [physicians, primary care] this term only
#35.	MeSH descriptor: [consultants] this term only
#36.	MeSH descriptor: [palliative care] this term only
#37.	MeSH descriptor: [geriatric assessment] this term only
#38.	MeSH descriptor: [nutrition assessment] this term only
#39.	MeSH descriptor: [mental health services] this term only
#40.	MeSH descriptor: [counseling] this term only
#41.	(or #2-#40)
#42.	#1 and #41
	Date limits: Inception – 6 December 2017

N.4.11 Monitoring

Searches for the following 3 questions were run as one search. The strategy was based on the following HTA:

Pufulete M, Maishman R, Dabner L, Mohiuddin S, Hollingworth W, Rogers CA et al. *Effectiveness and cost-effectiveness of serum B-type natriuretic peptide testing and monitoring in patients with heart failure in primary and secondary care: an evidence synthesis, cohort study and cost-effectiveness model*. **Health Technology Assessment**. 2017; 21(40)

- What is the clinical and cost effectiveness of biomarker-based monitoring, monitoring with cardiac MRI, and monitoring with repeated echocardiography in people with heart failure?
- What is the clinical and cost effectiveness of biomarker-based monitoring, monitoring with cardiac MRI, and monitoring with repeated echocardiography in people with heart failure who also have CKD?
- What is the clinical and cost effectiveness of biomarker-based monitoring, monitoring with cardiac MRI, and monitoring with repeated echocardiography in people with heart failure who also have atrial fibrillation?

Medline search terms

1.	exp heart Failure/
2.	heart failure.ti,ab.
3.	cardiac failure.ti,ab.
4.	or/1-3
5.	natriuretic peptide, brain/
6.	monitoring, physiologic/
7.	"health status indicators"/
8.	or/6-7
9.	5 and 8
10.	((bnp or probnp or ntprobnp or natriuretic peptide or natriuretic propeptide) adj5 (guide* or monitor* or target*)).ti,ab.
11.	((bnp or probnp or ntprobnp or natriuretic peptide or natriuretic propeptide) adj5 (retest* or serial or series)).ti,ab.
12.	((bnp or probnp or ntprobnp or natriuretic peptide or natriuretic propeptide) adj5 (manag* or

	tailor* or therap* or strateg*)).ti,ab.
13.	or/9-12
14.	4 and 13
15.	exp heart failure/
16.	cardiomyopathy, dilated/
17.	shock, cardiogenic/
18.	exp ventricular dysfunction/
19.	cardiac output, low/
20.	((heart or cardiac or myocardial) adj2 (failure or decompensation)).ti.
21.	((congestive or acute or decompensat* or chronic) adj2 "heart failure").ti,ab.
22.	((dilated or congestive) adj2 cardiomyopath*).ti.
23.	"cardiogenic shock".ti.
24.	((ventricular or ventricle*) adj2 (failure or insufficien* or dysfunction*)).ti.
25.	(("left ventricular" or "left ventricle") adj2 (failure or insufficien* or dysfunction*)).ti,ab.
26.	lvsd.ti,ab.
27.	or/15-26
28.	exp troponin/
29.	exp echocardiography/
30.	magnetic resonance imaging/
31.	or/28-30
32.	monitoring, physiologic/
33.	"health status indicators"/
34.	or/32-33
35.	31 and 34
36.	((troponin or echo* or doppler* or mri* or nmr* or magnetic resonance) adj5 (guide* or monitor* or target* or marker* or biomarker*)).ti,ab.
37.	((troponin or echo* or doppler* or mri* or nmr* or magnetic resonance) adj5 (repeat* or retest* or serial or series)).ti,ab.
38.	((troponin or echo* or doppler* or mri* or nmr* or magnetic resonance) adj5 (manag* or tailor* or therap* or strateg* or treat*)).ti,ab.
39.	((cmr or ((cardiac or cardiovascular) adj mr)) adj5 (guide* or monitor* or target* or marker* or biomarker*)).ti,ab.
40.	((cmr or ((cardiac or cardiovascular) adj mr)) adj5 (repeat* or retest* or serial or series)).ti,ab.
41.	((cmr or ((cardiac or cardiovascular) adj mr)) adj5 (manag* or tailor* or therap* or strateg* or treat*)).ti,ab.
42.	((bnp or probnp or ntprobnp or natriuretic peptide or natriuretic propeptide) adj5 (repeat* or treat* or marker* or biomarker*)).ti,ab.
43.	or/35-42
44.	27 and 43
45.	Excluded study designs and publication types [N.3.1]
46.	14 or 44
47.	46 not 45
48.	Limit 47 to English language
49.	Study filters RCT [N.3.2] or SR [N.3.3]
50.	48 and 49
51.	13 and 27

52.	51 not 14
53.	52 not 45
54.	Limit 53 to English language
55.	54 and 49
56.	50 or 55
	Date limits: 1946 – 6 December 2017

1 **Embase search terms**

1.	exp heart failure/
2.	heart failure.tw.
3.	cardiac failure.tw.
4.	or/1-3
5.	brain natriuretic peptide/
6.	monitoring/
7.	"disease course"/
8.	"pathophysiology"/
9.	patient monitoring/
10.	biological monitoring/
11.	hemodynamic monitoring/
12.	"symptom"/
13.	or/6-12
14.	5 and 13
15.	((bnp or probnp or ntprobnp or natriuretic peptide or natriuretic propeptide) adj5 (guide* or monitor* or target*)).ti,ab.
16.	((bnp or probnp or ntprobnp or natriuretic peptide or natriuretic propeptide) adj5 (retest* or serial or series)).ti,ab.
17.	((bnp or probnp or ntprobnp or natriuretic peptide or natriuretic propeptide) adj5 (manag* or tailor* or treat* or therap* or strateg*)).ti,ab.
18.	or/14-17
19.	4 and 18
20.	*heart failure/ or acute heart failure/ or *cardiogenic shock/ or *diastolic dysfunction/ or *forward heart failure/ or *high output heart failure/ or *systolic dysfunction/
21.	*congestive cardiomyopathy/ or exp *congestive heart failure/
22.	exp *heart ventricle failure/
23.	((heart or cardiac or myocardial) adj2 (failure or decompensation)).ti.
24.	((congestive or acute or decompensat* or chronic) adj2 "heart failure").ti,ab.
25.	((dilated or congestive) adj2 cardiomyopath*).ti.
26.	"cardiogenic shock".ti.
27.	((ventricular or ventricle*) adj2 (failure or insufficien* or dysfunction*)).ti.
28.	(("left ventricular" or "left ventricle") adj2 (failure or insufficien* or dysfunction*)).ti,ab.
29.	lvsd.ti,ab.
30.	or/20-29
31.	exp troponin/
32.	exp echocardiography/
33.	exp nuclear magnetic resonance imaging/
34.	or/31-33

35.	monitoring/
36.	"disease course"/
37.	"symptom"/
38.	"pathophysiology"/
39.	patient monitoring/
40.	biological monitoring/
41.	hemodynamic monitoring/
42.	or/35-41
43.	34 and 42
44.	((troponin or echo* or doppler* or mri* or nmr* or magnetic resonance) adj5 (guide* or monitor* or target* or marker* or biomarker*)).ti,ab.
45.	((troponin or echo* or doppler* or mri* or nmr* or magnetic resonance) adj5 (repeat* or retest* or serial or series)).ti,ab.
46.	((troponin or echo* or doppler* or mri* or nmr* or magnetic resonance) adj5 (manag* or tailor* or therap* or strateg* or treat*)).ti,ab.
47.	((cmr or ((cardiac or cardiovascular) adj mr)) adj5 (guide* or monitor* or target* or marker* or biomarker*)).ti,ab.
48.	((cmr or ((cardiac or cardiovascular) adj mr)) adj5 (repeat* or retest* or serial or series)).ti,ab.
49.	((cmr or ((cardiac or cardiovascular) adj mr)) adj5 (manag* or tailor* or therap* or strateg* or treat*)).ti,ab.
50.	((bnp or probnp or ntprobnp or natriuretic peptide or natriuretic propeptide) adj5 (repeat* or treat* or marker* or biomarker*)).ti,ab.
51.	or/43-50
52.	30 and 51
53.	Excluded study designs and publication types [N.3.1]
54.	52 not 53
55.	Limit 54 to English language
56.	Study filters RCT [N.3.2] or SR [N.3.3]
57.	55 and 56
58.	18 and 30
59.	58 not 19
60.	59 not 53
61.	61 and 56
62.	57 or 61
	Date limits: 1974 – 6 December 2017

1 **Cochrane search terms**

#1.	MeSH descriptor: [heart failure] explode all trees
#2.	heart failure:ti,ab
#3.	cardiac failure:ti,ab
#4.	#1 or #2 or #3
#5.	MeSH descriptor: [natriuretic peptide, brain] this term only
#6.	((bnp or probnp or ntprobnp or natriuretic next peptide or natriuretic next propeptide) near/5 (guide* or monitor* or target*)):ti,ab
#7.	((bnp or probnp or ntprobnp or natriuretic next peptide or natriuretic next propeptide) near/5 (retest* or serial or series)):ti,ab
#8.	((bnp or probnp or ntprobnp or natriuretic next peptide or natriuretic next propeptide) near/5

	(manag* or tailor* or therap* or strateg*)):ti,ab
#9.	(ntprobnp or "natriuretic peptide" or "natriuretic propeptide" or bnp or probnp):ti
#10.	(#5 or #6 or #7 or #8 or #9)
#11.	#4 and #10
#12.	#4 and #10
#13.	MeSH descriptor: [heart failure] explode all trees
#14.	MeSH descriptor: [cardiomyopathy, dilated] this term only
#15.	MeSH descriptor: [shock, cardiogenic] this term only
#16.	MeSH descriptor: [ventricular dysfunction] explode all trees
#17.	MeSH descriptor: [cardiac output, low] this term only
#18.	(heart or cardiac or myocardial) next (failure or decompensation):ti
#19.	((congestive or chronic) next ("heart failure")):ti,ab
#20.	((dilated or congestive) next cardiomyopath*):ti
#21.	("cardiogenic shock"):ti
#22.	((ventricular or ventricle) next (failure or insufficienc* or dysfunction*)):ti
#23.	lvsd:ti,ab
#24.	(("left ventricular" or "left ventricle") next (failure or insufficienc* or dysfunction*)):ti,ab
#25.	(#13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24)
#26.	MeSH descriptor: [troponin] explode all trees
#27.	MeSH descriptor: [echocardiography] explode all trees
#28.	MeSH descriptor: [magnetic resonance imaging] this term only
#29.	#27 or #28
#30.	MeSH descriptor: [monitoring, physiologic] this term only
#31.	MeSH descriptor: [health status indicators] this term only
#32.	#30 or #31
#33.	#29 and #32
#34.	((troponin or echo* or doppler* or mri* or nmr* or magnetic resonance) near/5 (guide* or monitor* or target* or marker* or biomarker*)):ti,ab
#35.	((troponin or echo* or doppler* or mri* or nmr* or magnetic resonance) near/5 (repeat* or retest* or serial or series)):ti,ab
#36.	((troponin or echo* or doppler* or mri* or nmr* or magnetic resonance) near/5 (manag* or tailor* or therap* or strateg* or treat*)):ti,ab
#37.	((cmr or ((cardiac or cardiovascular) next mr)) near/5 (guide* or monitor* or target* or marker* or biomarker*)):ti,ab
#38.	((cmr or ((cardiac or cardiovascular) next mr)) near/5 (repeat* or retest* or serial or series)):ti,ab
#39.	((cmr or ((cardiac or cardiovascular) next mr)) near/5 (manag* or tailor* or therap* or strateg* or treat*)):ti,ab
#40.	((bnp or probnp or ntprobnp or natriuretic peptide or natriuretic propeptide) near/5 (repeat* or treat* or marker* or biomarker*)):ti,ab
#41.	troponin:ti
#42.	#26 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41
#43.	#25 and #42
#44.	#10 and #25
#45.	#44 not #11
	Date limits: Inception – 6 December 2017

N.4.12 Mineralcorticoid receptor antagonists

Searches for the following 2 searches were run as one search:

- What is the clinical and cost effectiveness of mineralocorticoid receptor antagonists in people with heart failure with preserved ejection fraction?
- What is the clinical and cost effectiveness of adding a mineralocorticoid receptor antagonist to existing standard first line treatment in people with heart failure with reduced ejection fraction?

Medline search terms

1.	Standard population [N.2.1]
2.	Excluded study designs and publication types [N.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	mineralocorticoid receptor antagonists/
6.	(aldosterone adj2 antagonist*).ti,ab.
7.	spironolactone/
8.	(spironolactone or eplerenone).mp.
9.	(inspra or aldactone).ti,ab.
10.	(aldo or aldos).ti,ab.
11.	or/5-10
12.	Study filters RCT[N.3.2] or SR [N.3.3]
13.	4 and 11 and 12
	Date limits: 2009 – 6 December 2017

Embase search terms

1.	Standard population [N.2.1]
2.	Excluded study designs and publication types [N.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	aldosterone antagonist/
6.	(aldosterone adj2 antagonist*).ti,ab.
7.	eplerenone/ or spironolactone/
8.	(spironolactone or eplerenone).mp.
9.	(inspra or aldactone).ti,ab.
10.	(aldo or aldos).ti,ab.
11.	or/5-10
12.	Study filters RCT [N.3.2] or SR [N.3.3]
13.	4 and 11 and 12
	Date limits: 2009 – 6 December 2017

Cochrane search terms

#1.	Standard population [N.2.1]
#2.	MeSH descriptor: [mineralocorticoid receptor antagonists] explode all trees
#3.	(aldosterone next antagonist*):ti,ab
#4.	(spironolactone or eplerenone or aldactone or inspra):ti,ab
#5.	(aldo or aldos):ti,ab
#6.	(or #2-#5)

#7.	#1 and #6
	Date limits: 2009 – 6 December 2017

N.4.13 Pharma in Chronic kidney disease

- What is the clinical and cost effectiveness of pharmaceutical interventions for heart failure in people with heart failure that also have chronic kidney disease?

Medline search terms

1.	Standard population [N.2.1]
2.	Excluded study designs and publication types [N.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	exp kidney failure, chronic/
6.	renal insufficiency, chronic/
7.	kidney diseases/ and chronic.ti,ab.
8.	((chronic or progressive) adj3 (renal or kidney*)).ti,ab.
9.	ckd.ti,ab.
10.	((renal or kidney*) adj3 (insufficienc* or disease*)).ti,ab.
11.	((renal or kidney*) adj3 (function* or failure* or dysfunction*)).ti,ab.
12.	glomerular filtration rate/
13.	(glomerul* filtration rate* or gfr).ti,ab.
14.	diabetic neuropathies/
15.	exp glomerulonephritis/
16.	exp proteinuria/
17.	(glomerulosclerosis or glomerulonephritis or nephropath* or proteinuria* or albuminuria or microalbuminuria).ti,ab.
18.	(glomerular adj (sclerosis or nephritis)).ti,ab.
19.	acidosis, renal tubular/
20.	((renal or kidney* or distal or proximal or tubul*) adj3 acidos*).ti,ab.
21.	exp hypertension, renal/
22.	((renal or kidney* or renovascular) adj3 hypertensi*).ti,ab.
23.	exp hyperparathyroidism, secondary/
24.	((renal or kidney* or secondary) adj3 hyperparathyroidism).ti,ab.
25.	hyperuricemia/
26.	hyperuric?emi*.ti,ab.
27.	((renal or kidney*) adj3 osteo*).ti,ab.
28.	(or/5-27
29.	exp angiotensin-converting enzyme inhibitors/
30.	(("angiotensin-converting enzyme" or ace) adj2 (inhibitor* or antagonist*)).ti,ab.
31.	(captopril or cilazapril or enalapril or fosinopril or imidapril or lisinopril or moexipril or perindopril or quinapril or ramipril or trandolapril or transolapril).ti,ab.
32.	exp angiotensin-converting enzyme inhibitors/
33.	exp angiotensin receptor antagonists/
34.	(angiotensin adj3 receptor adj3 (antagonist* or blocker*)).ti,ab.
35.	(arb or arbs).ti,ab.
36.	(azilsartan or candesartan or eprosartan or irbesartan or losartan or olmesartan or telmisartan

	or valsartan).ti,ab.
37.	adrenergic beta-antagonists/ or adrenergic beta-1 receptor antagonists/
38.	bisoprolol/
39.	metoprolol/
40.	nebivolol/
41.	(carvedilol or metoprolol or bisoprolol or nebivolol).mp.
42.	(beta* adj3 (blockade or blocker* or blocking or antagonist*)).ti,ab.
43.	((beta-adrenoceptor or b-adrenoceptor or beta-adrenergic) adj3 (blockade or blocker* or blocking or antagonist*)).ti,ab.
44.	mineralocorticoid receptor antagonists/
45.	(aldosterone adj2 antagonist*).ti,ab.
46.	spironolactone/
47.	(spironolactone or eplerenone).mp.
48.	(inspra or aldactone).ti,ab.
49.	(aldo or aldos).ti,ab.
50.	exp digoxin/
51.	digoxin.mp.
52.	diuretics/
53.	diuretic*.mp.
54.	(bumetanide or co?amilo* or furosemide or torasemide).mp.
55.	(sacubitril adj3 valsartan).mp.
56.	exp isosorbide/
57.	exp hydralazine/
58.	(hydralazine adj3 (nitrate or dinitrate or mononitrate or isosorbide)).mp.
59.	ivabradine.mp.
60.	or/29-59
61.	4 and 28 and 60
62.	Study filters RCT [N.3.2] or SR [N.3.3]
63.	61 and 62
	Date limits: 1946 – 6 December 2017

1 **Embase search terms**

1.	Standard population [N.2.1]
2.	Excluded study designs and publication types [N.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	chronic kidney failure/
6.	chronic kidney disease/
7.	(kidney failure/ or kidney disease/) and chronic.ti,ab.
8.	((chronic or progressive) adj3 (renal or kidney*)).ti,ab.
9.	ckd.ti,ab.
10.	((renal or kidney*) adj3 (insufficienc* or disease*)).ti,ab.
11.	((renal or kidney*) adj3 (function* or failure* or dysfunction*)).ti,ab.
12.	glomerulus filtration rate/
13.	(glomerul* filtration rate* or gfr).ti,ab.
14.	diabetic neuropathy/

15.	exp glomerulonephritis/
16.	exp proteinuria/
17.	(glomerulosclerosis or glomerulonephritis or nephropath* or proteinuria* or albuminuria or microalbuminuria).ti,ab.
18.	(glomerular adj (sclerosis or nephritis)).ti,ab.
19.	kidney tubule acidosis/
20.	((renal or kidney* or distal or proximal or tubul*) adj3 acidos*).ti,ab.
21.	exp renovascular hypertension/
22.	((renal or kidney* or renovascular) adj3 hypertensi*).ti,ab.
23.	hyperuricemia/
24.	hyperuric?emi*.ti,ab.
25.	secondary hyperparathyroidism/
26.	((renal or kidney* or secondary) adj3 hyperparathyroidism).ti,ab.
27.	renal osteodystrophy/
28.	((renal or kidney*) adj3 osteo*).ti,ab.
29.	(or/5-28
30.	exp *dipeptidyl carboxypeptidase inhibitor/
31.	(("angiotensin-converting enzyme" or ace) adj2 (inhibitor* or antagonist*)).ti,ab.
32.	(captopril or cilazapril or enalapril or fosinopril or imidapril or lisinopril or moexipril or perindopril or quinapril or ramipril or trandolapril or transolapril).ti,ab.
33.	exp *angiotensin receptor antagonist/
34.	(angiotensin adj3 receptor adj3 (antagonist* or blocker*)).ti,ab.
35.	(arb or arbs).ti,ab.
36.	(azilsartan or candesartan or eprosartan or irbesartan or losartan or olmesartan or telmisartan or valsartan).ti,ab.
37.	*beta adrenergic receptor blocking agent/ or *beta 1 adrenergic receptor blocking agent/
38.	*bisoprolol/ or *bisoprolol fumarate/ or *bisoprolol fumarate plus hydrochlorothiazide/ or *carvedilol/ or *metoprolol/ or *metoprolol fumarate/ or *metoprolol succinate/ or *metoprolol tartrate/ or *nebivolol/
39.	(carvedilol or metoprolol or bisoprolol or nebivolol).mp.
40.	((beta-adrenoceptor or b-adrenoceptor or beta-adrenergic) adj3 (blockade or blocker* or blocking or antagonist*)).ti,ab.
41.	(beta* adj3 (blockade or blocker* or blocking or antagonist*)).ti,ab.
42.	*aldosterone antagonist/
43.	*eplerenone/ or *spironolactone/
44.	(aldosterone adj2 antagonist*).ti,ab.
45.	(spironolactone or eplerenone or inspra or aldactone).mp.
46.	(aldo or aldos).ti,ab.
47.	*digoxin/
48.	digoxin.mp.
49.	*diuretic agent/ or exp *loop diuretic agent/
50.	*amiloride plus furosemide/ or *bumetanide/ or *furosemide/ or *torasemide/
51.	(bumetanide or co?amilo* or furosemide or torasemide).mp.
52.	*sacubitril/ or *sacubitril plus valsartan/
53.	(sacubitril adj3 valsartan).mp.
54.	*hydralazine plus isosorbide dinitrate/

55.	(hydralazine adj3 (nitrate or dinitrate or mononitrate or isosorbide)).mp.
56.	*ivabradine/
57.	ivabradine.mp.
58.	or/30-57
59.	4 and 29 and 58
60.	Study filters RCT [N.3.2] or SR [N.3.3]
61.	59 and 60
	Date limits: 1974 – 6 December 2017

Cochrane search terms

#1.	Standard population [N.2.1]
#2.	MeSH descriptor: [renal insufficiency, chronic] this term only
#3.	MeSH descriptor: [kidney failure, chronic] explode all trees
#4.	MeSH descriptor: [kidney diseases] this term only
#5.	chronic:ti,ab
#6.	#4 and #5
#7.	((chronic or progressive) near/3 (renal or kidney)):ti,ab
#8.	ckd:ti,ab
#9.	((renal or kidney*) near/3 (insufficienc* or disease*)):ti,ab
#10.	((renal or kidney*) near/3 (function* or failure* or dysfunction*)):ti,ab
#11.	MeSH descriptor: [glomerular filtration rate] this term only
#12.	(glomerul* filtration rate* or gfr):ti,ab
#13.	MeSH descriptor: [diabetic neuropathies] this term only
#14.	MeSH descriptor: [glomerulonephritis] explode all trees
#15.	MeSH descriptor: [proteinuria] explode all trees
#16.	(glomerulosclerosis or glomerulonephritis or nephropath* or proteinuria* or albuminuria or microalbuminuria):ti,ab
#17.	(glomerular next (sclerosis or nephritis)):ti,ab
#18.	MeSH descriptor: [acidosis, renal tubular] this term only
#19.	((renal or kidney* or distal or proximal or tubul*) near/3 acidos*):ti,ab
#20.	MeSH descriptor: [hypertension, renal] explode all trees
#21.	((renal or kidney* or renovascular) near/3 hypertensi*):ti,ab
#22.	MeSH descriptor: [hyperparathyroidism, secondary] explode all trees
#23.	((renal or kidney* or secondary) near/3 hyperparathyroidism):ti,ab
#24.	MeSH descriptor: [hyperuricemia] this term only
#25.	hyperuric?emi*:ti,ab
#26.	((renal or kidney*) near/3 osteo*):ti,ab
#27.	#2 or #3 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26
#28.	#1 and #27
#29.	MeSH descriptor: [angiotensin-converting enzyme inhibitors] explode all trees
#30.	(angiotensin near/3 receptor near/3 (antagonist* or blocker*)):ti,ab
#31.	(captopril or cilazapril or enalapril or fosinopril or imidapril or lisinopril or moexipril or perindopril or quinapril or ramipril or trandolapril or transolapril):ti,ab
#32.	#29 or #30 or #31
#33.	MeSH descriptor: [angiotensin receptor antagonists] explode all trees

#34.	(angiotensin near/3 receptor near/3 (antagonist* or blocker*)):ti,ab
#35.	(arb or arbs):ti,ab
#36.	(azilsartan or candesartan or eprosartan or irbesartan or losartan or olmesartan or telmisartan or valsartan):ti,ab
#37.	#33 or #34 or #35 or #36
#38.	MeSH descriptor: [adrenergic beta-antagonists] this term only
#39.	MeSH descriptor: [adrenergic beta-1 receptor antagonists] this term only
#40.	MeSH descriptor: [bisoprolol] this term only
#41.	MeSH descriptor: [metoprolol] this term only
#42.	MeSH descriptor: [nebivolol] this term only
#43.	(carvedilol or metoprolol or bisoprolol or nebivolol):ti,ab
#44.	(beta* near/3 (blockade or blocker* or blocking or antagonist*)):ti,ab
#45.	((beta-adrenoceptor or b-adrenoceptor or beta-adrenergic) near/3 (blockade or blocker* or blocking or antagonist*)):ti,ab
#46.	#38 or #39 or #40 or #41 or #42 or #43 or #44 or #45
#47.	MeSH descriptor: [mineralocorticoid receptor antagonists] explode all trees
#48.	(aldosterone near/2 antagonist*):ti,ab
#49.	MeSH descriptor: [spironolactone] this term only
#50.	(spironolactone or eplerenone):ti,ab
#51.	(inspra or aldactone):ti,ab
#52.	(aldo or aldos):ti,ab
#53.	#47 or #48 or #49 or #50 or #51 or #52
#54.	MeSH descriptor: [digoxin] this term only
#55.	digoxin:ti,ab
#56.	#54 or #55
#57.	MeSH descriptor: [diuretics] this term only
#58.	diuretic*:ti,ab
#59.	(bumetanide or co?amilo* or furosemide or torasemide):ti,ab
#60.	#57 or #58 or #59
#61.	(sacubitril near/3 valsartan):ti,ab
#62.	MeSH descriptor: [isosorbide] explode all trees
#63.	MeSH descriptor: [hydralazine] explode all trees
#64.	#62 and #63
#65.	(hydralazine near/3 (nitrate or dinitrate or mononitrate or isosorbide)):ti,ab
#66.	#64 or #65
#67.	ivabradine:ti,ab
#68.	#43 or #37 or #46 or #53 or #56 or #60 or #61 or #66 or #67
#69.	#28 and #68
	Date limits: Inception – 6 December 2017

N.4.14 Referral risk tools

- In adults with heart failure, which validated risk tools best identify patients with heart failure who are at increased risk of mortality in the short term (up to 1 year)?

Medline search terms

1.	Standard population [N.2.1]

2.	Excluded study designs and publication types [N.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	seattle heart failure model.ti,ab.
6.	heart failure survival score*.ti,ab.
7.	acute decompensated heart failure national registry.ti,ab.
8.	heart failure risk calculator.ti,ab.
9.	maggic.ti,ab.
10.	(shocked adj predict*).ti,ab.
11.	heart failure risk score*.ti,ab.
12.	needs assessment tool progressive disease heart failure.ti,ab.
13.	nat-pd-hf.ti,ab.
14.	or/5-13
15.	("supportive and palliative indicators tool" or spict).ti,ab.
16.	(toronto adj3 risk).ti,ab.
17.	(surprise adj question*).ti,ab.
18.	four item risk.ti,ab.
19.	edmonton symptom assessment scale.ti,ab.
20.	palliative performance scale.ti,ab.
21.	risk readmission assessment tool.ti,ab.
22.	readmission risk score.ti,ab.
23.	(frankenstein* or saps* or apache* or encourage or adhere or pace).ti,ab.
24.	or/15-23
25.	4 and 24
26.	14 or 25
27.	((prognos* or predict* or risk*) adj4 (tool* or index or indices or indicat* or calculat* or score* or scoring or system* or criteria* or scale* or model* or stratif* or instrument*)).ti,ab.
28.	(decision adj2 (tool* or score or scoring or scale* or model*)).ti,ab.
29.	((score* or scoring) adj2 (tool* or system*)).ti,ab.
30.	or/27-29
31.	(palliat* or terminal* or dying* or eolc).ti,ab.
32.	(end adj2 life).ti,ab.
33.	((long term or longterm) adj2 (care* or caring or ill*)).ti,ab.
34.	(advance* adj2 (plan* or decision* or directive* or care or caring)).ti,ab.
35.	terminal care/ or palliative care/ or advance care planning/ or long-term care/
36.	or/31-35
37.	4 and 30 and 36
38.	26 or 37
39.	acute decompensated heart failure national registry.ti,ab.
40.	(maggic or "meta-analysis global group in chronic heart failure").ti,ab.
41.	(optimize-hf or "organized program to initiate lifesaving treatment in hospitalized patients with heart failure").ti,ab.
42.	(heartmate adj2 risk).ti,ab.
43.	(nat-pd-hf or "needs assessment tool progressive disease heart failure").ti,ab.
44.	("barcelona bio-heart failure risk calculator" or "bcn bio-hf calculator").ti,ab.

45.	((adhf or nt-probnp) adj3 (risk or score*)).ti,ab.
46.	("european collaboration on acute decompensated heart failure" or elan-hf).ti,ab.
47.	("biology study to tailored treatment in chronic heart failure" or biostat-chf).ti,ab.
48.	(hf-action or 3c-hf or "cvm-hf index" or i-preserve).ti,ab.
49.	or/39-48
50.	("supportive and palliative indicators tool" or spict).ti,ab.
51.	"gold standards framework prognostic indicator guide".ti,ab.
52.	("get with the guidelines" or gwtg).ti,ab.
53.	(toronto adj3 risk).ti,ab.
54.	(surprise adj question*).ti,ab.
55.	((four or "4") adj (item or variable) adj risk).ti,ab.
56.	"edmonton symptom assessment scale".ti,ab.
57.	"palliative performance scale".ti,ab.
58.	"risk readmission assessment tool".ti,ab.
59.	("resident assessment instrument" or rai-mds).ti,ab.
60.	"readmission risk score".ti,ab.
61.	"destination therapy risk score".ti,ab.
62.	(bardiche adj index).ti,ab.
63.	(acci or "adjusted charlson comorbidity index").ti,ab.
64.	(leitz-miller adj score*).ti,ab.
65.	(shocked adj predict*).ti,ab.
66.	(pace adj2 (risk or score*)).ti,ab.
67.	(abc adj3 score*).ti,ab.
68.	("muerte subita en insufi- ciencia cardiaca" or (music adj risk score*)).ti,ab.
69.	"association of health aging and body composition".ti,ab.
70.	("simplified acute physiology score" or saps).ti,ab.
71.	(("cardiopulmonary exercise test" or cpx) adj score*).ti,ab.
72.	(columbia adj (risk or score*)).ti,ab.
73.	("controlling nutritional status score*" or conut).ti,ab.
74.	("sequential organ failure assessment" or sofa).ti,ab.
75.	(congestion adj score*).ti,ab.
76.	penn hf study.ti,ab.
77.	("interagency registry for mechanically assisted circulatory support" or intermacs).ti,ab.
78.	((escape or frankenstein*) adj2 model).ti,ab.
79.	(charm adj (program* or model*)).ti,ab.
80.	("acute physiology and chronic health evaluation" or apache*).ti,ab.
81.	(dtrs or unicamp ii or phfs or everest or ahfrs or fhfrs or shfm or hfss).ti,ab.
82.	or/50-81
83.	4 and 82
84.	49 or 83
85.	((prognos* or predict* or risk*) adj4 (tool* or index or indices or indicat* or calculat* or score* or scoring or system* or criteria* or scale* or model* or stratif* or instrument*)).ti,ab.
86.	(decision adj2 (tool* or score or scoring or scale* or model*)).ti,ab.
87.	((score* or scoring) adj2 (tool* or system*)).ti,ab.
88.	((heart failure or hf) adj4 (score* or scoring or model* or calculator* or index*)).ti,ab.

89.	or/85-88
90.	validat*.ti,ab.
91.	4 and 89 and 90
92.	84 or 91
93.	38 or 92
	Date limits: 1946 - 14 August 2017

Embase search terms

1.	Standard population [N.2.1]
2.	Excluded study designs and publication types [N.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	seattle heart failure model.ti,ab.
6.	heart failure survival score*.ti,ab.
7.	acute decompensated heart failure national registry.ti,ab.
8.	heart failure risk calculator.ti,ab.
9.	maggic.ti,ab.
10.	(shocked adj predict*).ti,ab.
11.	heart failure risk score*.ti,ab.
12.	needs assessment tool progressive disease heart failure.ti,ab.
13.	nat-pd-hf.ti,ab.
14.	or/5-13
15.	("supportive and palliative indicators tool" or spict).ti,ab.
16.	(toronto adj3 risk).ti,ab.
17.	(surprise adj question*).ti,ab.
18.	four item risk.ti,ab.
19.	edmonton symptom assessment scale.ti,ab.
20.	palliative performance scale.ti,ab.
21.	risk readmission assessment tool.ti,ab.
22.	readmission risk score.ti,ab.
23.	(frankenstein* or saps* or apache* or encourage or adhere or pace).ti,ab.
24.	or/15-23
25.	4 and 24
26.	25 or 14
27.	((prognos* or predict* or risk*) adj4 (tool* or index or indices or indicat* or calculat* or score* or scoring or system* or criteria* or scale* or model* or stratif* or instrument*)).ti,ab.
28.	(decision adj2 (tool* or score or scoring or scale* or model*)).ti,ab.
29.	((score* or scoring) adj2 (tool* or system*)).ti,ab.
30.	or/27-29
31.	(palliat* or terminal* or dying* or eolc).ti,ab.
32.	(end adj2 life).ti,ab.
33.	((long term or longterm) adj2 (care* or caring or ill*)).ti,ab.
34.	(advance* adj2 (plan* or decision* or directive* or care or caring)).ti,ab.
35.	terminal care/ or advance care planning/ or palliative therapy/ or long term care/
36.	or/31-35
37.	4 and 30 and 36

38.	26 or 37
39.	acute decompensated heart failure national registry.ti,ab.
40.	(maggic or "meta-analysis global group in chronic heart failure").ti,ab.
41.	(optimize-hf or "organized program to initiate lifesaving treatment in hospitalized patients with heart failure").ti,ab.
42.	(heartmate adj2 risk).ti,ab.
43.	(nat-pd-hf or "needs assessment tool progressive disease heart failure").ti,ab.
44.	("barcelona bio-heart failure risk calculator" or "bcn bio-hf calculator").ti,ab.
45.	((adhf or nt-probnp) adj3 (risk or score*)).ti,ab.
46.	("european collaboration on acute decompensated heart failure" or elan-hf).ti,ab.
47.	("biology study to tailored treatment in chronic heart failure" or biostat-chf).ti,ab.
48.	(hf-action or 3c-hf or "cvm-hf index" or i-preserve).ti,ab.
49.	or/39-48
50.	("supportive and palliative indicators tool" or spict).ti,ab.
51.	"gold standards framework prognostic indicator guide".ti,ab.
52.	("get with the guidelines" or gwtg).ti,ab.
53.	(toronto adj3 risk).ti,ab.
54.	(surprise adj question*).ti,ab.
55.	((four or "4") adj (item or variable) adj risk).ti,ab.
56.	"edmonton symptom assessment scale".ti,ab.
57.	"palliative performance scale".ti,ab.
58.	"risk readmission assessment tool".ti,ab.
59.	("resident assessment instrument" or rai-mds).ti,ab.
60.	"readmission risk score".ti,ab.
61.	"destination therapy risk score".ti,ab.
62.	(bardiche adj index).ti,ab.
63.	(acci or "adjusted charlson comorbidity index").ti,ab.
64.	(leitz-miller adj score*).ti,ab.
65.	(shocked adj predict*).ti,ab.
66.	(pace adj2 (risk or score*)).ti,ab.
67.	(abc adj3 score*).ti,ab.
68.	("muerte subita en insufi- ciencia cardiaca" or (music adj risk score*)).ti,ab.
69.	"association of health aging and body composition".ti,ab.
70.	("simplified acute physiology score" or saps).ti,ab.
71.	(("cardiopulmonary exercise test" or cpx) adj score*).ti,ab.
72.	(columbia adj (risk or score*)).ti,ab.
73.	("controlling nutritional status score*" or conut).ti,ab.
74.	("sequential organ failure assessment" or sofa).ti,ab.
75.	(congestion adj score*).ti,ab.
76.	penn hf study.ti,ab.
77.	("interagency registry for mechanically assisted circulatory support" or intermacs).ti,ab.
78.	((escape or frankenstein*) adj2 model).ti,ab.
79.	(charm adj (program* or model*)).ti,ab.
80.	("acute physiology and chronic health evaluation" or apache*).ti,ab.
81.	(dtrs or unicamp ii or phfs or everest or ahfrs or fhfrs or shfm or hfss).ti,ab.

82.	or/50-81
83.	4 and 82
84.	49 or 83
85.	((prognos* or predict* or risk*) adj4 (tool* or index or indices or indicat* or calculat* or score* or scoring or system* or criteria* or scale* or model* or stratif* or instrument*)).ti,ab.
86.	((heart failure or hf) adj4 (score* or scoring or model* or calculator* or index*)).ti,ab.
87.	(decision adj2 (tool* or score or scoring or scale* or model*)).ti,ab.
88.	((score* or scoring) adj2 (tool* or system*)).ti,ab.
89.	or/85-88
90.	validat*.ti,ab.
91.	4 and 89 and 90
92.	84 or 91
93.	38 or 92
	Date limits: 1974 - 14 August 2017

1 **Cochrane search terms**

#1.	Standard population [N.2.1]
#2.	"seattle heart failure model":ti,ab
#3.	("heart failure survival score" or "heart failure survival scores"):ti,ab
#4.	"acute decompensated heart failure national registry":ti,ab
#5.	"heart failure risk calculator":ti,ab
#6.	maggic:ti,ab
#7.	(shocked next predict*):ti,ab
#8.	("heart failure risk score" or "heart failure risk scores"):ti,ab
#9.	"needs assessment tool progressive disease heart failure":ti,ab
#10.	nat-pd-hf:ti,ab
#11.	(or #2-#10)
#12.	"supportive and palliative indicators tool":ti,ab
#13.	(toronto near/3 risk):ti,ab
#14.	(surprise next question*):ti,ab
#15.	"four item risk":ti,ab
#16.	"edmonton symptom assessment scale":ti,ab
#17.	"palliative performance scale":ti,ab
#18.	"risk readmission assessment tool":ti,ab
#19.	"readmission risk score":ti,ab
#20.	(frankenstein* or saps* or apache* or encourage or adhere or pace or spict):ti,ab
#21.	(or #12-#20)
#22.	#1 and #21
#23.	((prognos* or predict* or risk*) near/4 (tool* or index or indices or indicat* or calculat* or score* or scoring or system* or criteria* or scale* or model* or stratif* or instrument*)):ti,ab
#24.	(decision near/2 (tool* or score or scoring or scale* or model*)):ti,ab
#25.	((score* or scoring) near/2 (tool* or system*)):ti,ab
#26.	(or #23-#25)
#27.	(palliat* or terminal* or dying* or eolc):ti,ab
#28.	(end near/2 life):ti,ab
#29.	((long term or long-term or longterm) near/2 (care* or caring or ill*)):ti,ab

#30.	(advance* near/2 (plan* or decision* or directive* or care or caring)):ti,ab
#31.	[mh ^"terminal care"]
#32.	[mh ^"palliative care"]
#33.	[mh ^"advance care planning"]
#34.	[mh ^"long-term care"]
#35.	(or #27-#34)
#36.	#1 and #26 and #35
#37.	#11 or #22 or #36
#38.	acute decompensated heart failure national registry:ti,ab
#39.	(maggic or "meta-analysis global group in chronic heart failure"):ti,ab
#40.	(("optimize-hf") or "organized program to initiate lifesaving treatment in hospitalized patients with heart failure"):ti,ab
#41.	(heartmate near/2 risk):ti,ab
#42.	("nat-pd-hf" or "needs assessment tool progressive disease heart failure"):ti,ab
#43.	("barcelona bio-heart failure risk calculator" or "bcn bio-hf calculator"):ti,ab
#44.	((adhf or "nt-probnp") near/3 (risk or score*)):ti,ab
#45.	("european collaboration on acute decompensated heart failure" or "elan-hf"):ti,ab
#46.	("biology study to tailored treatment in chronic heart failure" or "biostat-chf"):ti,ab
#47.	("hf-action" or "3c-hf" or "cvm-hf index" or "i-preserve"):ti,ab
#48.	(or #38-#47)
#49.	("supportive and palliative indicators tool" or spict):ti,ab
#50.	gold standards framework prognostic indicator guide:ti,ab
#51.	("get with the guidelines" or gwtg):ti,ab
#52.	(toronto near/3 risk):ti,ab
#53.	(surprise next question*):ti,ab
#54.	((four or "4") next (item or variable) next risk):ti,ab
#55.	edmonton symptom assessment scale:ti,ab
#56.	palliative performance scale:ti,ab
#57.	risk readmission assessment tool:ti,ab
#58.	("resident assessment instrument" or "rai-mds"):ti,ab
#59.	readmission risk score:ti,ab
#60.	destination therapy risk score:ti,ab
#61.	(bardiche next index):ti,ab
#62.	(acci or "adjusted charlson comorbidity index"):ti,ab
#63.	(leitz-miller next score*):ti,ab
#64.	(shocked next predict*):ti,ab
#65.	(pace near/2 (risk or score*)):ti,ab
#66.	(abc near/3 score*):ti,ab
#67.	("muerte subita en insufi- ciencia cardiaca" or (music next risk score*)):ti,ab
#68.	association of health aging and body composition:ti,ab
#69.	("simplified acute physiology score" or saps):ti,ab
#70.	(("cardiopulmonary exercise test" or cpx) next score*):ti,ab
#71.	(columbia next (risk or score*)):ti,ab
#72.	("controlling nutritional status score*" or conut):ti,ab
#73.	("sequential organ failure assessment" or sofa):ti,ab

#74.	(congestion next score*):ti,ab
#75.	penn hf study:ti,ab
#76.	("interagency registry for mechanically assisted circulatory support" or intermacs):ti,ab
#77.	((escape or frankenstein*) near/2 model):ti,ab
#78.	(charm next (program* or model*)):ti,ab
#79.	("acute physiology and chronic health evaluation" or apache*):ti,ab
#80.	(dtrs or "unicamp ii" or phfs or everest or ahfrs or fhfrs or shfm or hfss):ti,ab
#81.	(or #49-#80)
#82.	#1 and #81
#83.	#48 or #82
#84.	((prognos* or predict* or risk*) near/4 (tool* or index or indices or indicat* or calculat* or score* or scoring or system* or criteria* or scale* or model* or stratif* or instrument*)):ti,ab
#85.	(decision near/2 (tool* or score or scoring or scale* or model*)):ti,ab
#86.	((score* or scoring) near/2 (tool* or system*)):ti,ab
#87.	((heart failure or hf) near/4 (score* or scoring or model* or calculator* or index*)):ti,ab
#88.	(or #84-#87)
#89.	validat*:ti,ab
#90.	#1 and #88 and #89
#91.	#83 or #90
#92.	#37 or #91
	Date limits: Inception - 14 August 2017

N.4.15 Salt and Fluid

- What is the clinical and cost effectiveness of salt and/or fluid restriction in people with heart failure?

Medline search terms

1.	Standard population [N.2.1]
2.	Excluded study designs and publication types [N.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	diet, sodium-restricted/
6.	exp sodium, dietary/
7.	((salt or sodium) adj3 (restrict* or intake or low or diet* or free)).ti,ab.
8.	((fluid* or liquid* or water) adj3 (intake or restrict*)).ti,ab.
9.	(diet* adj2 program*).ti,ab.
10.	or/5-9
11.	Study filters RCT [N.3.2] or SR [N.3.3]
12.	4 and 10 and 11
	Date limits: 1946 – 6 December 2017

Embase search terms

1.	Standard population [N.2.1]
2.	Excluded study designs and publication types [N.3.1]
3.	1 not 2
4.	Limit 3 to English language

5.	sodium restriction/
6.	fluid intake/
7.	sodium intake/
8.	((salt or sodium) adj3 (restrict* or intake or low or diet* or free)).ti,ab.
9.	((fluid* or liquid* or water) adj3 (intake or restrict*)).ti,ab.
10.	(diet* adj2 program*).ti,ab.
11.	or/5-10
12.	Study filters RCT [N.3.2] or SR [N.3.3]
13.	4 and 11 and 12
	Date limits: 1974 – 6 December 2017

Cochrane search terms

#1.	Standard population [N.2.1]
#2.	[mh ^"diet, sodium-restricted"]
#3.	[mh "sodium, dietary"]
#4.	((salt or sodium) near/3 (restrict* or intake or low or diet* or free)):ti,ab
#5.	((fluid* or liquid* or water) near/3 (intake or restrict*)):ti,ab
#6.	(diet* near/2 program*):ti,ab
#7.	(or #2-#6)
#8.	#1 and #7
	Date limits: Inception – 6 December 2017

N.4.16 Telemonitoring

- What is the clinical and cost effectiveness of telemonitoring and self-monitoring using telephone technology, compared with usual care, in people with heart failure?

Medline search terms

1.	exp heart failure/
2.	((heart or cardiac or myocard*) adj2 (fail* or insufficien* or decomp*)).tw.
3.	1 or 2
4.	exp telemedicine/
5.	exp telecommunications/
6.	case management/
7.	exp comprehensive health care/
8.	disease management/
9.	tele med*.tw.
10.	telecare*.tw.
11.	telecardiol*.tw.
12.	telemonitor*.tw.
13.	teleconsult*.tw.
14.	teleconferenc*.tw.
15.	telecommunicat*.tw.
16.	telephon*.tw.
17.	telehealth*.tw.
18.	telemetry.tw.
19.	(remote* adj3 consult*).tw.

20.	tele-med*.tw.
21.	tele-consult*.tw.
22.	tele-conferenc*.tw.
23.	tele-health*.tw.
24.	home care services/
25.	home care services, hospital-based/
26.	disease management.tw.
27.	nurse clinicians/
28.	nurse practitioners/
29.	nurse led.tw.
30.	monitoring, ambulatory/
31.	telehome.tw.
32.	tele-home.tw.
33.	phone*.tw.
34.	clinical protocols/
35.	patient care planning/
36.	telefon*.tw.
37.	telemed*.tw.
38.	ehealth.tw.
39.	mobile health.tw.
40.	((remote* or distan*) adj2 (care or caring or monitor* or program* or help or support*)).tw.
41.	or/4-40
42.	3 and 41
43.	Excluded study designs and publication types [N.3.1]
44.	42 not 43
45.	Limit 44 to English language
46.	Study filters RCT [N.3.2] or SR [N.3.3]
47.	45 and 46
	Date limits: 2015 – 6 December 2017

Embase search terms

1.	exp heart failure/
2.	((heart or cardiac or myocard*) adj2 (fail* or insufficien* or decomp*)).tw.
3.	1 or 2
4.	exp telemedicine/
5.	exp telecommunications/
6.	case management/
7.	exp comprehensive health care/
8.	disease management/
9.	tele med*.tw.
10.	telecare*.tw.
11.	telecardiol*.tw.
12.	telemonitor*.tw.
13.	teleconsult*.tw.
14.	teleconferenc*.tw.

15.	telecommunicat*.tw.
16.	telephon*.tw.
17.	telehealth*.tw.
18.	telemetry.tw.
19.	(remote* adj3 consult*).tw.
20.	tele-med*.tw.
21.	tele-consult*.tw.
22.	tele-conferenc*.tw.
23.	tele-health*.tw.
24.	home care services/
25.	home care services, hospital-based/
26.	disease management.tw.
27.	nurse clinicians/
28.	nurse practitioners/
29.	nurse led.tw.
30.	monitoring, ambulatory/
31.	telehome.tw.
32.	tele-home.tw.
33.	phone*.tw.
34.	clinical protocols/
35.	patient care planning/
36.	telefon*.tw.
37.	telemed*.tw.
38.	ehealth.tw.
39.	mobile health.tw.
40.	((remote* or distan*) adj2 (care or caring or monitor* or program* or help or support*)).tw.
41.	or/4-40
42.	3 and 41
43.	Excluded study designs and publication types [N.3.1]
44.	42 not 43
45.	Limit 44 to English language
46.	Study filters RCT [N.3.2] or SR [N.3.3]
47.	45 and 46
	Date limits: 2015 – 6 December 2017

Cochrane search terms

#1.	MeSH descriptor: [heart failure] explode all trees
#2.	(heart or cardiac or myocard*) near/2 (fail* or insufficien* or decomp*)
#3.	#1 or #2
#4.	MeSH descriptor: [telemedicine] explode all trees
#5.	MeSH descriptor: [telecommunications] explode all trees
#6.	MeSH descriptor: [case management] this term only
#7.	MeSH descriptor: [comprehensive health care] explode all trees
#8.	MeSH descriptor: [disease management] this term only
#9.	MeSH descriptor: [home care services] this term only

#10.	MeSH descriptor: [home care services, hospital-based] this term only
#11.	MeSH descriptor: [nurse clinicians] this term only
#12.	MeSH descriptor: [nurse practitioners] this term only
#13.	MeSH descriptor: [monitoring, ambulatory] this term only
#14.	MeSH descriptor: [clinical protocols] this term only
#15.	MeSH descriptor: [patient care planning] this term only
#16.	tele*
#17.	(remote near/3 consult*)
#18.	disease next management
#19.	nurse next led
#20.	phone*
#21.	(manage* near/3 program*)
#22.	(nurse* near/3 manage*)
#23.	case next management
#24.	(home near/3 service*)
#25.	nurse next practitioner*
#26.	nurse next clinician*
#27.	care next plan*
#28.	ehealth
#29.	mobile next health
#30.	(remote* or distan*) near/2 (care or caring or monitor* or program* or help or support*)
#31.	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30
#32.	#3 and #31
	Date limits: 2015 – 6 December 2017

AMED search terms

1.	exp heart failure congestive/
2.	heart failure.tw.
3.	cardiac failure.tw.
4.	or/1-3
5.	exp telecommunications/
6.	exp comprehensive health care/
7.	disease management/
8.	telemed$.tw.
9.	telecare$.tw.
10.	telecardiol$.tw.
11.	telemonitor$.tw.
12.	teleconsult$.tw.
13.	teleconferenc$.tw.
14.	telecommunicat$.tw.
15.	telephon$.tw.
16.	telehealth$.tw.
17.	telemetry.tw.
18.	(remote$ adj3 consult$).tw.
19.	tele-med$.tw.

20.	tele-consult$.tw.
21.	tele-conferenc$.tw.
22.	tele-health$.tw.
23.	home care services/
24.	disease management.tw.
25.	nurse led.tw.
26.	telehome.tw.
27.	tele-home.tw.
28.	phone$.tw.
29.	clinical protocols/
30.	exp patient care management/
31.	nurses/
32.	rural health services/
33.	community health nursing/
34.	or/5-33
35.	4 and 34
36.	Limit 35 to English
	Date limits: 2015 – 6 December 2017

N.4.17 Transition

- What are the experiences/preferences of staff and patients during transition between different heart failure care settings (including primary, secondary and community care)?

Medline search terms

1.	Standard population [N.2.1]
2.	Excluded study designs and publication types [N.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	(transition* or transfer*).ti,ab.
6.	(referral* or referred or referring or refer or refers).ti,ab.
7.	discharge*.ti,ab.
8.	"referral and consultation"/
9.	*"continuity of patient care"/ or patient handoff/ or patient transfer/ or transitional care/ or patient discharge/
10.	((primary or secondary) adj3 (interface* or change*)).ti,ab.
11.	((care or caring or serv*) adj2 (continu* or change*)).ti,ab.
12.	or/5-11
13.	Study filter QUAL [N.3.8]
14.	4 and 12 and 13
	Date limits: 1946 – 4 January 2017

Embase search terms

1.	Standard population [N.2.1]
2.	Excluded study designs and publication types [N.3.1]
3.	1 not 2
4.	Limit 3 to English language

5.	(transition* or transfer*).ti,ab.
6.	(referral* or referred or referring or refer or refers).ti,ab.
7.	discharge*.ti,ab.
8.	((primary or secondary) adj3 (interface* or change*)).ti,ab.
9.	((care or caring or serv*) adj2 (continu* or change*)).ti,ab.
10.	hospital discharge/ or patient referral/ or clinical handover/ or transitional care/
11.	patient care/
12.	or/5-11
13.	Study filter QUAL [N.3.8]
14.	4 and 12 and 13
	Date limits: 1974 – 4 January 2017

PyscINFO search terms

S1.	if(("heart failure" or "cardiomyopathy, dilated" or "shock, cardiogenic" or "ventricular dysfunction" or "cardiac output, low")) or (su.exact.explode("heart") and su.exact.explode("failure")) or ti(((heart or cardiac or myocardial) near/2 (failure or decompensation))) or ti("cardiogenic shock") or ti(((dilated or congestive) n/2 cardiomyopath*)) or ti(((ventricular or ventricle*) n/2 (failure or insufficien* or dysfunction*))) or ti,ab((congestive or acute or decompensat* or chronic) near/2 "heart failure") or ti,ab(("left ventricular" or "left ventricle") near/2 (failure or insufficien* or dysfunction*)) or ti(lvsd) or ab(lvsd)
S2.	su.exact.explode("continuum of care") or (su.exact("professional referral") or su.exact("hospital discharge") or su.exact.explode("client transfer")) or ti,ab(transition* or transfer*) or ti,ab(referral* or referred or referring or refer or refers) or ti,ab(discharge*) or ti,ab((primary or secondary) near/3 (interface* or change*)) or ti,ab((care or caring or serv*) near/2 (continu* or change*))
S3.	((su.exact.explode("qualitative research") or su.exact("narratives") or su.exact.explode("questionnaires") or su.exact.explode("interviews") or su.exact.explode("health care services") or ti,ab(qualitative or interview* or focus group* or theme* or questionnaire* or survey*) or ti,ab(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* near/3 analys*) or theoretical-sampl* or purposive-sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*)))
S4.	S1 and S2 and S3
	Date limits: 1806 - 4 January 2017

CINAHL search terms

S1.	(MH "heart failure+")
S2.	(MH "cardiac output, decreased")
S3.	(MH "shock, cardiogenic")
S4.	(MH "ventricular dysfunction+")
S5.	ti heart n2 failure or ti heart n2 decompensation or ti cardiac n2 failure or ti cardiac n2 decompensation or ti myocardial n2 decompensation or ti myocardial n2 failure or tx congestive n2 "heart failure" or tx chronic n2 "heart failure" or ti dilated n2 cardiomyopath* or ti congestive n2 cardiomyopath* or ti cardiogenic n2 shock or tx lvsd
S6.	tx ventricular n2 failure or tx ventricular n2 dysfunction or tx ventricular n2 insufficiency or tx ventricle n2 failure or tx ventricle n2 dysfunction or tx ventricle n2 insufficiency
S7.	S1 or S2 or S3 or S4 or S5 or S6
S8.	ti ((transition* or transfer*)) or ab ((transition* or transfer*))

S9.	ti ((referral* or referred or referring or refer or refers)) or ab ((referral* or referred or referring or refer or refers))
S10.	ti discharge* or ab discharge*
S11.	ti ((primary or secondary)) and ti ((interface* or change*))
S12.	ab ((primary or secondary)) and ab ((interface* or change*))
S13.	ti ((care or caring or serv*)) and ti ((continu* or change*))
S14.	ab ((care or caring or serv*)) and ab ((continu* or change*))
S15.	MH continuity of patient care or MH patient discharge
S16.	MH "referral and consultation"
S17.	(MH "transfer, discharge")
S18.	(MH "hand off (patient safety)")
S19.	S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18
S20.	S7 and S19
S21.	Limit S20 to English language
	Date limits: Inception – 4 January 2017

N.5 Health economics search terms

N.5.1 Health economic (HE) reviews

Economic searches were conducted in Medline, Embase and the Centre for Research and Dissemination (CRD).

Medline & Embase search terms

1.	Standard population [N.2.1]
2.	Excluded study designs and publication types [N.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	Study filter HE [N.3.4]
6.	4 and 5
	Date parameters: 2009 – 06 December 2017

CRD search terms

#1.	Standard population [N.2.1]
	Date parameters: 2015 – 2017

N.5.2 Quality of life (QoL) reviews

Quality of life searches were conducted in Medline and Embase only

Medline & Embase search terms

1.	Standard population [N.2.1]
2.	Excluded study designs and publication types [N.3.1]
3.	1 not 2
4.	Limit 3 to English language
5.	Study filter QOL [N.3.5]
6.	4 and 5
	Date parameters: 2002 – 19 April 2016

Appendix O: Cost-effectiveness analysis: Thresholds model

O.1 Introduction

The priority for original economic analysis identified by the committee was to determine the most cost-effective diagnostic threshold when testing with natriuretic peptides (BNP or NT-proBNP) to refer for echocardiography and specialist clinical assessment.

People receive a natriuretic peptide test when it is suspected that they may have heart failure. If the level of natriuretic peptide is above the chosen threshold patients are referred for echocardiography and specialist clinical assessment to establish diagnosis of heart failure. If the level of natriuretic peptide is below the threshold they are not referred for echocardiography and specialist clinical assessment as it is considered that heart failure is unlikely and alternative diagnoses are investigated. Historically, the chosen thresholds (both NICE and European Society of Cardiology (ESC)[978]) were 100pg/ml (BNP) and 400pg/ml (NT-proBNP). However, in recent years the ESC has lowered the natriuretic peptide thresholds to 35pg/ml (BNP) 125pg/ml (NT-proBNP)[1164], due to concern that previously recommended thresholds were too high.

Given the ESC change, the committee discussed whether the threshold recommended in the 2010 Chronic Heart Failure (CHF) guideline may be too high, resulting in some patients with heart failure receiving a delayed diagnosis and either re-presenting to primary care at a later date with worsening symptoms or presenting to hospital due to a decompensation. Lowering the threshold could allow for earlier diagnosis and a better prognosis of these patients. However, the committee also noted that lowering the threshold may greatly increase cost to the NHS due to the greater number of referrals for echocardiography and specialist clinical assessment, many of which are unlikely to lead to a diagnosis of heart failure and therefore the diagnosis of other possible underlying conditions could be delayed.

There is limited previously published economic evidence comparing different thresholds. One recently published economic evaluation was identified in the literature[1012] which assesses the cost-effectiveness of

a) the diagnostic pathway as recommended in the 2010 CHF guideline (CG108) - patients with a history of myocardial infarction (MI) are referred straight for echocardiography, all other patients receive a NT-proBNP test and are referred for echocardiography at a threshold of 400pg/ml
b) Male, Infarction, Crepitations, Edema (MICE) clinical decision rule (as suggested by Mant et al. 2009[933] - patients are referred straight for echocardiography if the patient has a history of myocardial infarction; or basal crepitations; or ankle oedema in males. Otherwise an NT-proBNP test is carried out and patients are referred for echocardiography according to the following
    a. Female without ankle oedema: NT-proBNP > 620-1060pg/ml
    b. Female with ankle oedema: NT-proBNP > 190-520pg/ml
    c. Male without ankle oedema: NT-proBNP > 390-660pg/ml.
c) all patients receive an NT-proBNP test and are referred for echocardiography at a threshold of 125pg/ml.

This analysis was based on the diagnostic accuracy data reported in Taylor et al. 2016 identified in the clinical review[1365].

However, the committee considered this economic evaluation to have several limitations. Firstly, the analysis used diagnostic accuracy data where the level of NT-proBNP was used as a criterion in determining whether or not the patient had heart failure, therefore introducing incorporation bias to the diagnostic accuracy results. The committee were aware that the level of NT-proBNP is often used in practice to make a diagnosis of heart failure to demonstrate that symptoms of fluid retention or breathlessness are being triggered by a structural abnormality of the heart, but considered that when determining the diagnostic accuracy of a test in predicting whether the patient has heart failure this is not appropriate data to use. Secondly, the economic evaluation did not state the cost and QALY inputs or assumptions that were made for the model population that did not have heart failure.

The committee also discussed that a history of myocaridal infarction (MI) should no longer be a criterion for early echocardiography as the definition of MI has changed over time and now includes many scenarios that differ from what was included in the Mant et al. 2009 HTA which formed the basis of the recommendation in the 2010 guideline[933]. Therefore the comparators from this economc evaluation were not directly applicable. The committee therefore considered it important to undertake an original economic analysis to determine the most cost effective NT-proBNP threshold for referral for echocardiography and specialist clinical assessment.

O.2 Methods

O.2.1 Model overview

A cost-utility analysis was undertaken to determine the most cost effective level of natriuretic peptide to use as a threshold for referral from primary care for echocardiography and specialist clinical assessment. A decision tree with an attached Markov model was used to estimate lifetime quality-adjusted life years (QALYs) and costs from a current UK NHS and personal social services perspective (PSS). Waiting times for diagnostic imaging was also included in the model to account for the costs and effects of events occurring prior to final diagnosis due to waiting times, particularly for those who do not have heart failure, in which the true diagnosis is being delayed. In addition, the committee wished to explore the effects of the likely increase in waiting times for the lower thresholds due to increased volume of patients being referred for echocardiography, increasing the risk of hospitalisation prior to treatment, in sensitivity analyses. The analysis was conducted in accordance with the NICE reference case unless otherwise stated including discounting at 3.5% for costs and QALYs.

O.2.1.1 Population

The population entering the model are those presenting to primary care with signs and symptoms of heart failure, including breathlessness, fatigue or ankle swelling and upon clinical examination the general practioner (GP) suspects that the patient has heart failure.

The NICE 2010 Chronic Heart Failure guideline (CG108) recommendations state that patients with a previous history of MI should be referred for echocardiography without a natriuretic peptide test. However, as mentioned above, the committee decided that this was no longer appropriate.

People who first present to an acute emergency setting were excluded as this population is covered by the Acute Heart Failure guideline (CG187).

O.2.1.2 Comparators

Both BNP and NT-proBNP tests can be used to determine whether a patient should be referred for echocardiography. However, the committee excluded BNP testing from this analysis for the following reasons. Firstly, the clinical review suggests that NT-proBNP has a greater sensitivity over a range of thresholds compared to BNP. The committee emphasised the clinical importance of sensitivity over specificity as the test is used as a 'rule out' for heart failure. The committee primarily focused on the high quality studies from this review. The committee acknowledged the high sensitivity of BNP from a study conducted in 1997, but considered that the heart failure population has changed significantly since this study was conducted with a greater proportion of people with HF-PEF, which on a population level tend to have lower NT-proBNP levels than people with HF-REF . Therefore it is highly uncertain as to whether these results represent the diagnostic accuracy for BNP testing in current practice. Whereas, the majority of the high quality NT-proBNP studies are more recent studies and are more likely to be applicable to current practice. The committee acknowledged that comparing thresholds between BNP and NT-proBNP is inherently difficult as there is no conversion algorithm between them. However, the Zaphiriou study (high quality study assessing both BNP and NT-proBNP) assessed the recommended industry cut-offs for each test. When comparing this data, the committee noted that NT-proBNP thresholds have a consistently higher sensitivity than the BNP thresholds. Secondly, on a practical level and since the test will be requested mainly by primary care and be sent to the laboratories with inherent delay in transport, NTproBNP has a longer stability in blood samples than BNP (days vs 4-6 hours), therefore NTproBNP is more appropriate for testing in primary care. Thirdly, although it is unlikely at this stage for a patient not diagnosed with heart failure to be on Sacubitril Valsartan which interferes with BNP physiology (TA388), natriuretic peptides can also be used for monitoring heart failure patients, therefore it would be more useful to have NTproBNP as the baseline peptide in case monitoring was needed in a patient with heart failure who is subsequently treated with this new drug. Taking all of these considerations into account, the committee decided to only compare NT-proBNP thresholds in this analysis.

The following NT-proBNP thresholds were chosen as comparators:

- 400pg/ml – 2010 NICE recommended threshold and previous 2012 ESC threshold
- 125pg/ml – 2016 ESC threshold
- 280pg/ml – the optimal threshold found in one study included in clinical review[1442], and also lies close to the middle of the other two thresholds.

As a reference, a diagnostic strategy was also included where no NT-proBNP test is undertaken and all patients with suspected heart failure are referred for echocardiography plus specialist clinical assessment.

O.2.1.3 Time horizon

A lifetime horizon was chosen to fully capture the long-term costs and benefits derived from lowering the threshold and receiving an earlier heart failure diagnosis.

O.2.1.4 Deviations from NICE reference case

No deviations from the NICE reference case were taken.

O.2.2 Approach to modelling

The model is structured in two parts:

- A **decision tree** is used to calculate the proportion of the population that fall into one of a number of cohorts according to their underlying condition and test result. The decision tree calculates the proportion of patients who will receive a false negative (FN), false positive (FP), true negative (TN), or true positive (TP) NT-proBNP test result according to the sensitivity, specificity and prevalence data. Patients with a positive test result (levels above the chosen threshold) are then referred for echocardiography and specialist clinical assessment to determine if they have heart failure or not.

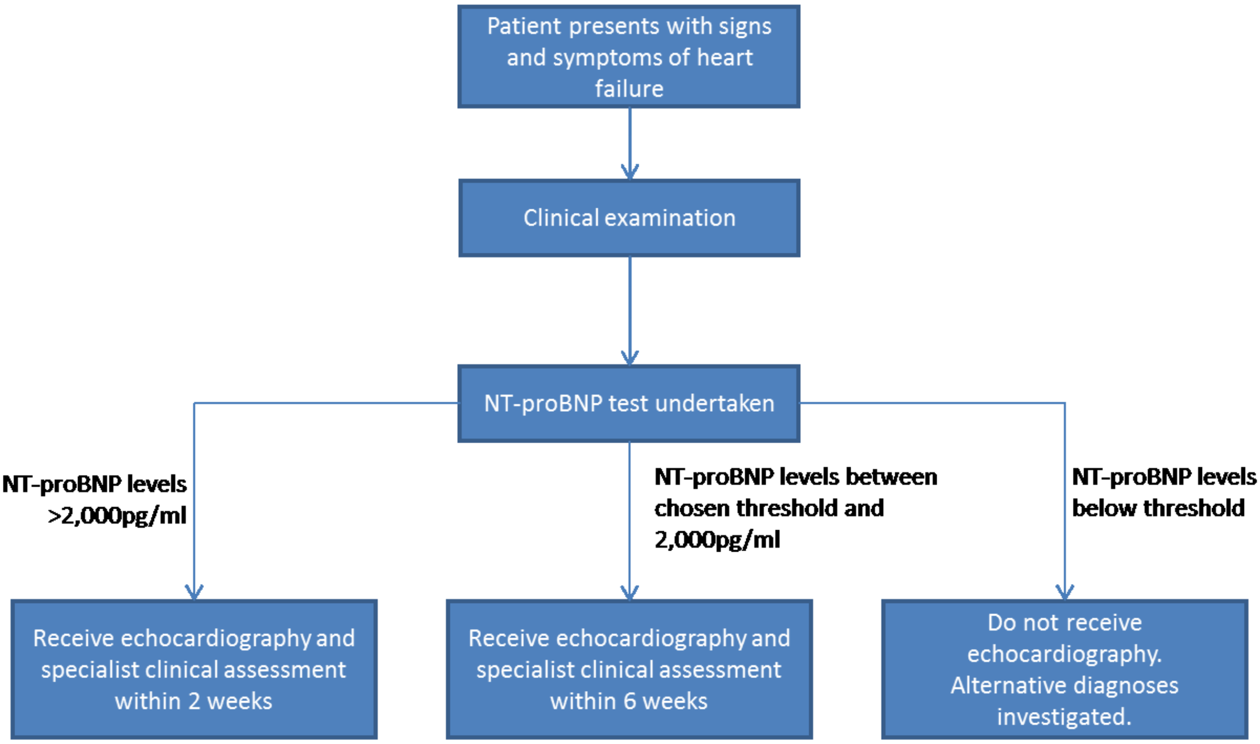
- A **Markov model** then evaluates patients' health and cost outcomes according to their cohort once the initial NT-proBNP test result is determined accounting for waiting times for diagnostic tests.

O.2.2.1 Model structure

<u>Diagnostic pathway decision tree</u>

The decision tree for the model is based on the following diagnostic pathway:

Figure 287: Diagnostic pathway in primary care



When patients enter the model a proportion will have heart failure as defined by the prevalence of heart failure in the population. The remaining population do not have heart failure, but could have an alternative condition. In reality patients with heart failure often have multiple comorbidities most notably atrial fibrillation and valvular diseases. Those latter conditions do raise the natriuretic peptides too, and require special management strategies over and above those demanded by the different types of heart failure which rely on the left ventricular ejection fraction for their classification. However, in order to simplify the model, the patients with heart failure in the modelled population are classified by ejection fraction (EF) alone as this will affect prognosis and possible treatment.

In patients with heart failure, the probability that the NT-proBNP test is positive (above the threshold) is determined by the test sensitivity. These patients receive a **true positive (TP)** test result and are referred for echocardiogram and specialist clinical assessment, and are diagnosed and treated for their heart failure. The committee considered that an echocardiogram plus specialist clinical assessment to be 100% accurate (see key assumptions below). The probability that the test is negative (below the threshold) in heart failure patients is determined by 1 – sensitivity. These patients receive a **false negative (FN)** test result and do not receive an echocardiogram and specialist clinical assessment, are not diagnosed and do not receive treatment for their heart failure.

In patients who do not have heart failure, the probability that the NT-proBNP test is negative is determined by the test specificity. These patients receive a **true negative (TN)** test result, do not receive an echocardiography and specialist clinical assessment but go on to be diagnosed and treated for their actual condition. The probability that the NT-proBNP test is positive in these patients is determined by 1 – specificity. These patients receive a **false positive (FP)** test result, are referred for echocardiography and specialist assessment, but are not diagnosed with heart failure. Some patients then have further investigations and diagnosis if necessary.

The literature suggests that the baseline NT-proBNP level of a patient at diagnosis is also a prognostic indicator for heart failure patients (both HF-REF and HF-PEF). In order to ensure the model reflects this, the committee wished to recognise the fact that although some patients with low NT-proBNP levels will have heart failure and initially be missed, the mortality and hospitalisation rates in these patients are likely to be lower than those with heart failure and high NT-proBNP levels. A UK study by Kubanek et al. 2009[807] was identified which assessed the differences in mortality and cardiovascular hospitalisation rates at different NT-proBNP levels of treated HF-REF patients split by quintiles. The lowest quintile in the study was defined by an NT-proBNP cut-off of <474pg/ml. The committee considered that there may also be a difference in mortality and morbidity below this level, however no data were identified that could be used to allow for this. Therefore, a pragmatic decision was made to use 400pg/ml as a cut-off to distinguish the difference in mortality and hospitalisation rates. Consequently, the decision tree divided the test cohorts (TP, FN, TN, FP) into those with NT-proBNP levels above and below 400pg/ml. The overall proportion of heart failure patients with NT-proBNP levels <400pg/ml could therefore be calculated from the diagnostic accuracy data of the 400pg/ml threshold (1- sensitivity).

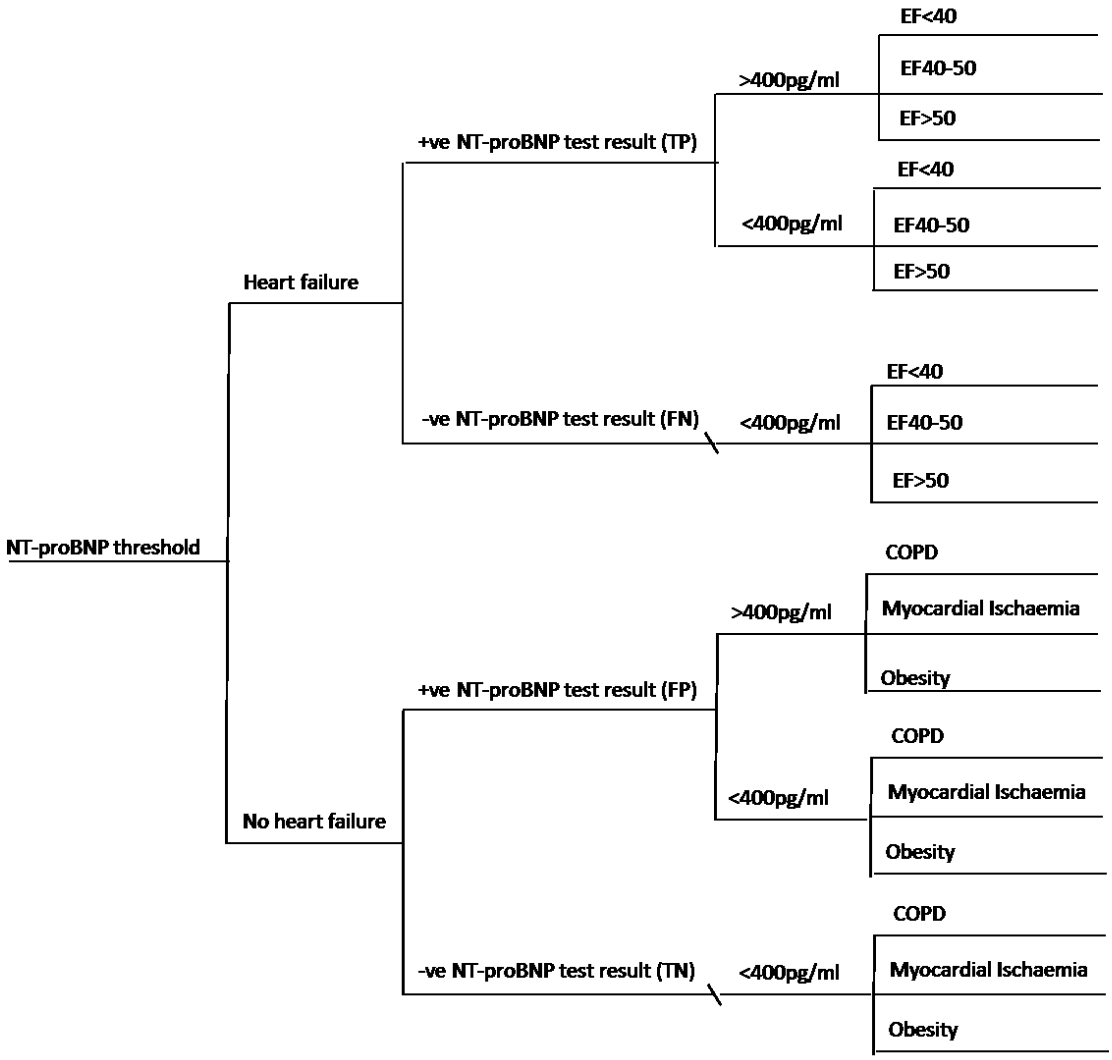
By distinguishing patients in this way, each NT-proBNP threshold identifies all heart failure patients with an NT-proBNP level >400pg/ml, and therefore with a higher risk of mortality and hospitalisation, as true positives who are then referred for echocardiography, receive their diagnosis and are treated for their heart failure. However, the proportion of patients with heart failure and NT-proBNP levels <400pg/ml who are identified as true positives will vary at each threshold. For example, at a diagnostic threshold of 280pg/ml a proportion of the heart failure patients with NT-proBNP levels <400pg/ml will be identified as true positives (those whose NT-proBNP level lies between 280 and 400pg/ml) and go on to be treated. The remaining patients with heart failure and levels below 280pg/ml will receive a false negative result. For further detail of how mortality and hospitalisation rates were adjusted please see O.2.3.6 .

The committee also considered that mortality and hospitalisation rates for those with NT-proBNP levels into the thousands would be even greater. However, as the proportion of patients with these very high NT-proBNP levels would be captured as true positives at all thresholds it was agreed that it was not necessary to specifically adjust mortality and hospitalisation rates for this population.

The last step of the decision tree divides the populations into their final diagnosis. If patients have heart failure they were categorised into one of the following: heart failure with an ejection fraction <40% (HF: EF<40), heart failure with an ejection fraction 40-50% (HF: EF40-50), or heart failure with an ejection fraction >50% (HF: EF>50).

There are multiple other possible diagnoses for people presenting with signs and symptoms consistent with heart failure but who do not have heart failure. For modelling purposes a pragmatic decision was made to choose three of the most common causes to represent a non-heart failure population. The three most common causes identified in Caruana et al. 2000[247], which the committee considered reflected clinical practice, were chronic obstructive pulmonary disease (COPD), myocardial ischaemia, and obesity.

Figure 288: Model structure: decision tree



From this decision tree the proportion of patients in each of the following cohorts below for each threshold are identified:

- TP, NT-proBNP > 400pg/ml, HF: EF<40
- TP, NT-proBNP > 400pg/ml, HF: EF40-50
- TP, NT-proBNP > 400pg/ml, HF: EF>50
- TP, NT-proBNP < 400pg/ml, HF: EF<40
- TP, NT-proBNP < 400pg/ml, HF: EF40-50
- TP, NT-proBNP < 400pg/ml, HF: EF>50

- FN, NT-proBNP < 400pg/ml, HF: EF<40
- FN, NT-proBNP < 400pg/ml, HF: EF40-50
- FN, NT-proBNP < 400pg/ml, HF: EF>50

- FP, NT-proBNP > 400pg/ml, COPD
- FP, NT-proBNP > 400pg/ml, Myocardial ischaemia
- FP, NT-proBNP > 400pg/ml, Obesity
- FP, NT-proBNP < 400pg/ml, COPD
- FP, NT-proBNP < 400pg/ml, Myocardial ischaemia
- FP, NT-proBNP <400pg/ml, Obesity

- TN, NT-proBNP < 400pg/ml, COPD
- TN, NT-proBNP < 400pg/ml, Myocardial Ischaemia
- TN, NT-proBNP <400pg/ml, Obesity

A Markov model for each of these cohorts is then used to determine the associated lifetime costs and QALYs.

Note that for the purposes of modelling the three types of heart failure mentioned above have been categorised as either heart failure with reduced ejection fraction (HF-REF) or heart failure with preserved ejection fraction (HF-PEF). The HF: EF 40-50 cohort are considered to have the same baseline probability of mortality and hospitalisations as HF: EF>50 patients. Therefore, the HF: EF<40 patients will be referred to as patients with HF-REF and the HF: EF 40-50 and HF: EF>50 patients will be referred to as patients with HF-PEF in the base-case analysis. Please see section O.2.2 'key assumptions' below for further explanation of how patients were categorised.

Markov model

A 2 week cycle length was chosen to account for the waiting times for echocardiography and specialist clinical assessment (more detail on waiting times outlined below).

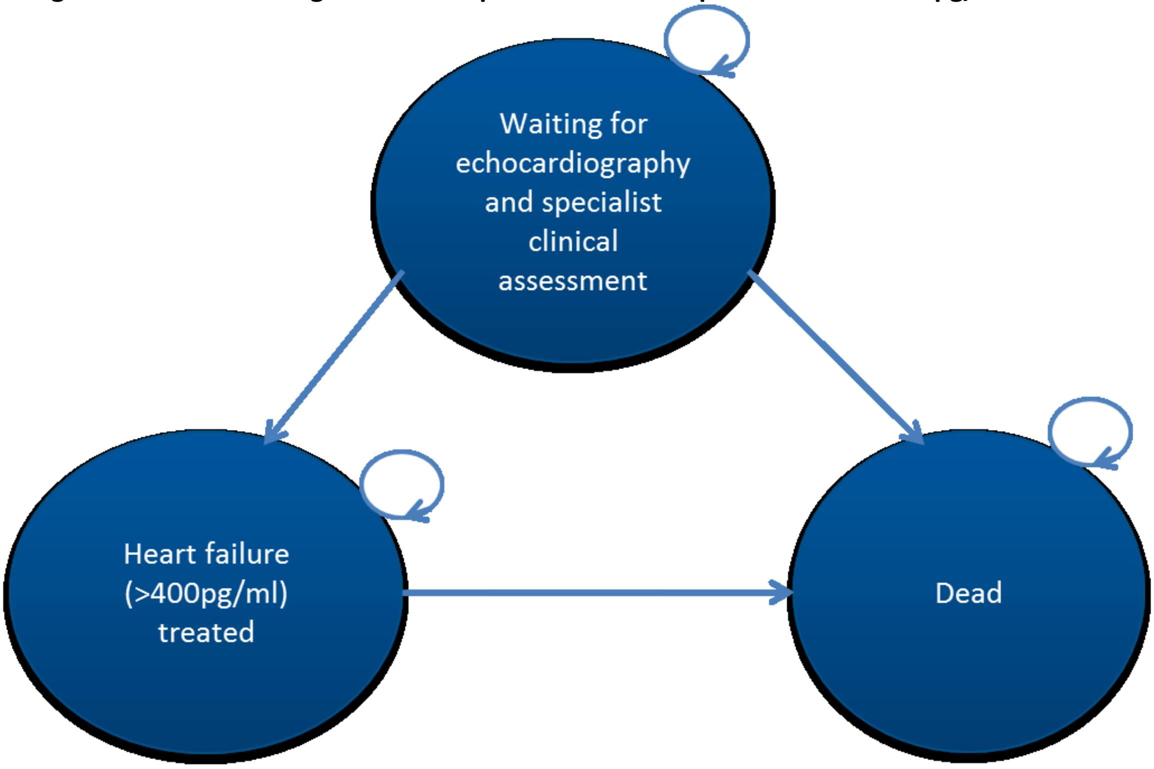
Markov health states:

1. True positives

NT-proBNP levels >400pg/ml

a) Initially all patients enter the 'Waiting for echocardiography and specialist clinical assessment' health state. This health state captures the risk and associated costs and QALYs of hospitalisation and mortality of untreated heart failure over a 6 week period.
If patients do not experience hospitalisation or mortality they receive an echocardiogram and specialist clinical assessment, are correctly diagnosed and transition to the 'Heart failure (>400pg/ml) treated' health state. If patients are hospitalised whilst in this health state it is assumed they were diagnosed during their admission. These patients incur the cost and a disutility of a heart failure hospitalisation and then transition to the 'Heart failure (>400pg/ml) treated' health state. The cost of diagnosis is assumed within the cost of hospitalisation.
b) The 'Heart failure (>400pg/ml) treated' health state captures the risk and associated costs and QALYs of hospitalisation and mortality of heart failure patients with NT-proBNP levels >400pg/ml. Patients only exit this health state due to mortality.

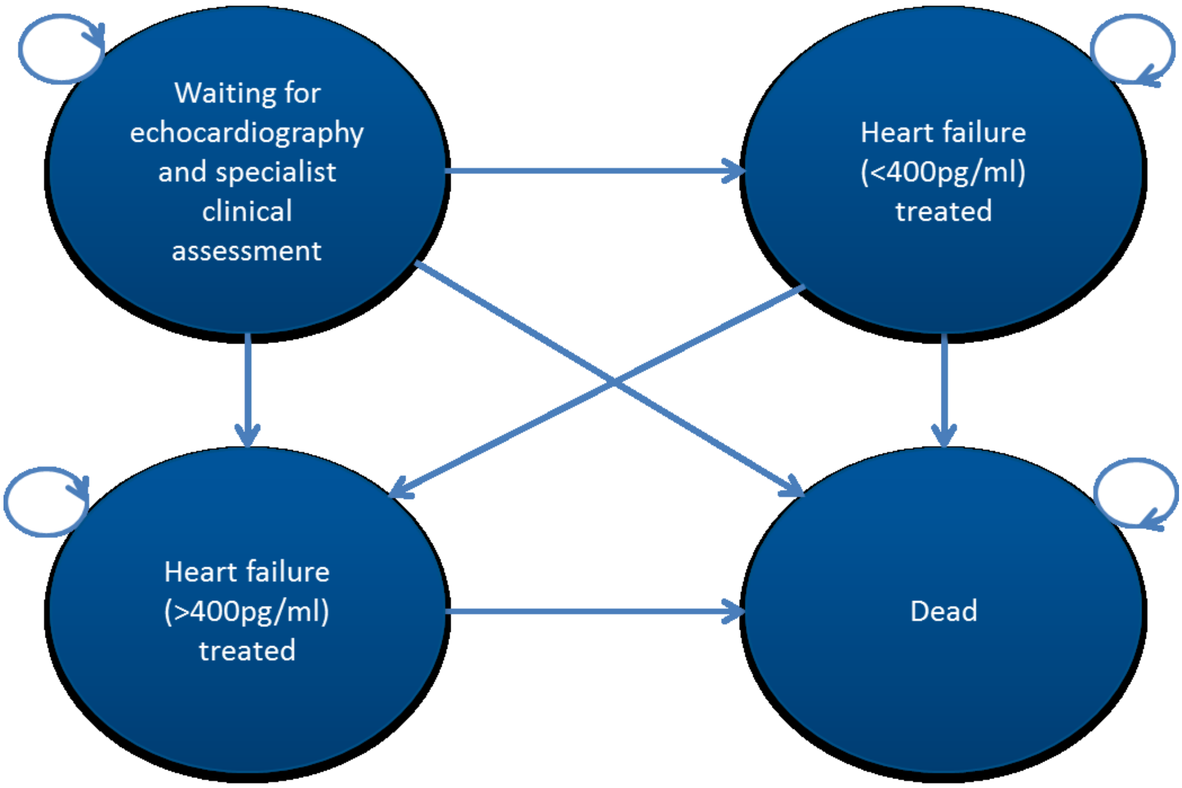
Figure 289: Markov diagram for true positives with NT-proBNP levels >400pg/ml



NT-proBNP levels <400pg/ml

a) Initially all patients enter the 'Waiting for echocardiography and specialist clinical assessment' health state. As described above, if patients do not experience a hospitalisation or mortality during the waiting period, they receive an echocardiogram and specialist clinical assessment and are correctly diagnosed and transition to the 'Heart failure (<400pg/ml) treated' health state. Similarly, if patients are hospitalised during that waiting period, they are diagnosed during their admission and incur the cost and a disutility of a heart failure hospitalisation. However, these patients then transition to the 'Heart failure (>400pg/ml) treated' health state as it assumed that their decompensation will result in their NT-proBNP levels being raised over 400pg/ml.
b) The 'Heart failure (<400pg/ml) treated' health state captures the risk and associated costs and QALYs of hospitalisation and mortality of heart failure in patients with NT-proBNP levels <400pg/ml receiving heart failure treatment. Again, if a patient experiences a hospitalisation it was assumed that they transition to the 'Heart failure (>400pg/ml) treated' health state. If patients do not experience a hospitalisation it was assumed that their condition would progress and their NT-proBNP levels would rise to over 400pg/ml. For HF-REF patients this was assumed to occur 5 years after initial presentation. However, for HF-PEF patients it was assumed that there is no mortality or morbidity benefit of treatment (for further explanation, please see key assumptions below), and therefore these patients do not receive treatment in the model. Consequently, HF-PEF patients were assumed to progress to higher severity 6 months after initial presentation.
c) The 'Heart failure (>400pg/ml) treated' health state captures the risk and associated costs and QALYs of hospitalisation and mortality of heart failure patients with NT-proBNP levels >400pg/ml. Patients only exit this health state due to mortality.

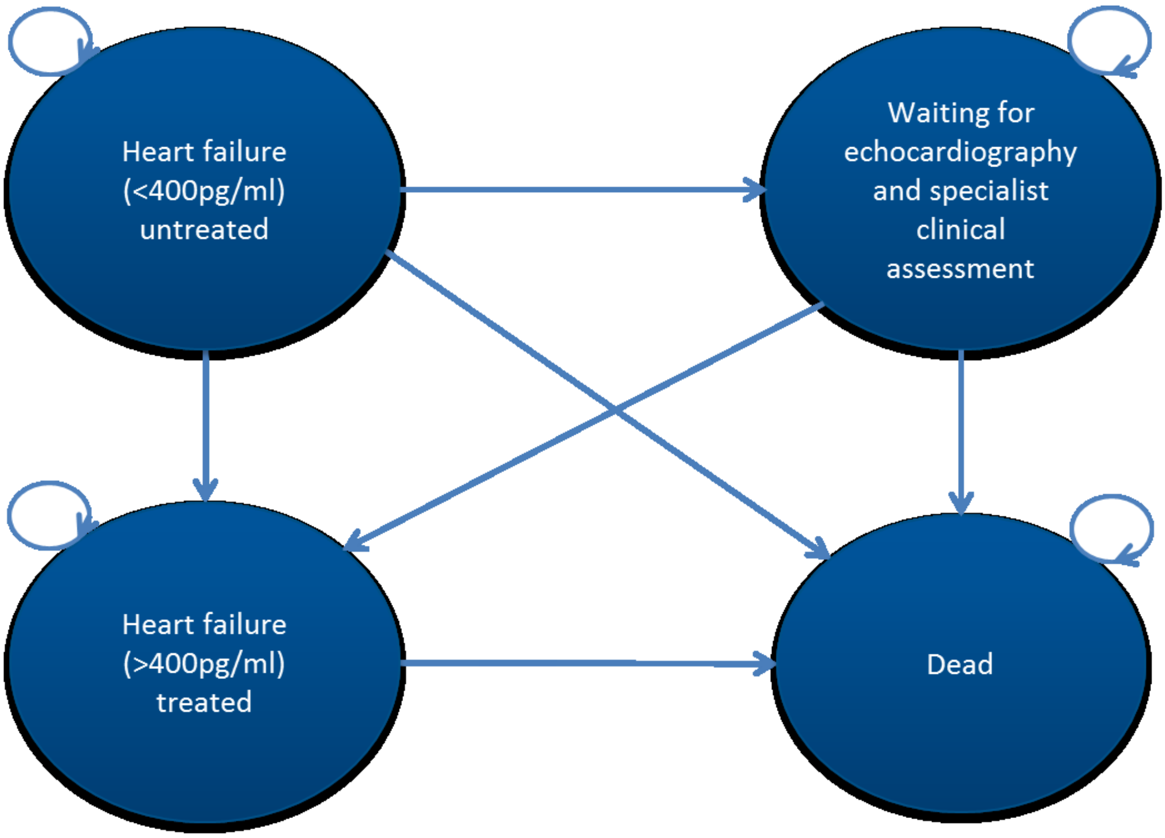
Figure 290: Markov diagram for low severity true positive test result patients



2. **False negatives (NT-proBNP levels <400pg/ml)**

   a) Initially all patients enter the 'Heart failure (<400pg/ml) untreated' health state where they are at risk of a heart failure hospitalisation or death. As above, if a hospitalisation occurs, it is assumed that patients have rapidly worsened and progressed to higher severity and they are diagnosed with heart failure during their hospitalisation. The cost of diagnosis is assumed within the cost of hospitalisation. These patients then move to the 'Heart failure (>400pg/ml) treated' health state.
   b) If patients do not experience a hospitalisation or mortality they re-present to their GP after 6 months (committee assumption in line with the Mant et al. 2009[933]). These patients will receive another NT-proBNP test, the results of which are assumed to be >400pg/ml and therefore at all thresholds these patients will be referred for echocardiography and move into the 'waiting for echocardiography' health state for 6 weeks before being diagnosed. As these patients' heart failure has been untreated the committee assumed that their heart failure will have worsened within these 6 months and the patients NT-proBNP levels will be greater than 400pg/ml and therefore they are now higher severity heart failure patients.
   c) Although initially all patients in this cohort start as low severity, by the time they receive treatment they have progressed to higher severity.
   d) The 'Heart failure (>400pg/ml) treated' health state captures the risk and associated costs and QALYs of hospitalisation and mortality of heart failure patients with NT-proBNP levels >400pg/ml. Patients only exit this health state due to mortality.

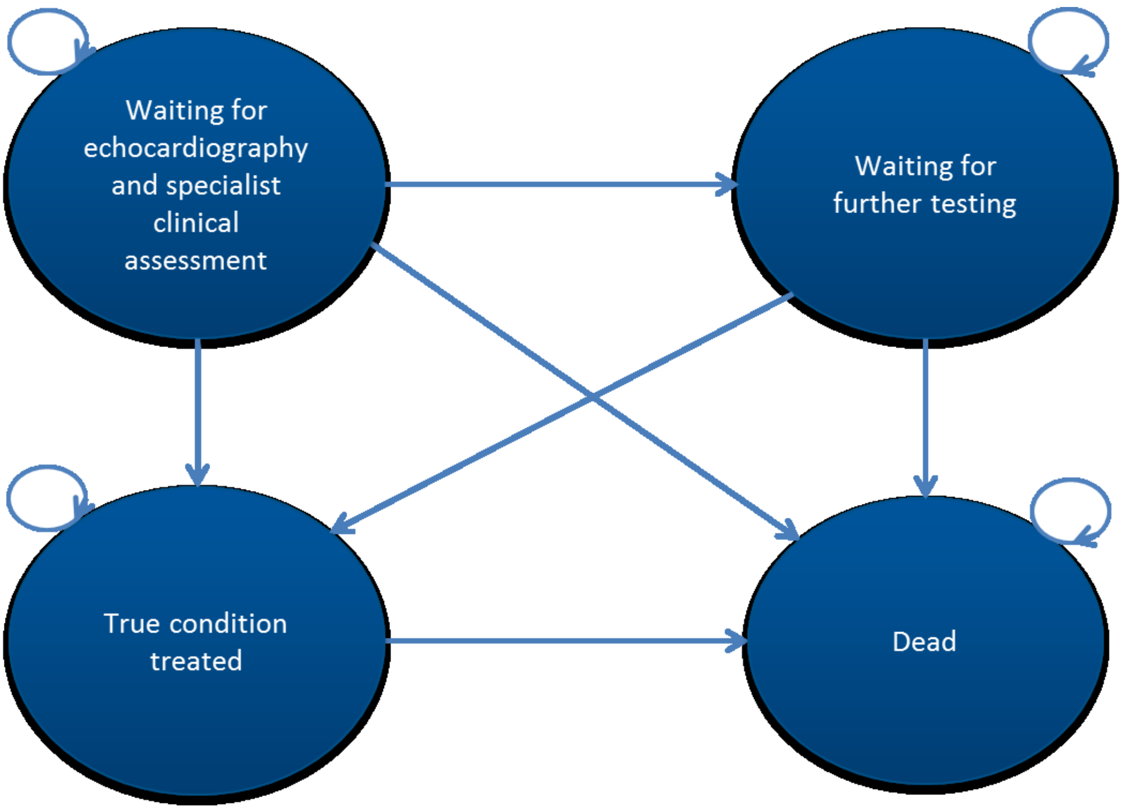
Figure 291: Markov diagram for low severity false negative test result patients



3. **False positives (NT-proBNP levels >400pg/ml and NT-proBNP levels <400pg/ml)**

a) Initially all false positive patients enter the 'Waiting for echocardiography and specialist clinical assessment' health state. This health state captures the probability and associated costs and QALYs of hospitalisation and mortality for the untreated true condition (simplified in the model to be either COPD, myocardial ischaemia, or obesity). For the purposes of the model it was assumed that patients NT-proBNP levels have no effect on the probability of mortality or hospitalisation for these conditions (see key assumptions below for further explanation). Once these patients receive an echocardiogram and specialist clinical assessment and it is established that they do not have heart failure, they transition to the 'waiting for further testing' health state.
b) Similarly to the 'waiting for echocardiography and specialist clinical assessment' health state, the 'waiting for further testing' health state captures the probability and associated costs and QALYs of hospitalisation and mortality for the untreated true condition. Similarly to heart failure, if a patient is hospitalised before diagnosis they are assumed to be diagnosed during their admission. If they do not experience a hospitalisation or mortality, they receive the relevant tests and are diagnosed with their underlying condition (if applicable) they transition to the 'True condition treated' health state. It was assumed for the purposes of the model that obese patients do not undergo further diagnostic testing, as their obesity is an already identifiedunderlying condition. These patients therefore transition straight to the 'true condition treated' health state.
c) The 'True condition treated' health state reflects the costs and QALYs of typical treatment for COPD,myocardial ischaemia or obese patients. This health stateincorporates the probability, cost and quality of life decrement of condition-specific hospitalisations and mortality.
d) Patients exit the model when they die and enter the 'dead' health state.

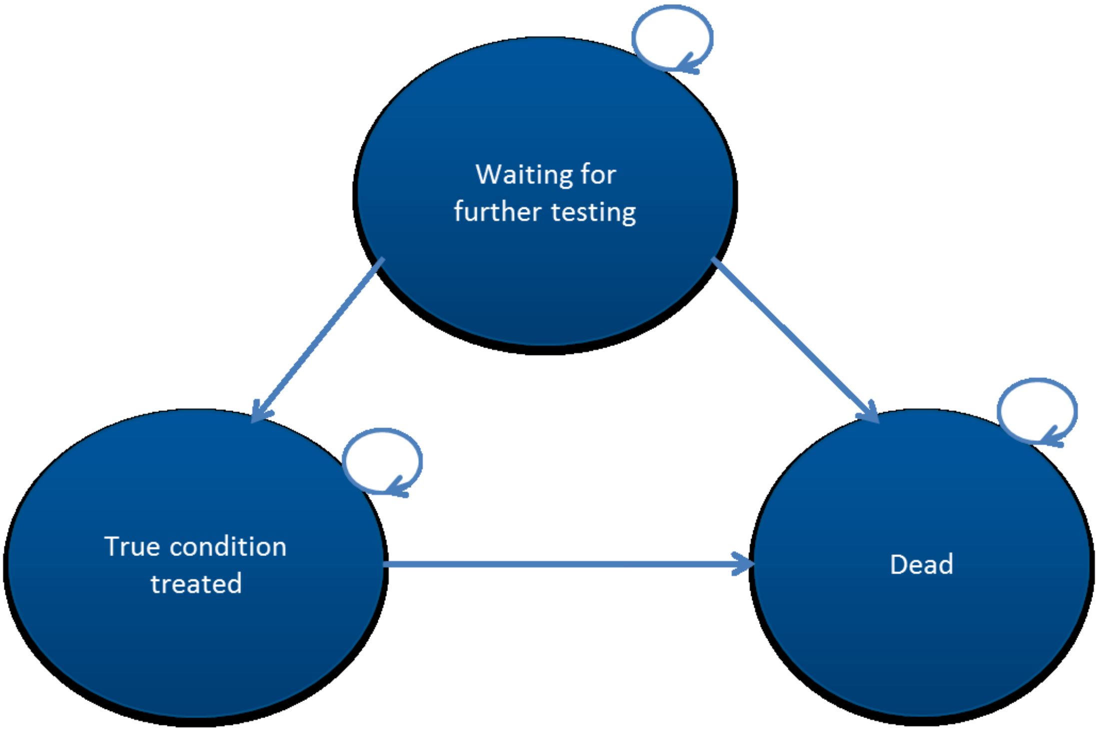
Figure 292: Markov diagram for false positive patients



4. True negatives

a) Initially patients enter the 'waiting for further testing' health state for their respective tests for diagnosis of their true condition if applicable. As previously mentioned above, people with obesity do not enter this health state.
b) In the 'waiting for further testing' health state, patients are at risk of hospitalisation and mortality due to their true condition. As previously mentioned, if a patient is hospitalised before diagnosis they are assumed to be diagnosed during their admission. If they are not hospitalised then they go on to receive their intended diagnostic tests and move to the 'true condition treated' health state.
c) In the 'true condition treated' health state the risk and associated costs and QALYs of hospitalisation and mortality of the true condition are captured (COPD or myocardial ischaemia).
d) Patients exit the model when they die and enter the 'dead' health state.

Figure 293: Markov diagram for true negative patients



O.2.2.2 Key assumptions

1. **Echocardiography plus specialist clinical assessment is 100% accurate** - this assumption means that no one who receives an echocardiogram and specialist clinical assessment is wrongly diagnosed. The committee acknowledged that in reality this may not be entirely true, but as this is the reference standard by which the accuracy of the NT-proBNP test is determined, the committee considered that this was a reasonable assumption and was likely to be very close to the truth.
2. **False negative patients are subsequently correctly diagnosed through one of two possible channels**:
   a. A patient is hospitalised due to their undiagnosed heart failure and are diagnosed during admission
   b. A patient re-presents to their GP 6 months later where the NT-proBNP test is repeated. The committee considered that after this we could assume that their NT-proBNP levels

would be over 400pg/ml and therefore the patient would be referred for an echocardiogram and specialist clinical assessment and be correctly diagnosed. Due to a lack of data about the true delay in heart failure diagnosis, a conservative assumption of 6 months was made in line with an economic analysis by Mant et al. 2009, and also used by Monahan et al. 2016.

3. **The HF: LVSD, EF 40-50 cohort are considered to have the same baseline probability of mortality and hospitalisations as HF: DD, EF>50 patients, and do not receive treatment**. The committee acknowledged that in clinical practice some of these patients may receive beta-blockers or ACEi, however as there no evidence for this cohort of patients the committee made **a conservative assumption** that these patients do not receive treatment. Therefore, the HF: LVSD, EF<40 patients will be referred to as patients with HF-REF and the HF: LVSD, EF 40-50 and HF: DD, EF>50 patients will be referred to as patients with HF-PEF in the base-case analysis.
4. **There is no mortality or morbidity benefit of treatment for HF-PEF patients**. The committee noted that in practice HF-PEF patients are likely to be receiving diuretics, which may reduce the number of hospitalisations but is unlikely to affect mortality. This could not be accounted for in the model as this treatment was introduced over 50 years ago and has not been subject to a randomised placebo-controlled trial.
5. **Heart failure for those with a NT-proBNP level < 400pg/ml will be less prognostically severe** compared to those above the threshold and therefore mortality and hospitalisation rates will be lower than those reported in the literature.
6. **An individual's NT-proBNP level does not affect the rate of hospitalisation or mortality for other (non-HF) conditions**. The committee acknowledged that this may not be true in reality; however was a reasonable assumption to make for the purposes of the model due to a lack of evidence to adjust otherwise.
7. In heart failure patients with NT-proBNP levels <400pg/ml (treated or untreated) a hospitalisation due to a decompensation in their heart failure causes their NT-proBNP levels to permanently be raised over 400pg/ml due to a worsening in their heart failure.[161]
8. Untreated heart failure patients (both HF-REF and HF-PEF) progress to having NT-proBNP levels >400pg/ml after 6 months if they have not already progressed due to hospitalisation. Due to assumption 4, all HF-PEF patients therefore progress to higher severity 6 months after first presentation.
9. Treated low severity HF-REF patients who do not experience a hospitalisation progress to having NT-proBNP levels >400pg/ml 5 years after first presentation.
10. The most common alternative conditions if a patient does not have heart failure are COPD, myocardial ischaemia, and obesity. The committee considered that the percentage of patients with these conditions would be 35% and 15%, and 50%, respectively.
11. Patients do not have multiple-morbidities. This was a pragmatic assumption for modelling purposes, but in reality a large proportion of the population are likely to have multiple morbidities particularly due to the age of the population.

O.2.2.3 Uncertainty

The model was built probabilistically to take account of the uncertainty around input parameter point estimates. A probability distribution was defined for each model input parameter where possible. When the model was run, a value for each of these inputs was randomly selected simultaneously from its respective probability distribution; mean costs and mean QALYs were calculated using these values. The model was run repeatedly – 2,500 times for the base case and 1,500 times for any sensitivity analysis – and results were summarised.

When running probabilistic analysis, multiple runs are required to take into account random variation in sampling. To ensure the number of model runs were sufficient in the probabilistic analysis, we checked for convergence in the incremental net monetary benefit, incremental discounted cost and incremental discounted QALYs for '400pg/ml threshold' versus 'echo all' by plotting the number of runs against the mean outcome at that point on a graph. The results had converged by the 1,000th iteration.

The way in which distributions are defined reflects the nature of the data, so for example utilities were given a beta distribution, which is bounded by 0 and 1, reflecting that a quality of life weighting will not be outside this range. All of the variables that were probabilistic in the model and their distributional parameters are detailed in Table 79 and in the relevant input summary tables in Table 90. Probability distributions in the analysis were parameterised using error estimates from data sources.

Table 79: Description of the type and properties of distributions used in the probabilistic sensitivity analysis

Parameter	Type of distribution	Properties of distribution
Probability of being in a particular subgroup	Dirichlet	Fitted to multinomial data. Represents a series of conditional distributions, bounded on 0–1 interval. Derived by the number of patients in the sample and the number of patients in a particular subgroup.
Transition probabilities and prevalence	Beta	Bounded between 0 and 1. Derived from mean of a domain or total quality of life score and its standard error, using the method of moments. Alpha and Beta values were calculated as follows: Alpha = $\text{mean}^2 \times [(1-\text{mean})/\text{SE}^2] - \text{mean}$ Beta = $\text{Alpha} \times [(1-\text{mean})/\text{mean}]$
Hazard/risk ratios	Log Normal	Bounded at 0. Derived from mean and standard deviation.
Utility	Beta	Bounded between 0 and 1. Derived from mean of a domain or total quality of life score and its standard error, using the method of moments. Alpha and Beta values were calculated as follows: Alpha = $\text{mean}^2 \times [(1-\text{mean})/\text{SE}^2] - \text{mean}$ Beta = $\text{Alpha} \times [(1-\text{mean})/\text{mean}]$
NHS Reference Costs	Gamma/ Log Normal	Bounded at 0. Derived from the mean and standard deviation.
Length of hospitalisation	Gamma	Bounded at 0. Derived from the mean and standard deviation.

Abbreviations: SE = standard error.

To parameterise reference costs probabilistically, a gamma distribution was applied. To fit each distribution, the standard deviation of the trust cost was estimated by matching the reported interquartile range to that calculated using the reported mean, and where appropriate the distribution's alpha and beta values. The distribution of best fit was that which provided the interquartile range of closest value to that reported by the NHS reference cost. Using the estimates derived from the distribution of best fit, the standard error of the mean NHS cost was estimated using the following formula and the probabilistic value drawn.

$$\text{SEM} = \frac{\text{SE of trust cost}}{\sqrt{n}}$$	Where: SEM=standard error of the true NHS mean SE=standard error of the trust cost *n*=number of data submissions

An ordered logit regression model was used to make the diagnostic accuracy data probabilistic to ensure that the sensitivity and specificity values maintained their order according to the threshold level.

The following variables were left deterministic (that is, they were not varied in the probabilistic analysis):

- the cost-effectiveness threshold of £20,000-£30,000 per QALY gained (which was deemed to be fixed by NICE),
- the resource, including time and cost of staff, required to implement each strategy (assumed to be fixed according to national pay scales and programme content) and manage heart failure
- baseline mortality and hospitalisation rates due to a lack of data
- drug costs, as these are considered to be fixed

In addition, various deterministic sensitivity analyses were undertaken to test the robustness of model assumptions. In these, one or more inputs were changed and the analysis rerun to evaluate the impact on results and whether conclusions on which intervention should be recommended would change. A sensitivity analysis using a discount rate of 1.5% for costs and 1.5% for health benefits is conducted. Further detail on the parameters chosen for deterministic sensitivity analysis is listed in section O.2.5.

O.2.3 Model inputs

O.2.3.1 Evidence base

Model inputs were based on clinical evidence identified in the systematic review undertaken for the guideline, supplemented by additional data sources. Model inputs were validated by the clinical members of the guideline committee throughout model development. Please see summary Table 90 below for final inputs included in the model.

O.2.3.2 Diagnostic accuracy

The diagnostic accuracy data were identified from a systematic review undertaken for this guideline update and presented to the committee for discussion. Unfortunately, as many different thresholds were assessed in each study the data could not be meta-analysed. It was therefore difficult to derive any clinically meaningful results from the data or determine if there was any heterogeneity.

To try and resolve this issue the authors of the papers identified in the clinical review were contacted for additional diagnostic accuracy data for the chosen thresholds (if not already available from the published papers) in the hope of undertaking a diagnostic meta-analysis for different thresholds to input into the economic model.

Three authors responded to the request for additional data. However, one set of results were markedly different to the other studies, and the trends of the results did not fit with clinical understanding. We contacted the author to clarify the results, but did not receive a response and therefore excluded these additional data from the meta-analysis.

Overall, data were available from three studies for the each of the chosen thresholdsfor meta-analysis. [1365],[1442],[1525] However, in doing this it became apparent that there is a large amount of heterogeneity between the studies. The committee discussed some of the potential reasons for this including the change in diagnostic criteria for diagnosing diastolic dysfunction on echocardiogram, and potential differences in the study populations. The committee therefore decided that it was not appropriate to use these results in the model and instead chose one of the diagnostic accuracy study results to use in the base-case analysis.

The committee considered that the REFER study by Taylor et al. 2017[1365] was most approporiate for the base-case analysis as it was a contemporary UK study that is most likely to reflect current practice in primary care. The committee acknowledged the high proportion of HF: DD, EF>50 patients in this study, but considered that this is likely to be representative of the population presenting in primary care.

As mentioned above, the REFER study provided information to the panel of cardiologists diagnosing heart failure in three steps. At each step the panel was asked to record whether or not they believed the patient had heart failure or not. At the first step the cardiologists were provided with the results of the clinical assessment *excluding* the MICE clinical decision rule variables. At the second step the cardiologists were provided with *all* information available from clinical assessment, ECG and echocardiogram. In the third step the panel were additionally provided with the NT-proBNP results. This was considered to introduce incorporation bias and therefore the step 2 diagnostic accuracy data were included in this model. Please see Table 80 below for the step 2 diagnostic accuracy data. The average sensitivity and specificity values from the the applied distirbutions have been reported below.

Table 80: Step 2 diagnostic accuracy data from Taylor et al. 2017[1365]

Diagnostic strategy	Sensitivity (95% CI)	Specificity (95% CI)
NT-proBNP threshold: 400pg/ml	0.567 (0.465-0.667)	0.778 (0.722-0.826)
NT-proBNP threshold: 280pg/ml	0.673 (0.574-0.761)	0.690 (0.627-0.747)
NT-proBNP threshold: 125pg/ml	0.861 (0.798-0.909)	0.424 (0.359-0.489)
Refer all for echocardiography	1.00	0.00
Refer all for echocardiography, triage according to NT-proBNP level	1.00	0.00

The diagnostic accuracy data from the other two studies were used in a sensitivity analysis (see Section O.2.5.1).

As mentioned in the model structure above, using this diagnostic accuracy data, the proportion of heart failure patients with NT-proBNP levels <400pg/ml was calculated (1- sensitivity). Consequently, in the base-case 43.3% of the heart failure population have NT-proBNP levels <400pg/ml.

O.2.3.3 Initial cohort settings

The initial cohort settings are based on patient characteristics of the REFER study by Taylor et al. 2016 (unpublished data).

- Prevalence of heart failure: 29%

Population with heart failure:

- Age: 77 years
- Proportion male: 50.6%
- Proportion HF: EF 40: 3.4%
- Proportion HF: EF 40-50: 10.1%
- Proportion HF: EF 50: 86.5%

Population with other conditions:

- Age: 72 years
- Proportion male: 36%

O.2.3.4 Heart failure mortality

Note the mortality rates specified below are for the more prognostically severe heart failure population (NT-proBNP>400pg/ml). See O.2.3.6 for explanation of how we adjusted these rates for less prognostically severe heart failure patients (NT-proBNP levels <400pg/ml).

Life tables for England, published by the Office for National Statistics (ONS) based on 2014-2016 mortality data[1073] were used to establish population all-cause mortality rates for men and women for ages 72 to 100 years. The life table mortality rates reflect a general population; therefore the literature was reviewed to identify standardised mortality ratios (SMR) to adjust the life table data separately for HF-REF and HF-PEF populations.

SMRs for an overall heart failure population were identified in the literature, but none were identified which distinguished between the different types of heart failure which the committee considered important as they have very different treatment pathways and prognoses.

Due to a lack of alternative data, the committee identified mortality data for untreated HF-REF and HF-PEF patients from randomised control trials (RCTs). The committee acknowledged that these patients were a younger, more selected population and agreed that this data could not be used directly for the model population. Instead, the studies were used to calculate crude SMRs. The trial population and general population were matched according to average age, proportion of males and females, as well as the year the study was undertaken to standardise the mortality rates as closely as possible. Having matched the populations, the mortality rate for the general population and the mortality rate from the study were divided to calculate the crude SMR.

The calculated SMRs were then applied to the most recent life tables for England, adjusted for the age and sex of the population in the model.

Baseline HF-REF

The control arm of the SOLVD-treatment trial[1311] was identified as the most suitable study for data in untreated HF-REF patients as this was one of the first studies undertaken in heart failure patients. Although some patients in the trial are taking beta-blockers and diuretics the effect of the latter in reducing mortality is likely to be small and the beta-blockers were only given to a small proportion of patients.

The study population were recruited into the trial between 1986 and 1989 and were followed up for an average of 3.5 years. Therefore, the UK life table for the years 1988-1990 was thought to be the most appropriate years to match the study population to. The average age of the study population was 61 and 80% of the population were male.

Table 81: Data used to calculated untreated HF-REF 'SMR'

Population	Source	Annual mortality rate
Untreated HF-REF	SOLVD-HF trial (average age 61)	0.15654
General population	Life table for England based on data for the years 1988-1990, adjusted for %male – age 61	0.01575

The data in Table 81 above were used and a crude 'SMR' for untreated HF-REF patients was estimated to be 9.94.

Baseline HF-PEF

The committee discussed two trials that would be most appropriate for the HF-PEF population: TOPCAT[1156] and I-PRESERVE[953]. The committee decided not to use the TOPCAT trial due to the concerns about the population recruited in the trial. . Therefore the control arm of the I-PRESERVE trial was used for the HF-PEF population. [953]The committee considered that the baseline medications (aside from diuretics) the patients were receiving in this trial were to treat co-morbidities (such as hypertension, diabetes, coronary artery disease, atrial fibrillation, and peripheral vascular disease) and would not affect their heart failure prognosis per se.

The study population were recruited into the trial between 2002 and 2005 and were followed up for an average of 4 years. Therefore, the life table for the years 2004-2006 was judged to be the most appropriate years to match the study population to. The average age of the study population was 72 and 39% of the population were male.

Table 82: Data used to calculate untreated HF-PEF 'SMR'

Population	Source	Annual mortality rate
Untreated HF-PEF	I-PRESERVE trial (average age 72)	0.0523
General population	Life table for England based on data for the years 2004-2006, adjusted for %male – age 72	0.0238

The data in Table 82 above were used and a crude 'SMR' for untreated HF-REF patients was estimated to be 2.20.

<u>Relative treatment effect</u>

HF-REF

Hazard ratios of all-cause mortality from a recently published network meta-analysis were applied to account for the effect of treatment[221]. On average most HF-REF patients are likely to be on triple therapy of angiotensin-converting-enzyme inhibitor (ACEi), beta-blocker (BB) and mineralcorticoid receptor antagonist (MRA). However, the effect of triple therapy in those with NT-proBNP levels below 400pg/ml is highly uncertain as most clinical trials require patients to have an NT-proBNP level greater than this. Therefore, for the purposes of the model a hazard ratio for triple therapy was chosen for the HF-REF patients with NT-proBNP levels greater than 400pg/ml, and a hazard ratio for double therapy (ACEi and BB) was chosen for those with HF-REF and NT-proBNP levels below 400pg/ml to reflect a lesser treatment effect in these patients.

Table 83: Hazard ratios for all-cause mortality for treated HF-REF patients

Population	Hazard ratio (95% CI)
Treated with ACEi, BB and MRA	0.440 (0.246 – 0.661)
Treated with ACEi and BB	0.569 (0.412 – 0.724)

HF-PEF

Due to the assumption that there is no mortality benefit for HF-PEF patients in receiving treatment, the I-PRESERVE data was applied for both untreated and 'treated' HF-PEF patients. Therefore no relative treatment effect was applied.

O.2.3.5 Heart failure hospitalisations

In the same way as the mortality rates, the hospitalisation rates specified below are for the more prognostically severe heart failure population. See O.2.3.6 for explanation of how we adjusted hospitalisation rates for less prognostically severe heart failure patients.

Baseline hospitalisation rates

Due to a lack of recent observational data the committee considered that the two trials identified above (SOLVD-HF and I-PRESERVE) would be the best sources for baseline untreated heart failure hospitalisation rates. The committee noted that the populations in these models were a younger, selected population, and noted that this would be a limitation of the model.

Relative treatment effect

HF-REF

The effect size estimates for HF-REF patients were obtained from systematic reviews with meta-analysis for ACEi and BB, and EMPHASIS-HF trial for MRA.

Table 84: Hazard ratios for heart failure hospitalisations of HF-REF drugs vs placebo

Treatment	Risk ratio	Source
ACEi	0.67 (0.61 – 0.74)	Flather et al. 2000[468]
BB	0.71 (0.65 – 0.77)	Kotecha et al. 2014[791]
MRA	0.58 (0.47 - 0.70)	EMPHASIS-HF adjusted hazard ratio [1523]

The trials assessing these treatments assessed the effects of these treatments additively. The committee also considered that these drugs have a slightly different function in treating heart failure, and hence considered that the assumption of independent treatment effects would hold.. Therefore the risk ratios for individual drug classes were multiplied to account for the additive effects of the treatments. Consequently, the overall risk reduction for HF-REF patients with NT-proBNP levels over 400pg/ml with applied effect of triple therapy was 0.276, and the risk reduction for HF-REF patients with NT-proBNP levels below 400pg/ml with the applied effect of double therapy was 0.476. The committee considered that this may be an overestimate and therefore agreed that this should be explored in a sensitivity analysis.

HF-PEF

Due to the assumption that there is no morbidity benefit for HF-PEF patients in receiving treatment, the I-PRESERVE data was applied for both untreated and 'treated' HF-PEF patients and no relative treatment effect was applied.

O.2.3.6 Adjustment for heart failure patients with NT-proBNP levels <400pg/ml

The mortality and hospitalisation data identified above was applied for the heart failure patients with NT-proBNP levels >400pg/ml. As previously mentioned, the rise in NT-proBNP irrespective of the type of heart failure is associated with a prognostic implication[1364]. In order to ensure the model reflects this, the committee wished to recognise the fact that although some patients with low NT-proBNP levels will have heart failure and initially be missed, the mortality and hospitalisation rates in these patients are likely to be lower than those with heart failure and high NT-proBNP levels.

The literature was searched and two studies were identified that stratify prognosis by NT-proBNP level. One was a large Danish study, the other a smaller UK study. Although a smaller study, this study was chosen to inform the adjustment in mortality and hospitalisation rates as it was a UK study, and reported the hazard ratios between the Kaplan-Meier curves to allow for the adjustment to be made.[807] The study assesses mortality and first cardiovascular hospitalisation rates for sub-groups of patients divided into quintiles according to baseline NT-proBNP.

The committee acknowledged that the patients in this study were receiving treatment for their heart failure, but considered the relative effect would also apply to those whose heart failure is untreated.

The committee considered that although the study only reported first cardiovascular hospitalisation rates, the hazard ratio would also likely apply to heart failure hospitalisations. The first quintile level is <474pg/ml and therefore the committee considered this would be representative of the less prognostically severe heart failure population. A hazard ratio was only reported for the mortality data comparing the first quartile (<474pg/ml) to the fourth (2230-5532pg/ml) and fifth quintile (>5533pg/ml). The committee considered that applying the hazard ratio comparing the first and fifth quintile was not appropriate as these high levels are not representative of the population assessed in the REFER study whose median NT-proBNP level is 715pg/ml (413-1559). Therefore, the hazard ratio that compared the first and fourth quintile was applied. The committee considered that this might still be an overestimate of the reduced risk for the less prognostically severe population; however this was the only data available and agreed that it was important to carry out a sensitivity analysis around this parameter.

Although hazard ratios were available comparing all quintiles to the first quintile for the hospitalisation data, for consistency the hazard ratio comparing the first and fourth quintile was applied.

The study was only conducted in HF-REF patients. The committee did not consider that there would be such a step gradient in mortality and heart failure hospitalisations for the HF-PEF population and therefore made a pragmatic assumption that less prognostically severe HF-PEF patients would only have half the risk reduction that less prognostically severe HF-REF patients would.

Table 85: Hazard ratios applied for low severity adjustment

Description	Hazard ratio	Source
Hazard ratio all-cause mortality, low severity vs higher severity HF-REF	0.272	Kubanek et al. 2009[807]
Risk ratio heart-failure hospitalisations, low severity vs higher severity HF-REF	0.274	Kubanek et al. 2009[807]
Hazard ratio all-cause mortality, low severity vs higher severity HF-PEF	0.544	GC assumption
Risk ratio heart-failure hospitalisations, low severity vs higher severity HF-PEF	0.548	GC assumption

O.2.3.7 Non-heart failure population

There are multiple other possible diagnoses for people presenting with signs and symptoms consistent with heart failure but who do not have heart failure. For modelling purposes a pragmatic decision was made to choose three of the most common causes to represent a non-heart failure population. The most common alternative diagnoses were primarily identified from committee experience and consensus alongside the findings of Caruana et al. 2000. [247] These were chronic obstructive pulmonary disease (COPD), myocardial ischaemia, and obesity. The committee noted that the study was dated and considered that the proportions of alternative diagnoses from the paper weren't directly applicable to current practice, as the incidence of obesity has increased over the years. Therefore the committee agreed to conservatively increase the percentage of obese patients and decrease the proportion of COPD and myocardial ischaemia To ensure conservative estimates were made for this population it was assumed that 15% of the patients had an true diagnosis of myocardial ischaemia, 35% had a true diagnosis of COPD, and 50% were obese.

O.2.3.8 Non-heart failure population mortality

As with the heart failure population life tables for England were adjusted using previously published standardised mortality ratios (SMR) for COPD, myocardial ischaemia and obesity populations.

COPD and myocardial ischaemia

Previously published SMRs were identified for COPD and myocardial ischaemia patients. However, the SMRs for these populations were for treated rather than untreated patients.

The SMR for COPD was taken from Diaz-Guzman et al. 2011[382]. This US study used baseline data from NHANES III and follow-up mortality data to assess mortality rates in the COPD and general population controlling for baseline lung function.

The SMR for myocardial ischaemia patients was taken from a paper by the Emerging Risk Factors Collaboration[438]. This study reported the mortality rate for people with previous myocardial infarction. Data were collected from a systematic review of 91 papers but also from the UK Biobank. The SMR identified was calculated using the UK biobank data as this was considered to be more representative of the UK population.

Table 86: Calculated SMRs for patients with other conditions

Population	SMR (95% CI)
COPD	1.28 (1.13-1.45)
Myocardial Ischaemia	2.10 (1.90-2.30)

Due to a lack of available evidence to adjust the mortality rates for an untreated COPD population, a conservative assumption was made that there would be a 30% risk reduction in mortality due to treatment for COPD patients. The committee considered that when taking into account smoking cessation programmes and rehabilition for COPD patients with was a reasonable assumption.

The breathless patient whose symptoms are caused by myocardial ischaemia, may or may not have angina, and careful history taking may well pick up a predictable relationship to exertion or the subtle description of discomfort not recognised by many patients as chest pain. Missing the diagnosis is likely to lead to harm due to the delay in the diagnosis in those who may have unstable coronary artery disease who could then present with acute coronary syndrome within the subsequent few months. However, these constitute a small proportion of such group of patients. The majority of the remaining patients will continue to have stable coronary artery disease. Even those have a risk of presenting with myocardial infarction and a risk of mortality which can be modified by the combination of therapies used in the treatment of coronary artery disease including Aspirin, Beta-blockers, ACEI and statins. Anti-platelet therapy is most likely to have a significant effect in reducing the risk of mortality within the first 6 months. Due to the broad definition of myocardial ischaemia, the committee made assumptions about the treatment effect on mortality largely upon consensus. However, data to support these assumptions has been identified in the NICE nSTEMI and unstable angina guidelines. A meta-analysis demonstrates a relative risk ratio of 0.60 for vasuclar events when assessing aspirin compared to placebo (no treatment).[1046] The vascular events outcome was a composite outcome of non-fatal myocardial infarction, non-fatal stroke, and death from a vascular or unknown cause. Although not a direct outcome, this was considered to be fairly representative of mortality. In addition, a meta-analysis was identified assessing aspirin in patients with stable cardiovasuclar disease. [156] This analysis demonstrated a RR of 0.885 for all-cause mortality for a single therapeutic intervention.

The committee considered that the risk of mortality in the model population is likely to sit between these two study populations. The committee were satisfied that the chosen treatment effect should lie between these two estimates.

. One large randomised trial was also identified comparing simvastatin to placebo in patients with angina or with a previous history of myocardial infarction.[1183] This study demonstrates a 30% risk reduction in mortality for those on statin therapy. Overall, considering all this evidence, the committee considered that a 30% risk reduction was likely to be a good representation of the treatment effect for those being treated with myocardial ischaemia in both the short term and the long term.

To determine the mortality rate for those with myocardial ischeamia who are untreated the inverse of this effect was applied to the treated population mortality rates.

Obesity

No published SMR was identified for an obese population, however the committee considered that the general population life tables would be sufficient for this population. In the majority of people with obesity lifestyle advice is given. The committee therefore made a conservative assumption that there would be no treatment effect on mortality in this population.

O.2.3.9 Non-heart failure population hospitalisation rate

COPD

The committee considered that hospitalisation rates for COPD and heart failure patients were similar and therefore a pragmatic assumption was made that treated COPD patients would have the same hospitalisation rate as HF-REF patients with NT-proBNP levels >400pg/ml. In the absence of evidence the committee also made a pragmatic assumption that there was 30% risk reduction in hospitalisations in treated patients. The inverse of this treatment effect was applied to determine the hospitalisation rate of untreated COPD patients.

Myocardial ischaemia

Again a pragmatic assumption was made for this population. The committee acknowledged that hospitalisation rates for myocardial ischaemia patients would be much lower than for heart failure. It was assumed that treated myocardial ischaemia patients would have a third of the hospitalisation rate of treated HF-REF patients with NT-proBNP levels over 400pg/ml. Once again, in the absence of evidence the committee made a pragmatic assumption that there was 30% risk reduction in hospitalisations in treated patients. The inverse of this treatment effect was applied to determine the hospitalisation rate of untreated COPD patients.

Obesity

As with mortality, the committee did not consider that there would be any treatment effect for hospitalisation rates in an obese population pre and post investigation for heart failure and therefore this was not explicitly included in the model.

O.2.3.10 Utilities

EQ-5D data was collected for all patients in the REFER study at baseline and 6-month follow-up. The authors were contacted and the EQ-5D data for the patients diagnosed with heart failure at step 2 (for consistency with the diagnostic accuracy data) in the study were provided, and for the remaining patients who did not have heart failure. As the majority of the population in the model have HF-PEF the committee did not consider that there would be significant quality of life benefit for these patients. Therefore a conservative assumption was made that there was no quality of life benefit from treatment, and the 6-month follow-up EQ-5D score collected for the patients with heart failure from REFER was applied to both the untreated and treated HF-REF and HF-PEF population. The 6-month follow-up EQ-5D score for the patients without heart failure were applied as a conservative assumption to the people with COPD, myocardial ischaemia, and obesity for the lifetime horizon of the model.

These utility values remained constant for the life time horizon of the model with only a decrease in utility during a hospitalisation. This is a simplification, as in reality heart failure tends to worsen over time and therefore you would expect quality of life to also decrease over time. This assumption was also applied for the untreated heart failure patients. The committee considered this to be a reasonable assumption as these patients have less prognostically severe heart failure, and therefore it is unlikely they would experience a significant reduction in quality of life in the 6 months they are untreated, unless they were hospitalised.

Table 87: 6 month utility values from the REFER study (unpublished)

Population	Mean utility value (SD)
Heart failure patients	0.581 (0.343)
COPD, myocardial ischaemia, and obese population	0.573 (0.313)

Utility decrement of hospitalisation

The utility decrement applied for a heart failure hospitalisation was identified from Reed et al. 2013.[1191] This study reports the utility scores of patients in the treatment and control groups in decompensated heart-failure patients in the ASCEND-HF trial. The paper reports an average EQ-5D score for patients admitted with an acute decompensation of their heart failure when admitted, 24 hours after admission, at discharge, and 30 days after discharge. The utility decrement applied for hospitalisation in the model was calculated by subtracting the 30-day EQ-5D score from the EQ-5D score at admission giving a utility decrement of 0.19. The utility decrement of hospitalisation was applied for the average length of time of a hospital stay (7 days) as determined from NHS reference costs 2015/16 codes for a heart failure hospitalisation.[373]

The committee considered that COPD and myocardial ischaemia patients would experience a similar utility decrement for a COPD related hospital admission as a HF patient would for a HF admission. The committee considered that any hospitalisations for myocardial ischaemia were likely to be due to acute coronary syndrome. Therefore the same utility decrement was applied for COPD patients, and half the utility decrement was applied for myocardial ischaemia patients. These utility decrements were applied for the average length of stay for the related hospital admissions as determined by the NHS reference cost codes.

O.2.3.11 Resource use

<u>Resource use in heart failure patients</u>

Diagnostic work-up

The costs of the standard clinical investigations at the GP when patients first present with signs and symptoms of heart failure were included in the model. This consisted of the NT-proBNP test, full blood count as well as biochemistry tests for liver, kidney, thyroid, glucose and diabetes, a chest x-ray and an ECG. The cost of echocardiography and a specialist clinical assessment (first cardiology consultant lead appointment) were also added for the patients who receive a positive NT-proBNP result (both TPs and FPs).

The cost of repeating the initial diagnostic tests, excluding another chest x-ray due to the dangers of radiation exposure, was applied to the false negatives who have not yet been diagnosed with heart failure that represent to their GP after 6 months. For those hospitalised before receiving diagnosis, it was assumed that the cost of diagnosis is captured in the cost of the hospitalisation.

The costs of further diagnostic tests if patients did not have heart failure were also included. It was considered that if a patient had myocardial ischaemia that it would also be identified through echocardiography and clinical assessment by a cardiologist. However, in addition, these patients would also receive a computerised tomography coronary angiogram (CTCA) in accordance with the NICE guidance for chest pain (CG95). Therefore, if a patient had already received an echocardiogram as they had received a false positive NT-proBNP test, the only additional cost would be the CTCA. The diagnostic tests included for COPD patients included a spirometry (with reversibility testing) and referral to a respiratory medicine consultant.

Medication

The cost of the drug therapies for HF-REF patients were included in the model. For the HF-REF patients with NT-proBNP levels <400pg/ml this consisted of ACEi and BB therapy, and for HF-REF patients with NT-proBNP levels >400pg/ml this consisted of ACEi, BB and MRA therapy.

It was noted that heart failure patients are also likely to incur a cost of diuretic treatment, however as we do not account for this effect in the model, we do not account for the cost of this treatment either.

Appointments

The number of appointments involved in managing patients in their first year after diagnosis was considered to be much higher than the following years for HF-REF patients that require uptitration of medication. Therefore a higher cost of appointments was applied for the first year of the model, followed by an average for the following years. Furthermore, the cost of managing heart failure patients was considered to vary according to whether a person was being treated for HF-REF or HF-PEF and whether or not they had NT-proBNP levels above or below 400pg/ml. Table 88 below outlines the resources expected on average per person per year for each of these groups, for the first year and then the following years.

Table 88: Appointment resource

Severity of heart failure	HF-REF	HF-PEF
First year after diagnosis		
<400pg/ml	2 x outpatient cardiology appointment 2 x GP appointment 10 x Specialist heart failure nurse appointment (30 mins)	1 x GP appointment 1 x outpatient cardiology appointment 1 x specialist heart failure nurse appointment
>400pg/ml	2 x outpatient cardiology appointment 2 x GP appointment 10 x Specialist heart failure nurse appointment (30 mins)	1 x GP appointment 1 x outpatient cardiology appointment 1 x specialist heart failure nurse appointment
Subsequent years		
<400pg/ml	1 x outpatient cardiology appointment 1 x GP appointment 2 x Specialist heart failure nurse appointment (30 mins)	1 x GP appointment
>400pg/ml	2 x outpatient cardiology appointment 3 x GP appointment 2 x Specialist heart failure nurse appointment (30 mins)	2 x GP appointment

In accordance with the key assumption that untreated heart failure patients with NT-proBNP levels <400pg/ml progress to having NT-proBNP levels >400pg/ml if untreated for 6 months, the FN HF patients incur management costs of higher severity HF patients straight away when they are correctly diagnosed after 6 months.

O.2.3.12 Unit costs

Diagnostic costs

All diagnostic test costs were identified from NHS reference costs 2015/16, except for the cost of the NT-proBNP test and spirometry as these were not available.[372] To estimate the cost of an NT-proBNP test the committee chair contacted a range of hospital trusts known to test using NT-proBNP to ask the cost assigned to the test. Five hospital trusts responded, and an average of these was taken to input into the model.

The cost of spirometry was assumed to be equivalent to a 50 minute appointment with a healthcare assistant in primary care (equivalent to a band 3 clinical support worker)[333]. The 50 minute appointment would include an initial baseline spirometry assessment (20mins) after which the patient is administered a drug (salbutamol) to see if there is a reversible component to any breathing problem (10mins). Spirometry is then repeated to see if there is any improvement (20mins).

NHS reference costs 2010/11 was used to determine the unit cost of an ECG.[371] A NHS reference cost code for ECG was not available in more recent versions. However, the committee did not think that the cost of an ECG will have changed substantially since 2010 and agreed that this was suitable.

Drug costs

The annual cost of medication for each class was calculated by weighting the cost of the maximum dose recommended for heart failure patients in the BNFfor each drug by the proportion of each drug prescribed within that class according to the number of prescriptions issued as reported in the Prescription Cost Analysis (PCA) 2015. [703],[593] Although, the PCA does not differentiate by indication, when these proportions were presented to the committee they agreed that they were broadly representative of heart failure prescribing practice for angiotensin-converting enzyme inhibitors (ACEi) and mineralocorticoid receptor antagonists (MRA); however made some minor adjustments to increase the proportion of carvedilol and nebivolol proportions for beta-blocker to reflect prescribing practice for heart failure patients. Drug costs were identified from the May 2017 Drug tariff.[1055].

Table 89: Drug costs

Drug	Proportion prescribed	Annual cost of maximum dose (£)	Weighted annual cost (£)
Beta-blockers			
Bisoprolol	90%	11.34	16.10
Carvedilol	5%	66.22	
Nebivolol	5%	51.62	
Angiotensin-converting enzyme inhibitors (ACEi)			
Ramipril	83.39%	16.82	18.53
Perindopril Erbumine	10.2%	17.40	
Enalapril	6.18%	29.98	
Lisinopril	0.06%	13.95	
Perindopril Arginine	0.17%	129.85	
Mineralocorticoid Receptor Antagonists			
Spironolactone	83.78%	41.19	45.30
Eplerenone	16.22%	66.48	

Appointments

The cost of a GP appointment was identified from PSSRU 2016.[333] In addition, the cost of an appointment with a specialist heart failure nurse was calculated using the hourly cost of a band 6 specialist nurse identified from PSSRU 2016. This hourly cost was then adjusted to determine the cost of a single 30-minute appointment.

Hospitalisations

The cost of a heart failure hospitalisation was applied. HRG codes for 'heart failure or shock' (EB03A-E) were selected and then weighted by activity according to NHS reference cost (2016/17) to calculate an average cost of hospitalisation. [373]

The cost of a COPD hospitalisation was weighted according to HRG codes for 'chronic obstructive pulmonary disease or bronchitis' (DZ65A-K), and for myocardial ischaemia HRG codes for 'actual or suspected myocardial infarction' (EB10A-E).

Management cost of non-heart failure patients

Once patients with other conditions were being treated an annual cost of management was applied. The annual cost of managing COPD was identified from the NICE COPD clinical guideline (CG101) which outlined the average annual cost according to GOLD severity classification.[1047] This was weighted by the proportion of patients in each of these classifications as reported in Haughney et al. 2014[584]. A range was provided for each classification; a conservative assumption was made to include the highest cost estimate.

The annual cost of managing myocardial ischaemia was identified from the NICE Unstable angina and NSTEMI: early management clinical guideline (CG94). [1046]

No cost input was included in the model for the obese population as the committee considered that there would be no change in management for this population, and therefore this was not necessary.

Please see Table 11 below for all unit costs applied in the model.

O.2.3.13 Summary table of model inputs

Model inputs were based on clinical evidence identified in the systematic review undertaken for the guideline, supplemented by additional data sources as required. Model inputs were validated with clinical members of the Committee. A summary of the model inputs used in the base-case (primary) analysis is provided in Table 90 below.

Table 90: Overview of base-case parameters used in the model

Parameter description	Point estimate	Source	Distribution and parameters
Population			
Time horizon	Lifetime	Committee consensus	Not applied
Annual discount rate (costs and effects)	0.035	NICE reference case	Not applied
Average age of heart failure patients at first presentation	77	unpublished REFER data	Not applied
Average age of patients with other conditions at first presentation	72	unpublished REFER data	Not applied
Proportion of 'other conditions' with COPD	0.35	Estimated from Caruana et al. 2000[247]	Not applied
Proportion of 'other conditions' with myocardial ischaemia	0.15	Estimated from Caruana et al. 2000[247]	Not applied
Proportion of 'other conditions' with no additional diagnosis (e.g. obese)	0.50	Estimated from Caruana et al. 2000[247]	Not applied
Diagnosis parameters			
Prevalence of heart failure	0.290	unpublished REFER data	Beta; alpha = 89, beta = 215

Parameter description	Point estimate	Source	Distribution and parameters
Sensitivity of NT-proBNP test – threshold 400pg/ml	0.584	Taylor et al. 2017[1365]	Ordinal logistic regression
Specificity of NT-proBNP test – threshold 400pg/ml	0.791	Taylor et al. 2017[1365]	Ordinal logistic regression
Sensitivity of NT-proBNP test – threshold 280pg/ml	0.663	unpublished REFER data	Ordinal logistic regression
Specificity of NT-proBNP test – threshold 280pg/ml	0.693	unpublished REFER data	Ordinal logistic regression
Sensitivity of NT-proBNP test – threshold 125pg/ml	0.843	Taylor et al. 2017[1365]	Ordinal logistic regression
Specificity of NT-proBNP test– threshold 125pg/ml	0.419	Taylor et al. 2017[1365]	Ordinal logistic regression
Sensitivity of echocardiography plus clinical assessment	1.000	Committee assumption	Not applied
Specificity of echocardiography plus clinical assessment	1.000	Committee assumption	Not applied
Heart failure population cohorts			
Proportion of patients who receive a true positive test result at 400pg/ml threshold that are >400pg/ml (higher severity)	1.00	Calculated from unpublished REFER data	Not applied – determined by dividing the sensitivity of the 400pg/ml threshold by the sensitivity of each threshold
Proportion of patients who receive a true positive test result at 280pg/ml threshold that are >400pg/ml (higher severity)	0.881	Calculated from unpublished REFER data	
Proportion of patients who receive a true positive test result at 125pg/ml threshold that are >400pg/ml (higher severity)	0.693	Calculated from unpublished REFER data	
Proportion of patients that are >400pg/ml (higher severity) in the heart failure population if no NT-proBNP test is undertaken and all patients receive an echocardiography	0.584	Calculated from unpublished REFER data	
Proportion of true positive patients with NT-proBNP levels >400pg/ml (higher severity) that have LVSD<40	0.039	Calculated from unpublished REFER data	Dirichlet; LVSD<40: 2, LVSD40-50: 4, DD50: 46
Proportion of true positive patients with NT-proBNP levels >400pg/ml (higher severity) that have LVSD40-50	0.080	Calculated from unpublished REFER data	
Proportion of true positive patients with NT-proBNP levels >400pg/ml (higher severity) that have DD50	0.885	Calculated from unpublished REFER data	
Proportion of true positive patients at 280pg/ml threshold with NT-proBNP levels <400pg/ml	0.000	Calculated from unpublished REFER data	Dirichlet; LVSD<40: 0, LVSD40-50: 1, DD50: 6

Parameter description	Point estimate	Source	Distribution and parameters
(low severity) that have LVSD<40			
Proportion of true positive patients at 280pg/ml threshold with NT-proBNP levels <400pg/ml (low severity) that have LVSD40-50	0.143	Calculated from unpublished REFER data	
Proportion of true positive patients at 280pg/ml threshold with NT-proBNP levels <400pg/ml (low severity) that have DD50	0.857	Calculated from unpublished REFER data	
Proportion of true positive patients at 125pg/ml threshold with NT-proBNP levels <400pg/ml (low severity) that have LVSD<40	0.000	Calculated from unpublished REFER data	Dirichlet; LVSD<40: 0, LVSD40-50: 4, DD50: 19
Proportion of true positive patients at 125pg/ml threshold with NT-proBNP levels <400pg/ml (low severity) that have LVSD40-50	0.174	Calculated from unpublished REFER data	
Proportion of true positive patients at 125pg/ml threshold with NT-proBNP levels <400pg/ml (low severity) that have DD50	0.826	Calculated from unpublished REFER data	
Proportion of <400pg/ml (low severity) patients in the heart failure population if no NT-proBNP test is undertaken and all patients receive an echocardiography that have LVSD<40	0.027	Calculated from unpublished REFER data	Dirichlet; LVSD<40: 1, LVSD40-50: 5, DD50: 31
Proportion of <400pg/ml (low severity) patients in the heart failure population if no NT-proBNP test is undertaken and all patients receive an echocardiography that have LVSD40-50	0.135	Calculated from unpublished REFER data	
Proportion of <400pg/ml (low severity) patients in the heart failure population if no NT-proBNP test is undertaken and all patients receive an echocardiography that have DD50	0.838	Calculated from unpublished REFER data	
Proportion of false negative patients at 400pg/ml threshold with NT-proBNP levels <400pg/ml (low severity) that have LVSD<40	0.270	Calculated from unpublished REFER data	Dirichlet; LVSD<40: 1, LVSD40-50: 5, DD50: 31
Proportion of false negative patients at 400pg/ml threshold with NT-proBNP levels <400pg/ml (low severity) that have LVSD40-	0.135	Calculated from unpublished REFER data	

Parameter description	Point estimate	Source	Distribution and parameters
50			
Proportion of false negative patients at 400pg/ml threshold with NT-proBNP levels <400pg/ml (low severity) that have DD50	0.838	Calculated from unpublished REFER data	
Proportion of false negative patients at 280pg/ml threshold with NT-proBNP levels <400pg/ml (low severity) that have LVSD<40	0.333	Calculated from unpublished REFER data	Dirichlet; LVSD<40: 1, LVSD40-50: 4, DD50: 25
Proportion of false negative patients at 280pg/ml threshold with NT-proBNP levels <400pg/ml (low severity) that have LVSD40-50	0.133	Calculated from unpublished REFER data	
Proportion of false negative patients at 280pg/ml threshold with NT-proBNP levels <400pg/ml (low severity) that have DD50	0.833	Calculated from unpublished REFER data	
Proportion of false negative patients at 125pg/ml threshold with NT-proBNP levels <400pg/ml (low severity) that have LVSD<40	0.714	Calculated from unpublished REFER data	Dirichlet; LVSD<40: 1, LVSD40-50: 1, DD50: 12
Proportion of false negative patients at 125pg/ml threshold with NT-proBNP levels <400pg/ml (low severity) that have LVSD40-50	0.714	Calculated from unpublished REFER data	
Proportion of false negative patients at 125pg/ml threshold with NT-proBNP levels <400pg/ml (low severity) that have DD50	0.857	Calculated from unpublished REFER data	
SMRs			
Untreated HF-REF	9.91	Estimated from SOLVD[1311]	Log normal; u= 2.277, sigma = 0.198
HF-PEF	2.19	Estimated from I-PRESERVE trial[953]	Log normal; u= 0.767, sigma = 0.198
Treated COPD	1.28	Diaz-Guzman et al. 2011[382].	Log normal; u = 0.247, sigma = 0.064
Treated myocardial ischaemia	2.10	Emerging Risk Factors Collaboration[438]	Log normal; u = 0.742, sigma =0.049
Hospitalisation rates			
Annual heart failure hospitalisation rate for HF-PEF patients	0.044	I-PRESERVE trial[953]	Not applied
Annual heart failure hospitalisation rate for higher severity untreated HF-REF patients	0.2192	SOLVD trial[1311]	Not applied
Annual COPD hospitalisation rate for treated COPD	0.0605	Committee assumption that same as higher severity HF-REF	Not applied

Parameter description	Point estimate	Source	Distribution and parameters
Annual myocardial ischaemia hospitalisation rate for treated myocardial ischaemia	0.0201	Committee assumption that 1/3 of the rate of higher severity HF-REF	Not applied
Relative treatment effects			
All-cause mortality hazard ratio for a HF-REF treated with ACEi, BB, and MRA	0.440	Burnett et al. 2017	Log normal; u = -0.821, sigma = 0.234
All-cause mortality hazard ratio for a HF-REF treated with ACEi and BB	0.569	Burnett et al. 2017	Log normal; u= -0.564, sigma = 0.143
Heart failure hospitalisation relative risk reduction for HF-REF treated with ACEi	0.67 (0.61 – 0.74)	Flather et al. 2000	Log normal; u = -0.400, sigma = 0.049
Heart failure hospitalisation relative risk reduction for HF-REF treated with BB	0.71 (0.65 – 0.77)	Kotecha et al. 2014	Log normal; u = - -0.342, sigma = 0.043
Heart failure hospitalisation relative risk reduction for HF-REF treated with MRA	0.58 (0.47 - 0.70)	EMPHASIS-HF adjusted hazard ratio [1523]	Log normal; u = -0.545, sigma = 0.102
All-cause mortality risk ratio for treated COPD compared to untreated	0.7	Committee assumption	Triangular; min. =0.6, likeliest = 0.7, max. =0.9
COPD hospitalisation risk ratio for treated COPD compared to untreated COPD	0.7	Committee assumption	Triangular; min. =0.6, likeliest = 0.7, max. =0.9
All-cause mortality risk ratio for myocardial ischaemia treated with statin therapy compared to placebo	0.7	Scandanvian Simvastatin Survival study[1184]	Log normal; u = -0.357, sigma = 0.098
Myocardial ischaemia hosptialisation risk ratio for treated myocardial ischemia compared to untreated.	0.7	Committee assumption	Triangular; min. =0.6, likeliest = 0.7, max. =0.9
Severity adjustment			
Hazard ratio all-cause mortality, low severity vs higher severity HF-REF	0.272	Kubanek et al. 2009[807]	Lognormal; mean = -1.302, SE = 0.347
Risk ratio heart-failure hospitalisations, low severity vs higher severity HF-REF	0.274	Kubanek et al. 2009[807]	Lognormal; mean = -1.295, SE = 0.351
Hazard ratio all-cause mortality, low severity vs higher severity HF-PEF	0.636	GC assumption that HF-PEF experience half the risk reduction than HF-REF	Not applied, but calculated according to distributions above
Risk ratio heart-failure hospitalisations, low severity vs higher severity HF-PEF	0.637	GC assumption that HF-PEF experience half the risk reduction than HF-REF	Not applied, but calculated according to distributions above
Utility			
Utility heart failure patients	0.581	unpublished REFER	Beta; mean = 0.58, SD = 0.343

Parameter description	Point estimate	Source	Distribution and parameters
(untreated and treated)		data	
Utility at baseline of acute decompensation for heart failure (used to calculate utility decrement of heart failure hospitalisation)	0.550	Reed et al. 2013[1191]	Beta; mean = 0.55, SD = 0.290
Utility 30 days after acute decompensation for heart failure (used to calculate utility decrement of heart failure hospitalisation)	0.740	Reed et al. 2013[1191]	Beta; mean = 0.74, SD = 0.250
Duration of disutility from heart failure hospitalisation (days)	7/365	NHS Reference costs 15/16	Gamma; mean = 7; SD = 2.903
Utility of 'other condition' (treated and untreated)	0.573	unpublished REFER data	Beta; mean = 0.573, SD = 0.313
Duration of disutility from COPD hospitalisation	5/365	NHS Reference costs 15/16	Gamma; mean = 5; SD = 3.302
Duration of disutility from myocardial ischaemia hospitalisation	5/365	NHS Reference costs 15/16	Gamma; mean = 5; SD = 2.107
Resource use			
Number of GP appointments per year			
All HF-REF – year 1	2	Committee assumption	Not applied
All HF-PEF – year 1	1	Committee assumption	Not applied
Low severity HF-REF – post year 1	1	Committee assumption	Not applied
High severity HF-REF – post year 1	3	Committee assumption	Not applied
Low severity HF-PEF – post year 1	1	Committee assumption	Not applied
High severity HF-PEF – post year 1	2	Committee assumption	Not applied
Number of outpatient cardiology appointments per year			
All HF-REF – year 1	2	Committee assumption	Not applied
All HF-PEF – year 1	1	Committee assumption	Not applied
Low severity HF-REF – post year 1	1	Committee assumption	Not applied
High severity HF-REF – post year 1	2	Committee assumption	Not applied
Low severity HF-PEF – post year 1	0	Committee assumption	Not applied
High severity HF-PEF – post year 1	0	Committee assumption	Not applied
Number of specialist heart failure nurse appointments (30 mins) per year			
All HF-REF – year 1	10	Committee assumption	Not applied
All HF-PEF – year 1	1	Committee assumption	Not applied
Low severity HF-REF – post year 1	2	Committee assumption	Not applied
High severity HF-REF – post year 1	2	Committee assumption	Not applied
Low severity HF-PEF – post year 1	0	Committee assumption	Not applied
High severity HF-PEF – post year	0	Committee assumption	Not applied

Parameter description	Point estimate	Source	Distribution and parameters
1			
Unit costs			
NT-proBNP test	£ 26.07	Unpublished data	Log normal; u = 3.20 ; sigma = 0.341
Direct access plain film chest x-ray	£ 30.00	NHS Reference costs 15/16	Gamma; mean = 30, SD = 8.6
ECG	£ 37.00	NHS Reference costs 10/11.	Gamma; mean = 37, SD = 25.75
Full blood count	£ 3.00	NHS Reference costs 15/16	Gamma; mean = 3, SD =1.6
Clinical biochemistry	£ 1.00	NHS Reference costs 15/16	Not applied.
Echocardiography	£ 83.20	NHS Reference costs 15/16	Gamma; mean = 83.20, SD = 39
Consultant led cardiology first outpatient appointment	£ 156.00	NHS Reference costs 15/16	Gamma; mean = 156, SD = 26
Spirometry	£20.83	50 minute appointment with a Band 3 clinical support worker PSSRU 2016	Not applied
Consultant respiratory medicine outpatient appointment	£186.00	NHS reference costs 15/16	Gamma; mean =186, SD =61
Computerised tomography cardiovascular angiography (CTCA)	£137.00	NHS reference costs 15/16	Gamma; mean =137, SD = 66
Annual cost of ACEi	£ 18.53	Drug tariff May 2017	Not applied
Annual cost of BB	£16.10	Drug tariff May 2017	Not applied
Annual cost of MRA	£50.64	Drug tariff May 2017	Not applied
Consultant or non-consultant led cardiology follow-up appointment [activity weighted average of HRG codes WF01A-D for cardiology (service code 320)]	£ 114.13	NHS Reference costs 15/16	Gamma; mean = 114.13, SD = 39.5
GP appointment (lasting 9.2 minutes)	£ 36.00	PSSRU 2016	Not applied
30 minute heart failure specialist nurse appointment per hour	£ 54.00	PSSRU 2016	Not applied
Heart failure hospitalisation [activity weighted average of HRG codes EB03A-E]	£ 2,849	NHS Reference costs 15/16	Gamma; mean = 2,848, SD = 895
COPD hospitalisation [activity weighted average of HRG codes]	£1,935.83	NHS Reference costs 15/16	Gamma; mean =1935.83, SD = 506
Myocardial ischaemia hospitalisation [activity weighted average of HRG codes]	£2,176.61	NHS Reference costs 15/16	Gamma; mean =2176.61, SD = 681.5
Annual cost of COPD management	£ 589.91	NICE CG101 weighted by proportion of patients according to	Not applied

Parameter description	Point estimate	Source	Distribution and parameters
		GOLD classification as reported in Haughney et al 2014	
Annual cost of myocardial ischaemia management	£ 264	NICE CG94	Not applied

O.2.4 Computations

The model was constructed in TreeAge Pro 2016 and was evaluated by Monte Carlo cohort simulation.

O.2.4.1 Mortality and hospitalisations

Mortality and hospitalisation rates were converted into transition probabilities for the respective cycle length (2 weeks) before inputting into the Markov model. The probability of an event over the time horizon specified by the literature was converted into an annual rate, before being converted into a probability appropriate for the cycle length. The above conversions were done using the following formulae:

$Selected\ rate\ (r) = \dfrac{-\ln(1-P)}{t}$	Where *P*=probability of event over time *t* *t*=time over which probability occurs
$Transition\ Probability\ (P) = 1 - e^{-rt}$	Where *r*=selected rate *t*=cycle length

Constant mortality and hospitalisation rates were applied for full-lifetime horizon.

To calculate QALYs for each cycle, Q(t), the time spent in each health state of the model (2 weeks or 0.0385 years) was weighted by a utility value that is dependent on the time spent in the model and the treatment effect on mortality and hospitalisations. A half-cycle correction was applied. QALYs were then discounted to reflect time preference (discount rate 3.5%). QALYs during the first cycle were not discounted. The total discounted QALYs were the sum of the discounted QALYs per cycle.

Discount formula:

$\text{Discounted total} = \dfrac{\text{Total}}{(1+r)^n}$	Where: *r*=discount rate per annum *n*=time (years)

O.2.5 Sensitivity and scenario analyses

O.2.5.1 Diagnostic accuracy studies (SA1&2)

Due to the heterogeneity found between the diagnostic accuracy studies two scenario analyses were conducted to reflect the populations and diagnostic accuracy data from Verdu et al. 2012 (SA1) and Zaphiriou et al.2005 (SA2). It was considered important that these were also run probabilistically. However, when applying the ordinal logistic regression to the Verdu study data, the mean specificity values did not match the original study values. This was thought to be due to the fact that both 280pg/ml and 125pg/ml have a sensitivity of 1.00 and don't follow an order as such. Therefore the Verdu study was run both probabilistically (using the ordinal logistic regression model data) and deterministically (using the reported study data). The average estimates for the sensitivity and specificity values for Zaphiriou were consistent with the original data and were therefore only run probabilistically.see below as used in the probabilistic sensitivity anlayses.

The sensitivity and specificity values from the Verdu study, used in the deterministic sensitivity analysis are reported in Table 91 below. The average sensitivity and specificity values from theapplied ordinal logistic regression model distributions have been reported in Table 92 and **Table 93** below.

Both papers did not report the proportion of the population by LVSD<40 and LVSD40-50 but grouped these together and reported the proportion of patients with LVSD and ejection fraction of less than 50%. A pragmatic decision was made for modelling purposes for these patients to be cateogorised as HF-REF, resulting in 30% HF-REF in the Verdu study and 76% in Zaphiriou. Although this is inconsistent with the base case analysis, the committee did not think they could make a informed assumption about the proportion of LVSD<40. Neither did they consider it suitable to assume the same proportions as in the base case analysis. The different proportions of HF-REF and HF-PEF, and the life tables were adjusted to reflect the different study populations.

Table 91: Diagnostic accuracy data from Verdu et al. 2012[1442]

Diagnostic strategy	Sensitivity (95% CI)	Specificity (95% CI)
NT-proBNP threshold: 400pg/ml	0.88 (0.77- 0.96)	0.90 (0.84 - 0.94)
NT-proBNP threshold: 280pg/ml	1.00 (0.93- 1.00)	0.88 (0.82- 0.93)
NT-proBNP threshold: 125pg/ml	1.00 (0.93- 1.00)	0.66 (0.58 - 0.73)

Table 92: Diagnostic accuracy data from ordinal logistic regression model (Verdu et al. 2012[1442])

Diagnostic strategy	Sensitivity (95% CI)	Specificity (95% CI)
NT-proBNP threshold: 400pg/ml	0.886 (0.784 - 0.951)	0.918 (0.870 - 0.952)
NT-proBNP threshold: 280pg/ml	0.924 (0.848-0.970)	0.876 (0.818- 0.920)
NT-proBNP threshold: 125pg/ml	0.978 (0.950-0.993)	0.657 (0.582 - 0.726)

Table 93: Diagnostic accuracy data from ordinal logistic regression model (Zaphiriou et al. 2005[1525])

Diagnostic strategy	Sensitivity (95% CI)	Specificity (95% CI)
NT-proBNP threshold: 400pg/ml	0.845 (0.768 - 0.905)	0.696 (0.632 – 0.756)
NT-proBNP threshold: 280pg/ml	0.882 (0.815 – 0.929)	0.626 (0.558 – 0.691)
NT-proBNP threshold: 125pg/ml	0.958 (0.930 – 0.977)	0.350 (0.286- 0.418)

O.2.5.2 HF-REF classification (SA3)

There are very few (if any) trials that have been undertaken in patients with LVSD and an ejection fraction of 40-50% to determine whether or not there is any benefit in providing treatment to these patients. Therefore in the base-case analysis the committee agreed to make an assumption that these patients have the baseline mortality and hospitalisation rates of those with diastolic dysfunction with ejection fraction >50%. However, as this highly uncertain the committee considered it important to explore this assumption in a scenario analysis.

We therefore assumed that these patients had the same untreated mortality and hospitalisation rates and received treatment with the same treatment benefit as those with LVSD with ejection fraction <40% on triple therapy i.e. the proportion of HF-REF patients in the model increased from 3.4% to 13.5%.

Realistically, the committee expect that the LVSD40-50% patients would have mortality and hospitalisation rates that lie somewhere between those with LVSD with ejection fraction <40% and those with diastolic dysfunction with ejection fraction >50%.

O.2.5.3 Progression from heart failure with NT-proBNP levels <400pg/ml to heart failure with NT-proBNP levels >400pg/ml (SA4)

A one-way sensitivity analysis was conducted to explore the uncertainty of the assumption that the HF-REF patients with NT-proBNP levels <400pg/ml that are diagnosed early and treated remain with NT-proBNP levels <400pg/ml for 5 years, after which they progress to having NT-proBNP levels >400pg/ml heart failure with a minimum value of 1 year, and a maximum of 10 years.

O.2.5.4 Re-presentation of false negative patients to GP (SA5)

A sensitivity analysis was conducted assessing the effect of delaying re-presenting to the GP after a false negative NT-proBNP result to a maximum of 12 months. In line with this untreated HF-PEF patients with NT-proBNP levels below 400pg/ml were also assumed not to progress to over 400pg/ml for 12 months.

O.2.5.5 Mortality and hospitalisation rates for heart failure patients with NT-proBNP levels <400pg/ml (SA6)

The committee were interested in assessing how the mortality and hospitalisation rate reduction applied for heart failure patients with NT-proBNP levels <400pg/ml affects the results. The 95% confidence interval range was therefore applied for the HF-REF patients according to Kubanek et al. 2009. This study was only undertaken in HF-REF patients, and therefore in the base-case the committee assumed that the HF-PEF patients would have half the risk reduction. However, as this assumption was highly uncertain the committee considered it important to also vary this assumption to see how it would affect the model results. This assumption was therefore also adjusted so that HF-PEF patients have 25% to 100% of the risk reduction that HF-REF patients incur. A three-way sensitivity analysis was conducted to assess how the model results are affected when both of these assumptions are varied.

O.2.5.6 Non-heart failure population (SA7)

Due to the uncertainty in the assumptions around the proportions of conditions for the non-heart failure population sensitivity analyses were undertaken to vary these proportions. Maximum and minimum proportions were set for each of the three chosen conditions. The difference in proportions from the base-case were then split equally between the remaining two conditions. Please see [table] below outlining the proportions assessed in the sensitivity analyses.

In addition, similarly to the analysis undertaken by Monahan et al.2017 the committee wished to assess the effect on the model results of assuming that none of the non-heart failure population had alternative diagnoses that were misdiagnosed due to investigations for heart failure. [1012] Therefore a sensitvity analysis was undertaken, so that the non-heart failure population were all obese and therefore there was no change in management or detriment to heart failure testing.

Table 94: Sensitivity analysis proportions of conditions in non-heart failure population

	COPD	Myocardial ischaemia	Obesity
SA7a – min. COPD: 20%	20	23	57

	COPD	Myocardial ischaemia	Obesity
SA7b – max. COPD: 50%	50	7	43
SA7c – min. myocardial ischaemia: 5%	40	5	55
SA7d - max. myocardial ischaemia: 50%	17	50	33
SA7e - min. obesity: 30%	45	25	30
SA7f – max. obesity: 70%	25	5	70
SA7g: 100% obese	0	0	100

O.2.5.7 Mortality rates for untreated heart failure (SA8)

Due to a lack of clinical data available for the mortality rates for HF-REF and HF-PEF patients crude SMRs were calculated from large randomised control trial data (explained in methods above). The committee discussed that the populations in these trials were younger, likely selected patients, and did not include identifiable UK patient cohorts and therefore these calculations may not be very accurate. Therefore the committee considered it was important to assess the effect of these in one-way sensitivity analyses. A minimum SMR of 5 and a maximum of 15 was assessed for people with untreated HF-REF, and a minimum SMR of 1.5 and a maximum of 4 was assessed for people with HF-PEF.

O.2.5.8 Treatment effect for HF-REF (SA9)

The committee noted that the treatment effect applied for heart failure hospitalisations may be overestimated for people with HF-REF on triple or double therapy. Therefore the treatment effect for heart failure hospitalisation was agreed to be assessed in a two way sensitivity analysis where both those on triple and double therapy would only receive the treatment effect from ACEi alone [0.67 (0.61-0.74)].

The committee also noted the wide confidence intervals around the hazard ratios for mortality for those on double and triple therapy and therefore this was also assessed in a two way sensitivity analysis using the confidence intervals as the upper and lower values.

O.2.5.9 Treatment effect for COPD and myocardial ischaemia (SA10)

Due to the lack of mortality and hospitalisation data for the untreated COPD and myocardial ischaemia populations the committee considered it to be important that sensitivity analyses were conducted to test the robustness of the model results to changes in these parameters. Essentially these sensitivity analyses show how the treatment effect for COPD and myocardial ischaemia patients affects the model results.

To assess the effect of COPD and myocardial ischaemia treatment on mortality a two-way sensitivity analysis was undertaken where the treatment effect ranged from no effect to an 50% risk reduction for both COPD and myocardial ischaemia.

In addition, another two way sensitivity analysis was undertaken to assess the impact of the treatment effect on hospitalisations again ranging from no effect to an 50% risk reduction for both COPD and myocardial ischaemia.

O.2.5.10 Cost of NT-proBNP (SA11)

A one-way sensitivity analysis was conducted to assess the effect of altering the cost of the NT-proBNP test. A minimum cost of £15 and a maximum cost of £50 was explored. The committee were aware that NT-proBNP tests are due to come off patent in the next couple of years and therefore were particularly interested in a cost reduction of the test.

O.2.5.11 Cost of referral (SA12)

The committee acknowledged that in reality echocardiography is unlikely to be 100% accurate, but agreed that if an echocardiography was unclear it was likely that patients would then be referred for a cardiac magnetic resonance imaging scan (cMRI). Therefore, in this scenario analysis we assumed up to a maximum of 30% of patients who received an echocardiography would also incur the cost of a cMRI. For simplicity it was assumed that the cost of this was captured in the cost of a hospital admission for those diagnosed due to a hospitalisation prior to testing.

O.2.5.12 Cost of appointments for people with heart failure (SA13)

Due to the assumptions the committee made around the number of appointments people diagnosed with heart failure have in the first year and subsequently, two sensitivity analyses were undertaken, one doubling the number of appointments in the the first year and another doubling the number of appointments in subsequent years for people diagnosed with heart failure.

O.2.5.13 Waiting times for echocardiography and specialist clinical assessment (SA14)

There is a large amount of pressure on waiting lists for echocardiography clinics. Therefore the committee wanted to assess how longer waiting times would affect the model results for those with NT-proBNP levels below 400pg/ml. The committee agreed to maintain the 2010 Chronic Heart Failure guideline recommendations that patients with NT-proBNP levels greater than 2,000pg/ml wait 2 weeks for echocardiography and specialist clinical assessment, and those with NT-proBNP levels between 400-2,000pg/ml wait 6 weeks for echocardiography and specialist clinical assessment given the clear relationship between NT-proBNP level and prognosis. However, as it was not possible to determine the proportion of patients in the study population who had levels over 2,000pg/ml, it was assumed that all those over 400pg/ml would wait 6 weeks for echocardiography and specialist clinical assessment. To reflect a worst case scenario, patients with NT-proBNP levels below 400pg/ml were assumed to wait 18 weeks before receiving an echocardiography and specialist clinical assessment, in line with the referral to treatment targets for outpatient review.

For the strategy of all people receiving an echocardiography and specialist clinical assessment, the level of NT-proBNP would be unknown and therefore all patients waited 18 weeks for an echocardiography and specialist clinical assessment in this scenario.

O.2.5.14 Waiting time for spirometry (SA15)

The committee considered that a national average waiting time for spirometry is likely to be 6 weeks, but were conscious that in many places spirometry can be done much sooner, in some cases at point of presentation at a GP practice. Therefore a scenario analysis was undertaken where all spirometry tests are undertaken immediately.

O.2.5.15 Discount rate (SA16)

A sensitivity analysis using a discount rate of 1.5% for health benefits was conducted.

O.2.6 Model validation

The model was developed in consultation with the Committee; model structure, inputs and results were presented to and discussed with the Committee for clinical validation and interpretation.

The model was systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given inputs. The model was peer reviewed by a second experienced health economist from the NGC; this included systematic checking of the model calculations. The model methods were also peer reviewed from a clinical perspective by Professor Martin Cowie.

O.2.7 Estimation of cost-effectiveness

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with 2 alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold the result is considered to be cost-effective. If both costs are lower and QALYs are higher the option is said to dominate and an ICER is not calculated.

$$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$$ Where: Costs(A) = total costs for option A; QALYs(A) = total QALYs for option A	Cost-effective if: • ICER < Threshold

When there are more than 2 comparators, as in this analysis, options must be ranked in order of increasing cost then options ruled out by dominance or extended dominance before calculating ICERs excluding these options. An option is said to be dominated, and ruled out, if another intervention is less costly and more effective. An option is said to be extendedly dominated if a combination of 2 other options would prove to be less costly and more effective.

It is also possible, for a particular cost-effectiveness threshold, to re-express cost-effectiveness results in term of net monetary benefit (NMB). This is calculated by multiplying the total QALYs for a comparator by the threshold cost per QALY value (for example, £20,000) and then subtracting the total costs (formula below). The decision rule then applied is that the comparator with the highest NMB is the most cost-effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost.

$$Net\ Monetary\ Benefit\ (X) = \left(QALYs(X) \times \lambda\right) - Costs(X)$$ *Where: λ = threshold (£20,000 per QALY gained)*	Cost-effective if: • Highest net benefit

Both methods of determining cost-effectiveness will identify exactly the same optimal strategy. For ease of computation NMB is used in this analysis to identify the optimal strategy.

Results are also presented graphically where total costs and total QALYs for each diagnostic strategy are shown. Comparisons not ruled out by dominance or extended dominance are joined by a line on the graph where the slope represents the incremental cost-effectiveness ratio.

O.2.8 Interpreting Results

NICE's report 'Social value judgements: principles for the development of NICE guidance'[1048] sets out the principles that Committees should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost-effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- The intervention costs less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

As there are several interventions, the NMB is used to rank the strategies on the basis of their relative cost-effectiveness. The highest NMB identifies the optimal strategy at a willingness to pay of £20,000 per QALY gained.

O.3 Results

O.3.1 Base-case

In the base-case analysis 400pg/ml was found to be the most cost effective NT-proBNP threshold. Results are summarised below in Table 95 with regards to costs, QALYs and cost-effectiveness (net monetary benefit, and probability of cost effective at £20,000 per QALY threshold), Table 96 with regards to ranking of the strategies.

A threshold of 400pg/ml produces both the highest incremental QALYs and the highest incremental cost versus echo all, and has the highest net monetary benefit at £20,000 per QALY and is therefore the most cost effective diagnostic threshold for referral to echocardiography. The probability of 400pg/ml being the most cost effective option at £20,000 per QALY is 77%.

Table 95: Base case analysis results (probabilistic analysis)

Diagnostic strategy	Mean per patient		NMB at £20,000 threshold	Probability most CE option at £20,000 per QALY
	Costs	QALYs		
Echo all	£ 1,682	4.894	£96,200	14%
NT-proBNP threshold: 125pg/ml	£ 2,080	4.960	£97,120	1%
NT-proBNP threshold: 280pg/ml	£ 2,297	5.004	£97,779	8%
NT-proBNP threshold: 400pg/ml	£ 2,360	5.018	£97,990	77%

Abbreviations: CE = cost effective;CI: confirdence interval; QALYS: quality adjusted life years;.NMB: net monetary benefit.

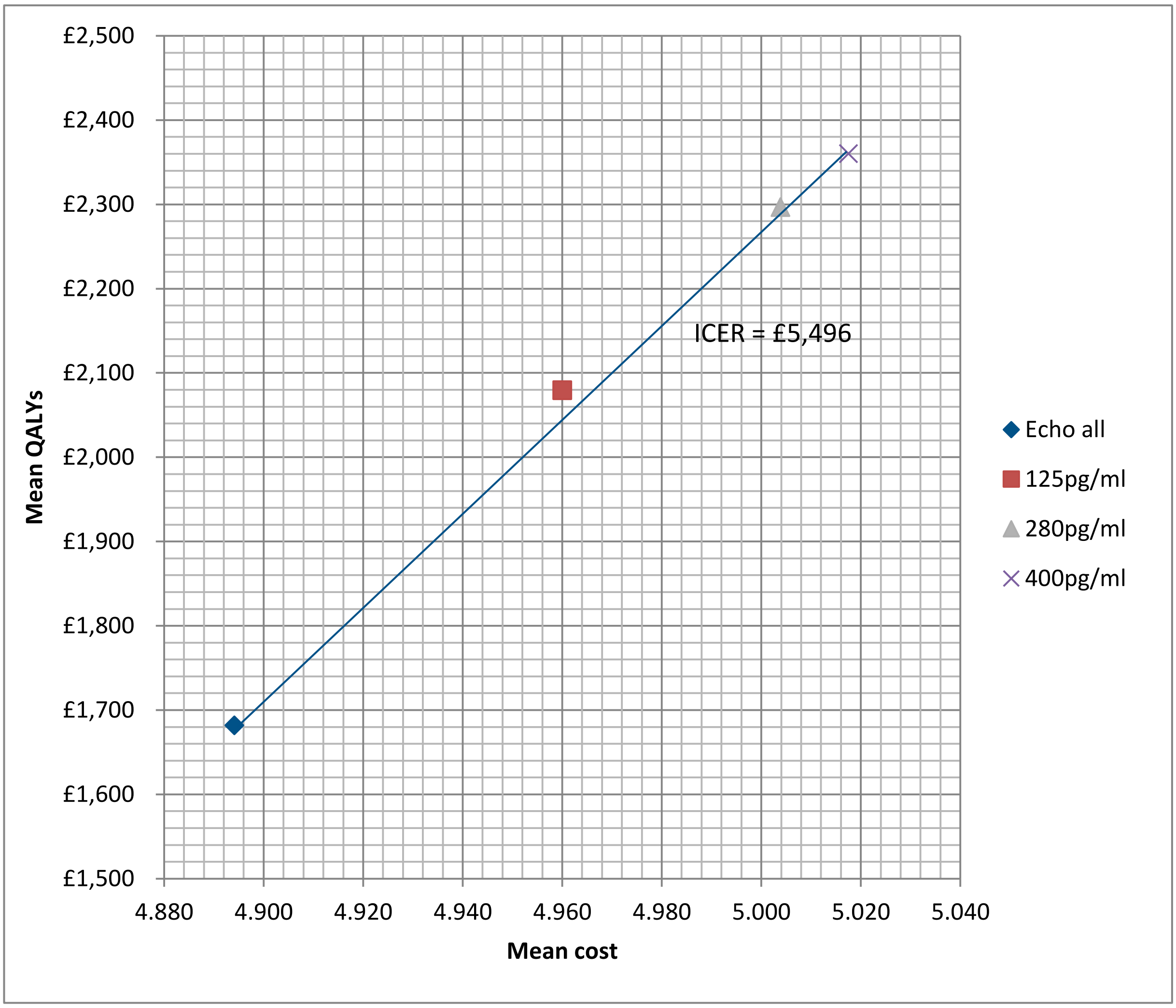
Table 96: Base case analysis ranking results

Diagnostic strategy	Probability ranked 1	Probability ranked 2	Probability ranked 3	Probability ranked 4
Echo all	14%	1%	3%	82%
NT-proBNP threshold: 125pg/ml	1%	13%	82%	5%
NT-proBNP threshold: 280pg/ml	8%	78%	9%	5%

Diagnostic strategy	Probability ranked 1	Probability ranked 2	Probability ranked 3	Probability ranked 4
NT-proBNP threshold: 400pg/ml	77%	8%	6%	9%

The mean costs and QALYs from the probabilistic analysis have also been presented graphically on the cost-effectiveness plane in **Figure 294**. The cost-effectiveness ratio of 400pg/ml versus echo all is £5,496.

Figure 294: Base-case cost-effectiveness plane showing mean costs and QALYs of each diagnostic strategy



The disaggregated costs and QALYs from the probabilistic base case analysis are summarised in Table 97, Table 98 and Table 99 below.

Table 97: Breakdown of diagnostic costs

Diagnostic strategy	Mean cost per patient to diagnose	Mean cost of

	Heart failure	COPD	Myocaridal ischaemia	echocardiography and specialist clinical assessment per patient
Echo all	£ 106	£ 309	£ 77	£ 235
NT-proBNP threshold: 125pg/ml	£ 148	£ 220	£ 69	£ 155
NT-proBNP threshold: 280pg/ml	£ 183	£ 160	£ 62	£ 98
NT-proBNP threshold: 400pg/ml	£ 200	£ 140	£ 60	£ 76

Table 98: Breakdown of management costs

Diagnostic strategy	Heart failure	COPD	Myocardial ischaemia
Echo all	£ 379	£ 651	£ 36
NT-proBNP threshold: 125pg/ml	£ 334	£ 1,096	£ 131
NT-proBNP threshold: 280pg/ml	£ 276	£ 1,375	£ 190
NT-proBNP threshold: 400pg/ml	£243	£ 1,466	£ 210

Table 99: Breakdown of QALYs

Diagnostic strategy	Heart failure population	Non-heart failure population
Echo all	0.9978	3.8968
NT-proBNP threshold: 125pg/ml	0.9937	3.9668
NT-proBNP threshold: 280pg/ml	0.9935	4.0107
NT-proBNP threshold: 400pg/ml	0.9929	4.0251

O.3.2 Sensitivity and scenario analyses

The results of the scenario and sensitivity analyses are summarised in Table 100 below. The results of the two diagnostic accuracy scenario analyses were run probabilistically are presented in more detail below. As previously mentioned, the Verdu scenario analysis was also run deterministically. All remaining sensitivity analyses were run deterministically.

Of the 15 sensitivity analyses conducted, as detailed in section O.2.5, only one scenario analysis led to a change in the optimal strategy.

Table 100: Sensitivity analysis results (SA1 –SA15)

Analysis	Incremental cost vs echo all			Incremental QALYs vs echo all			Optimal strategy
	125	280	400	125	280	400	
Base case							
Base case (deterministic)	£400	£619	£683	0.07	0.11	0.12	400pg/ml
Base case (probabilistic)	£398	£615	£678	0.07	0.11	0.12	400pg/ml
SA1a: Scenario analysis – Verdu (deterministic)	£698	£922	£925	0.12	0.16	0.15	280pg/ml
SA1b: Scenario analysis – Verdu (probabilistic)	£690	£903	£939	0.11	0.15	0.15	400pg/ml
SA2: Scenario analysis – Zaphiriou (probabilistic)	£317	£530	£579	0.04	0.05	0.05	280pg/ml
Sensitivity analyses (deterministic)							
SA3: Proportion of HF-REF	£399	£612	£673	0.06	0.09	0.10	400pg/ml
SA4: Time to progression							
6 months	£399	£618	£682	0.07	0.11	0.13	400pg/ml
1 year	£399	£618	£682	0.07	0.11	0.13	400pg/ml
2 years	£399	£618	£683	0.07	0.11	0.12	400pg/ml
3 years	£399	£619	£683	0.07	0.11	0.12	400pg/ml
4 years	£400	£619	£683	0.07	0.11	0.12	400pg/ml
SA5: Time to re-presentation to GP - 12 months	£399	£618	£682	0.07	0.11	0.12	400pg/ml
SA6: <400pg/ml mortality and hospitalisation adjustment	This was run as a 3-way sensitivity analysis. This had no effect on the overall result.						400pg/ml
SA7a: Adjusting proportions for non-heart failure population. Min. COPD: 20%	£ 290	£ 440	£ 482	0.06	0.10	0.11	400pg/ml
SA7b: Adjusting proportions for non-heart failure population. Max. COPD: 50%	£ 510	£ 798	£ 885	0.07	0.12	0.13	400pg/ml
SA7c: Adjusting proportions for non-heart failure population. Min. myocardial ischaemia: 5%	£ 390	£ 603	£ 665	0.05	0.09	0.10	400pg/ml
SA7d: Adjusting proportions for non-heart failure population.	£ 430	£ 668	£ 738	0.11	0.17	0.20	400pg/ml

Analysis	Incremental cost vs echo all			Incremental QALYs vs echo all			Optimal strategy
	125	280	400	125	280	400	
Max. myocardial ischaemia: 50%							
SA7e: Adjusting proportions for non-heart failure population. Min. obesity: 30%	£ 571	£ 898	£ 997	0.10	0.16	0.18	400pg/ml
SA7f: Adjusting proportions for non-heart failure population. Max. obesity: 70%	£ 229	£ 340	£ 370	0.04	0.06	0.07	400pg/ml
SA7g: Adjusting proportions for non-heart failure population (all obese)	-£72	-£149	-£181	-0.004	-0.004	-0.005	400pg/ml
SA8a: SMRs for HF-REF							
Minimum value: 5	£400	£619	£684	0.07	0.11	0.12	400pg/ml
Maximum value: 15	£400	£619	£683	0.07	0.11	0.12	400pg/ml
SA8b: SMRs for HF-PEF							
Minimum value: 1.5	£398	£614	£676	0.07	0.11	0.12	400pg/ml
maximum value: 4	£403	£627	£694	0.07	0.11	0.12	400pg/ml
SA9a: Reduced treatment effect for heart failure hosptalisations. Both HF-REF on triple therapy and those on double therapy 0.67	This was run as a 2-way sensitivity analysis. P This had no effect on the overall result.						400pg/ml
SA9b: Treatment effect for heart failure mortality HF-REF (double and triple therapy)	This was run as a 2-way sensitivity analysis. This had no effect on the overall result.						400pg/ml
SA10a: Treatment effect for COPD and myocardial ischaemia hospitalisations	This was run as a 2-way sensitivity analysis. This had no effect on the overall result.						400pg/ml
SA10b: treatment effect for COPD and myocardial ischaemia mortality	This was run as a 2-way sensitivity analysis. This had no effect on the overall result.						400pg/ml
SA11: Cost of NT-proNP test							
Minimum cost: £10	£383	£602	£665	0.07	0.11	0.12	400pg/ml
Maximum cost: £50	£425	£645	£710	0.07	0.11	0.12	400pg/ml
SA12: Cost of echocardiography and specialist clinical assessment	£377	£579	£637	0.07	0.11	0.12	400pg/ml
SA13a: Double 1st year appointment costs for people with heart failure	£392	£602	£661	0.07	0.11	0.12	400pg/ml
SA13b: Double on-going	£386	£204	£645	0.07	0.11	0.12	400pg/ml

Analysis	Incremental cost vs echo all			Incremental QALYs vs echo all			Optimal strategy
	125	280	400	125	280	400	
appointment costs for people with heart failure							
SA14: Waiting times echocardiography (18 weeks <400pg/ml)	£415	£638	£704	0.07	0.11	0.12	400pg/ml
SA15: Waiting time spirometry	£14	£24	£35	0.02	0.04	0.05	400pg/ml
SA16: Discount rate 1.5%	£451	£702	£776	0.08	0.14	0.15	400pg/ml

O.3.2.1 Diagnostic accuracy scenario analyses (SA1 & SA2)

SA1a - Verdu et al. 2012 (deterministic)

In this scenario analysis 280pg/ml was found to be the most cost effective NT-proBNP threshold. Results are summarised below in Table 101 in terms of costs, QALYS, and cost effectiveness (net monetary benefit).

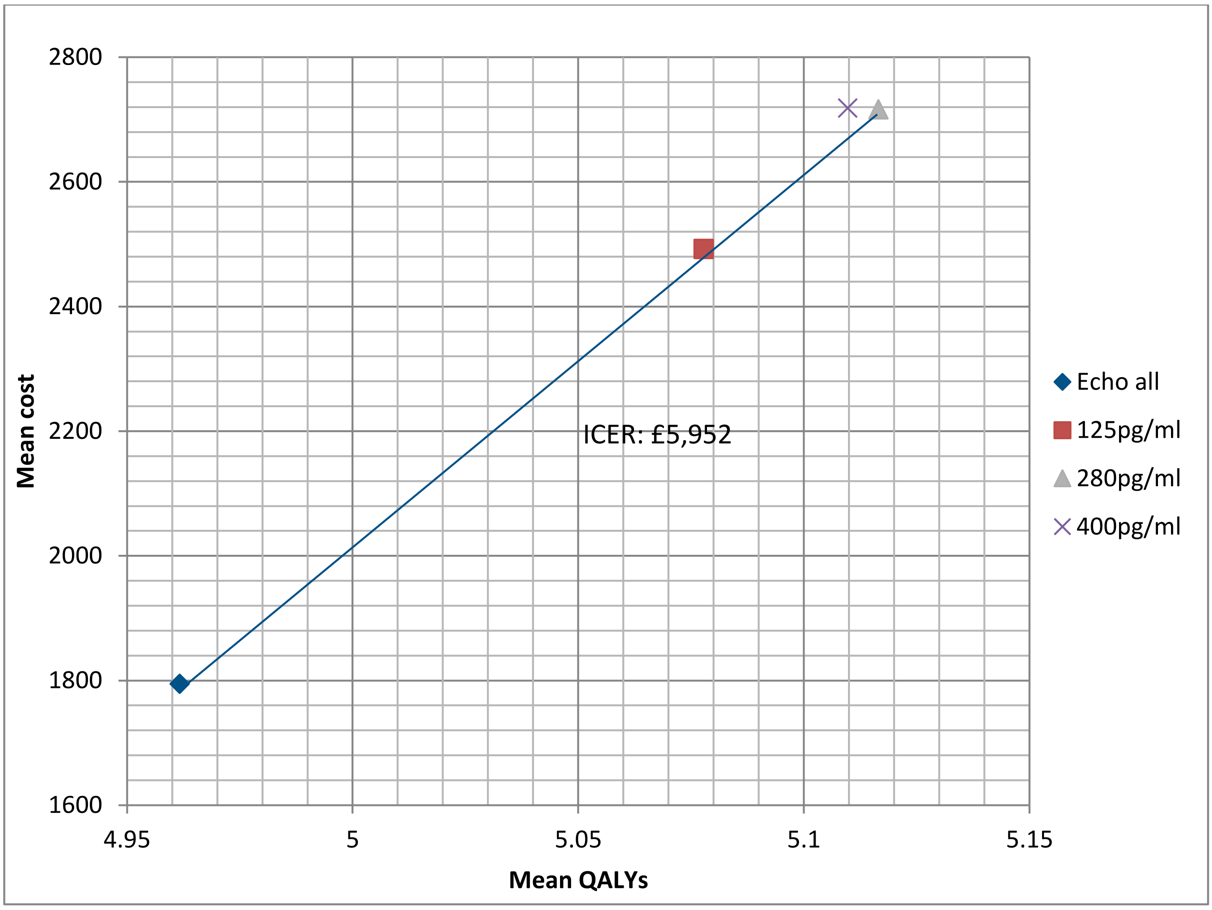
Table 101: Verdu et al. 2012 results (deterministic analysis)

Diagnostic strategy	Mean per patient		NMB at £20,000 threshold
	Costs	QALYs	
Echo all	£1,794	4.962	£97,439
NT-proBNP threshold: 125pg/ml	£2,492	5.078	£99,064
NT-proBNP threshold: 280pg/ml	£2,716	5.117	£99,615
NT-proBNP threshold: 400pg/ml	£2,719	5.110	£99,476

Abbreviations: QALYS: quality adjusted life years; NMB: net monetary benefit.

A threshold of 280pg/ml dominates 400pg/ml with higher mean QALYs and a lower mean cost, and extendedly dominates 125pg/ml. The incremental cost effectiveness ratio of 280pg/ml compared to echo all is £5,952 per QALY gained. This is shown in Figure 295 below.

Figure 295: Verdu et al. 2012 diagnostic accuracy study (deterministic) cost-effectiveness plane showing the mean costs and QALYs of each diagnostic strategy



SA1b - Verdu et al. 2012 (probabilistic)

In this scenario analysis 400pg/ml was found to be the most cost effective NT-proBNP threshold. Results are summarised below in Table 102 below in terms of costs, QALYs and cost-effectiveness (net monetary benefit, and probability of cost effective at £20,000 per QALY threshold), and Table 103 with regards to ranking of the strategies.

A threshold of 400pg/ml produces both the highest incremental QALYs and the highest incremental cost versus echo all, and has the highest net monetary benefit at £20,000 per QALY and is therefore the most cost effective diagnostic threshold for referral to echocardiography. The probability of 400pg/ml being the most cost effective option at £20,000 per QALY is 62%.

Table 102: Verdu et al. 2012 diagnostic study analysis results (probabilistic analysis)

Diagnostic strategy	Mean per patient		NMB at £20,000 threshold	Probability most CE option at £20,000 per QALY
	Costs	QALYs		
Echo all	£1,812	4.991	£98,006	16%
NT-proBNP threshold: 125pg/ml	£2,502	5.105	£99,606	5%
NT-proBNP threshold: 280pg/ml	£2,716	5.139	£100,063	17%
NT-proBNP threshold: 400pg/ml	£2,751	5.143	£100,100	62%

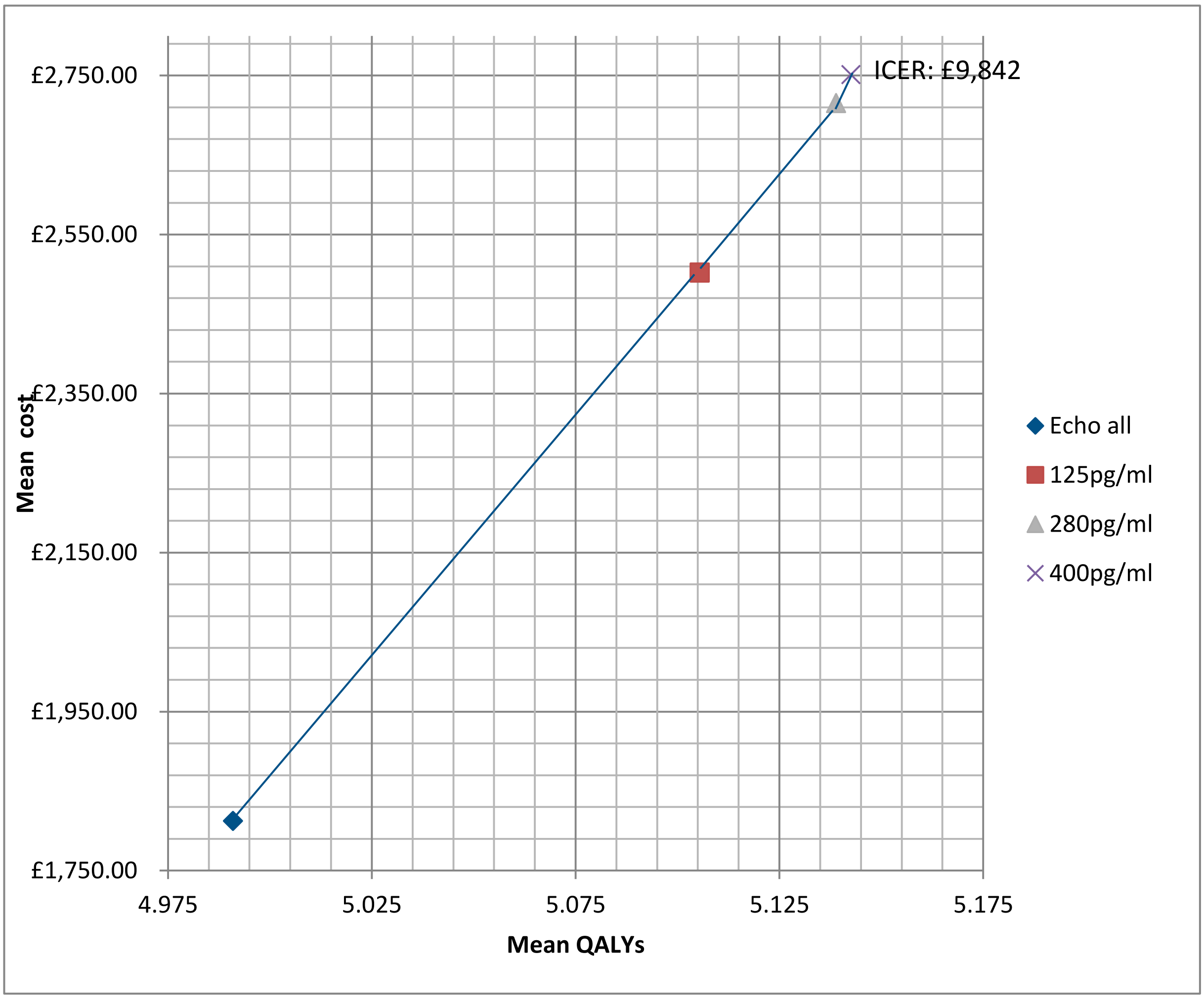
Abbreviations: CE = cost effective; QALYS: quality adjusted life years; NMB: net monetary benefit.

Table 103: Verdu et al. 2012 diagnostic study analysis ranking results

Diagnostic strategy	Probability ranked 1	Probability ranked 2	Probability ranked 3	Probability ranked 4
Echo all	16%	1%	1%	82%
NT-proBNP threshold: 125pg/ml	5%	19%	75%	0%
NT-proBNP threshold: 280pg/ml	17%	66%	17%	0%
NT-proBNP threshold: 400pg/ml	62%	14%	6%	18%

The mean costs and QALYs from the probabilistic analysis have also been presented graphically on the cost-effectiveness plane in **Figure 296**. The incremental cost-effectiveness ratio of 400pg/ml versus 280pg/ml is £9,842.

Figure 296: Verdu et al. 2012 diagnostic accuracy study (probabilistic) cost-effectiveness plane showing the mean costs and QALYs of each diagnostic strategy



SA2 - Zaphiriou et al. 2005

In this scenario analysis 280pg/ml was found to have the highest net monetary benefit. Results are summarised below in Table 104 in terms of costs, QALYs and cost-effectiveness (net monetary benefit, ranking and probability of cost effective at £20,000 per QALY threshold), and Table 103 with regards to ranking of the strategies.

Table 104: Zaphiriou et al. 2005 diagnostic study analysis results (probabilistic analysis)

Diagnostic strategy	Mean per patient		NMB at £20,000 threshold	Probability most CE option at £20,000 per QALY
	Costs	QALYs		
Echo all	£2099	4.482	£87,534	30%
NT-proBNP threshold: 125pg/ml	£2,415	4.520	£87,977	16%
NT-proBNP threshold: 280pg/ml	£2,629	4.534	£88,047	19%
NT-proBNP threshold: 400pg/ml	£2,677	4.531	£87,945	35%

Abbreviations: CE = cost effective; QALYS: quality adjusted life years; NMB: net monetary benefit.

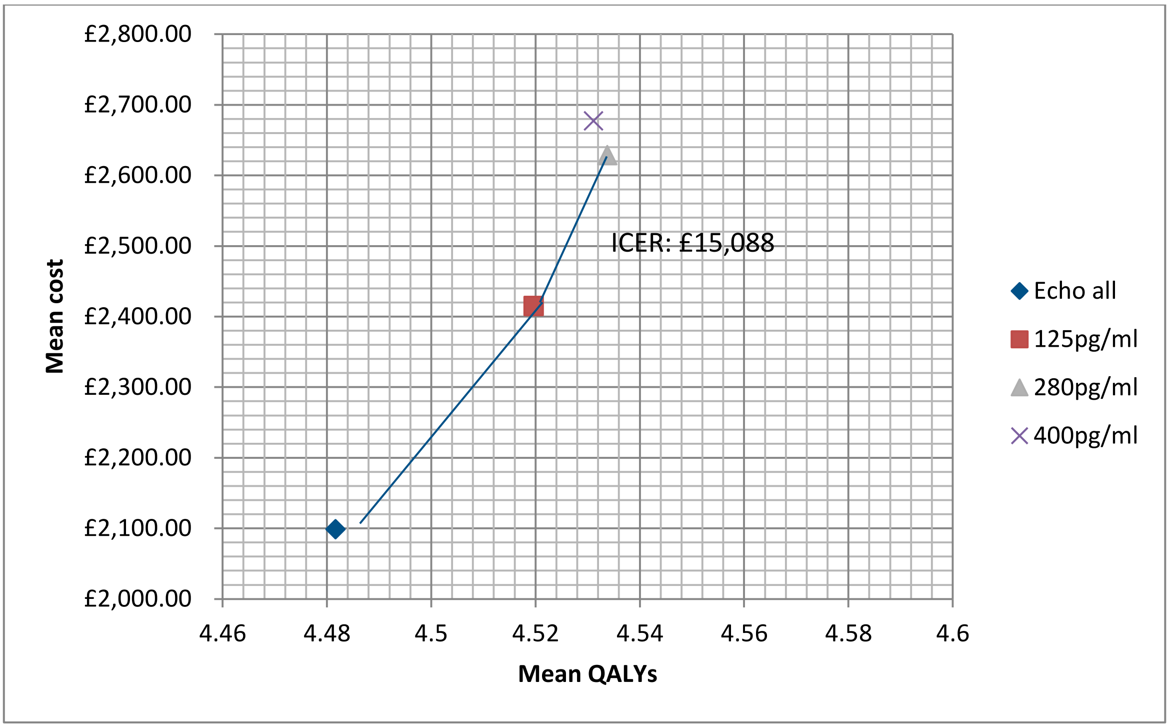
Table 105: Zaphiriou et al. 2005 diagnsotic study analysis ranking results

Diagnostic strategy	Probability ranked 1	Probability ranked 2	Probability ranked 3	Probability ranked 4
Echo all	30%	7%	4%	58%
NT-proBNP threshold: 125pg/ml	16%	36%	48%	0%
NT-proBNP threshold: 280pg/ml	19%	44%	37%	0%
NT-proBNP threshold: 400pg/ml	35%	13%	11%	41%

The mean costs and QALYs from the probabilistic analysis have also been presented graphically on the cost-effectiveness plane in Figure 297. The incremental cost-effectiveness ratio of 280pg/ml versus 125pg/ml is £15,088.

Figure 297: Zaphiriou et al. 2005 diagnostic accuracy study cost-effectiveness plane showing the mean costs and QALYs of each diagnostic strategy

ICER = £19,458



O.4 Discussion

O.4.1 Summary of results

This analysis found 400pg/ml to be the most cost effective NT-proBNP threshold to use for referring people presenting to primary care with signs and symptoms of heart failure for echocardiography. This conclusion was robust to all sensitivity analyses on the base-case analysis.

This result appears to be driven by the cost reductions and QALY benefits of diagnosing other conditions in the non-heart failure population earlier, and consequently the model results are driven by the specificity rather than the sensitivity of the strategies. This suggests that the benefits of diagnosing COPD and myocardial ischaemia, which are more common than heart failure and can be well treated, are greater than those for the earlier diagnosis of heart failure. Vice versa the effects of missing the COPD and myocardial ischaemia populations are greater than missing people with heart failure.

O.4.2 Limitations and interpretation

This analysis suggests that 400pg/ml is the most cost effective threshold for referring patients presenting to primary care with signs and symptoms of heart failure. Many uncertainties in the model structure, and assumptions were explored in sensitivity analyses.

The primary limitation of this model is that the diagnostic accuracy data was taken from one diagnostic accuracy study. This was due to the significant inconsistency in the results when a meta-analysis of three studies was undertaken. The committee discussed the diagnostic accuracy studies chosen for the meta-analysis at length to agree on chosing one of the studies for the base case analysis.

The committee were aware of the limitations of the diagnostic accuracy study by Taylor et al. 2016 chosen for the base case analysis. Particularly, the committee were concerned about the low proportion of HF-REF in the study, as they would have expected the proportion of HF-REF patients presenting to primary care to be higher.

The diagnostic accuracy study by Verdu et al. 2012 was not considered to be appropriate for the base case analysis as it was a Spanish study and not considered to be representative of current UK practice, as it might represent a different model of care and investigation and therefore was not generalisable to a UK population. The committee discussed that Zaphiriou et al.2005 was a UK study, however was conducted over ten years ago and again is unlikely to represent the current UK population presenting to primary care. Additionally, the criteria for diagnosing HF-PEF patients on echocardiography were not specifically defined as they are today.

The study by Taylor et al. 2016 were recruited from 28 practices across central England between 2011 and 2013. Therefore, this population was considered by the committee to be the most representative of current the population presenting to primary care in current UK practice. The committee raised concern about the low proportion of HF-REF patients identified in this study. The committee considered that this may be due to study selection bias, as patients with severe symptoms, who are thought to be of high risk, are often not recruited into these types of clinical studies due to concern that there would be a delay in their treatment. The committee considered that the patients considered to be of high risk are more likely to have HF-REF than HF-PEF. However, the extent of possible selection bias is unknown. The committee acknowledged that the proportion of HF-REF patients in the heart failure population seems to be gradually declining, but still considered the proportion of HF-REF patients in the study to be low. The committee were concerned that this may bias the model results, as were there more clinical benefit to diagnosing heart failure the greater the benefit of earlier detection and therefore a lower NT-proBNP threshold. This effect was demonstrated in one of the sensitivity analyses (SA3): as the proportion of HF-REF in the model was increased, the cost effectiveness of 400pg/ml decreased – although the ICER was still well below the £20,000 threshold. The committee also acknowledged that were there clinically effective treatment for HF-PEF patients, then a lower NT-proBNP threshold is likely to be most cost effective.

Due to uncertainty around the diagnostic accuracy of the NT-proBNP test, two scenario analyses were undertaken to assess the diagnostic accuracy data and from two other study populations included in the clinical review.

A further limitation of the anlaysis is that when applying the ordinal logistic regression model to the Verdu data to enable the results to be run probabilistically, the mean sensitivity values were not consistent with the reported study values. Therefore the Verdu study was run both probabilistically (using the ordinal logistic regression model data) and deterministically (using the reported study data).

The inconsistency in the mean values from the regression model and those reported in the study was thought to be due to the fact that the sensitivity of 280pg/ml and 125pg/ml threshold were both 100%. Ordinal logisitic regression was thought to be the most suitable method to fit a distribution to the diagnostic accuracy data to ensure that the sensitivity and specificity values maintained their order according to the threshold level for each run. Using this method one assumes that the model is predicting values that the data would show if you had a greater sample size.

The probabilistic analysis for Verdu found 400pg/ml to be the most cost effective NT-proBNP threshold, however when run deterministically using the reported study values 280pg/ml was found to be the most cost-effective threshold. This is likely to be due to the fact that this threshold had both the highest sensitivity and highest specificity.

The other scenario analyses (Zaphiriou) found 280pg/ml to be the most cost effective NT-proBNP threshold. The committee considered that the change in result from the Zaphiriou study was due to the high proportion of HF-REF patients in the population, supporting their previous hypothesis that the greater the proportion of heart failure likely to see benefits from treatment the more likely a lower threshold will be more cost effective.

The results of the scenario analyses were much more uncertain than those of the base case. One reasoning for this was considered to be due to the fact that the sensitivity and specificity values of the NT-proBNP across the thresholds are much closer in these studies compared to those in the base case diagnostic accuracy study.

Another limitation of this model is that many structural assumptions were required with little clinical evidence to allow direct estimates to be made for them. Many of these were explored in the sensitivity analyses above, and did not change the base-case anlaysis results. In particular, it is difficult to test the assumptions made with regards to the non-heart failure population. It was not practical to model all other possible conditions that patients may have if they do not have heart failure. The committee discussed that although COPD, myocardial ischaemia, and obesity are common alternative conditions there are multiple other alternative conditions that patients could have, such as pulmonary fibrosis. As the model is primarily driven by the test specificity, this population is a very important to assess. The make-up of the non-heart failure population could affect the results depending on the cost and QALY impact of delaying the diagnosis of other underlying conditions. This was assessed in one of the sensitivity analyses (SA7) assessing may different proportions of other conditions. None of these affected the overall result, except for one where it was assumed that the non-heart failure population had no additional diagnoses (represented in the model as an obese population). This analysis demonstrated echo all to be the most costly and most effective strategy, however this was not cost effective at the £20,000 threshold (ICER: £35,000) due to the very small QALY gain.

Lastly, the costs and treatment effects of rehabilitation were not taken into account in the model, due to the very small proportion of patients that undertake rehabilitation. Therefore the overall cost and treatment effect of heart failure management may be underestimated in the model, although this is likely to be small.

O.4.3 Generalisability to other populations or settings

The committee considered that the results of the base case analysis are generalisable to the UK population for patients presenting to primary care with signs and symptoms of heart failure. This threshold is not applicable for people presenting in an acute setting with signs and symptoms of heart failure. A threshold of 300pg/ml for NT-proBNP is recommended in the Acute Heart Failure guideline (CG187).

O.4.4 Comparisons with published studies

One economic evaluation (Monahan et al. 2017) was identified assessing different NT-proBNP thresholds in the diagnostic pathway for patients presenting with signs and symptoms of heart failure, as mentioned in the introduction.[1012] This study also used the diagnostic accuracy data from the study by Taylor et al. 2016, however the sensitivity and specificity of the strategies were calculated based on a reference standard that included the level of NT-proBNP to diagnose heart failure, therefore introducing incorporation bias.

Monahan et al. 2017 compared various diagnostic strategies including the MICE clinical decision rule using upper and lower NT-proBNP cut-off values, the 2010 NICE guideline recommended strategy (patients with a history of myocardial infarction (MI) are referred straight for echocardiography, all other patients receive a NT-proBNP test and are referred for echocardiography at a threshold of 400pg/ml), NT-proBNP threshold of 125pg/ml, echocardiography for all, and do nothing. The analysis found the 2010 NICE guideline strategy to be the most cost effective strategy (ICER: £4,400 per QALY gained) for patients presenting to primary care with signs and symptoms of heart failure. In this analysis the echocardiography for all stratgey was most effective and most costly, closely followed by a NT-proBNP threshold of 125 pg/ml. However, the ICERs for these diagnostic strategies were not cost effective at the NICE threshold of £20,000-£30,000 per QALY gained (£125,000 and £69,000 respectively) due to a very small QALY gain in early diagnosis.

In contrast to Monahan et al. 2017, the echocardiography for all strategy in the guideline analysis has the lowest costs and QALYs, followed by a NT-proBNP threshold of 125pg/ml. The committee noted that Monahan et al. 2017 did not report on any assumptions, costs or QALYs applied to the population who do not have heart failure in the model. Therefore as a result the committee could only deduce that this was not taken into account or assumed that there were no alternative diagnoses for this population. Consequently, the committee acknowledged that the results of the study are driven by the sensivity of each of the strategies (sensitivity increases as the threshold decreases) as you would expect that the strategy with the highest sensitivity would achieve the greatest benefits for the heart failure patients due to a greater proportion of patients receiving an early diagnosis.

The original anlaysis undertaken for this guideline incorporated the costs and QALYs of the non heart failure population, and the cost and QALY effect of a delayed diagnosis for some of these patients due to investigations for heart failure. As a result the model results seem to be driven by the specificity of the diagnostic strategies (as the NT-proBNP threshold decreases, specificity decreases) and the low prevalence of heart failure in the study population. The results of this analysis still do reflect the increased benefit to heart failure patients due to the increase in sensitivity of the test as the NT-proBNP threshold decreases, however this is significantly outweighed by the loss of benefit to the non heart failure population of a delayed diagnosis of their underlying condition. As mentioned above, to assess the effect of this, we conducted a sensitivity analyses (SA7) where it was assumed that the non-heart failure population had no additional diagnoses (represented in the model as an obese population). This analysis demonstrated similar results to the study with echo all having the greatest QALY benefit as well as the highest cost, however it was not cost effective at the £20,000-£30,000 threshold.

Overall, the committee noted that it was interesting that despite the two different approaches to modelling the overall optimal strategy for both was an NT-proBNP threshold of 400pg/ml. The committee discussed the pathway for those with a history of myocardial infarction being referred for echocardiography and no longer considered this to be appropriate as the definition of myocardial infarction has changed over time.

O.4.5 Conclusions

An original cost-utility analysis found that 400pg/ml is the most effective NT-proBNP threshold to use for referring people presenting with signs and symptoms of heart failure for echocardiography compared to 280pg/ml, 125pg/ml and referring all patients straight for echocardiography. It was cost effective compared to referring all patients for echocardiography (ICER:£6,076 per QALY gained). This was assessed as directly applicable with potentially serious limitations.

O.4.6 Implications for future research

As discussed above, the committee were primarily concerned about the diagnostic accuracy studies assessed in this model. Their main concerns were the small sample size, and the populations being recruited being representative of the current UK population presenting to primary care. Therefore, the committee considered it be important for further, larger diagnostic accuracy studies to be undertaken in this area to allow better estimates of the true diagnostic accuracy of the NT-proBNP test thresholds and hence which is the most clinically and cost effective threshold.

Appendix P: Research recommendations

P.1 Diuretic therapy for managing fluid overload in people with advanced heart failure in the community

Research question:

In people with advanced heart failure and significant peripheral fluid overload, what is the clinical and cost effectiveness of oral, subcutaneous and intravenous diuretic therapy in the community?

Why this is important:

This research is critical to inform practice of how best to manage people with advanced heart failure in the community if they develop significant peripheral fluid overload. These people are more likely to have multiple admissions which, together with fluid overload, has a negative impact on their quality of life. Management in the community can minimise disruption for the person and reduce costs from hospital admissions. Knowledge of the most clinically and cost-effective routes of administration for diuretic therapy will dictate the level of resource needed to provide the service. Intravenous and subcutaneous diuretics need to be administered by nursing or healthcare staff, whereas oral formulations do not.

Criteria for selecting high-priority research recommendations:

PICO question	Population: People with advanced heart failure (NYHA III or IV) in the community Interventions/comparators: • IV diuretics (furosemide or torsemide) (continuous or bolus) + oral metolazone/thiazides • IV diuretics (furosemide or torsemide) (continuous or bolus) alone • Subcutaneous diuretics (furosemide or torsemide) +/- oral metolazone/thiazides • Oral diuretics (bumetanide or furosomide and/or metolazone/thiazides). All compared to one another Outcomes: Critical outcomes • Improvement in Quality of life • Reduction in unplanned hospitalisations (count rate) • Reduction in unplanned hospitalisations (number of bed days) Important outcomes • Improvement in dyspnoea • Weight reduction • Change in oedema • Change in NYHA class • Patient and carer satisfaction • Improved mobility/ reduced pain (due to reduced leg swelling) • Mortality

Importance to patients or the population	Diuretic regimens which produce good outcomes with minimum disruption for patients in their preferred setting of care are likely to improve their quality of life. Oral therapy is preferred to IV and SC routes due to patient convenience, flexibility in timing and location of administration. It may also reduce the use of health care resources for inpatient and ambulatory patient care services. However, this is only if the oral route was found to be as effective as the IV or SC route. If this is not the case, then patients would derive a better outcome from using IV or SC diuretic therapy, leading to a better quality of life and less admissions to hospital.
Relevance to NICE guidance	Research in this area will enable NICE to advise healthcare professionals and patients on the clinical and cost effectiveness of various routes of administration of diuretic regimens, in the community, when managing patients with advanced heart failure and significant peripheral fluid overload.
Relevance to the NHS	If the administration of IV or SC diuretics in the community was found to be more clinically and cost effective, this would require additional resource to provide this service in the community.
National priorities	Heart failure management is a national priority and is included in the Quality and Outcomes Framework (QOF). The national heart failure audit is evidence that HF is a national priority due to its impact on QoL and cost to the NHS.
Current evidence base	No randomised controlled studies were found that addressed the review question,
Equality	The intervention would be appropriate for people who were less mobile, frail older adults and those that find hospital based care extremely challenging. For example people with sight loss or visual impairment.
Study design	A three arm, open label, randomised control trial comparing all three routes of diuretic administration.
Feasibility	The research can be carried out in a realistic timescale. The design of the study should ensure that all patients are receiving appropriate therapy. A placebo control would be inappropriate in this context.
Other comments	N/A
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.

P.2 Cardiac MRI versus other imaging techniques for diagnosing heart failure

Research question: What is the optimal imaging technique for the diagnosis of heart failure?

Why this is important:

The role of cardiac MRI in the detection and characterisation of several structural and functional cardiac abnormalities has become well established over the past 25 years. In people with heart failure, cardiac MRI provides reliable and reproducible assessments of the left ventricular (and to a degree the right ventricular) shapes, volumes and ejection fractions. It also provides spatial assessments of the congenital and acquired structural abnormalities of the heart and their interrelationships with the remainder of the heart, as well as functional and haemodynamic assessments of these abnormalities on the heart's performance. Finally, cardiac MRI provides valuable information about the myocardial structure and metabolism, including the presence of inflammation, scarring, fibrosis and infiltration. Much of this information could be provided by other non-invasive imaging techniques, chiefly echocardiography. This question aims to find the optimal imaging technique for the clinical diagnosis of heart failure.

Criteria for selecting high-priority research recommendations:

PICO question	Objective: To compare three strategies of the use of cMR as a compulsory test following echocardiography in all patients with suspected heart failure; or selectively in some of those diagnosed as having heart faiure by echocardiography or indeed not use cMR at all and rely exclusively on echocardiography? Population: People with suspected heart failure in a community or outpatient setting, in the UK. Diagnostic algorithm: A. cMR to follow the use of echocardiography in all patients. B. cMR to be used selectively in patients with HFREF or HFPEF based on criteria to characterise the aetiology of either condition on the basis that the outcome of the cMR would materially alter the management of the patient. C. To do echocardiography only in the diagnosis of patients with suspected heart failure. Target condition: Diagnosis and management outcomes in patients suspected of having heart failure Statistical outcomes: Sensitivity, specificity, negative predictive value, positive predictive value, potential re-classification (in strategies A and B only) and cost-effectiveness of each of the three potential strategies.
Importance to patients or the population	Improved diagnostic accuracy, precision of characterisation of the aetiology of heart failure and potential alteration in the management plan in a way that could potentially improve the morbidity and mortality rates of patients with heart failure.
Relevance to NICE guidance	Determine the need and optimal utility of cMR in the diagnosis and further management of patients with suspected or proven heart failure.
Relevance to the NHS	The use of cMR in the diagnosis and management of patients with heart failure in the UK is increasing, but remains un-regulated and subject to local availability and expertise. It is vital that the NHS is provided with the evidence-base to justify the best strategy to deploy in the assessment of the growing population of patients with suspected heart failure for the benefit of these patients in a manner that takes account of the cost-effectivensss as well as the potential

	therapeutic implications for the patients and their carers.
National priorities	This research recommendation could potentially have a significant impact on the configuration of services and the workforce, and help the NHS to plan services for the future.
Current evidence base	While echocardiography is an established technique in the detection and characterisation of the abnormalities of the heart that describe the different types of heart failure; and while cMR has also many advantages over echocardiography in some respects and in some patients, there is: 1) no current systematic comparison between the techniques in the general assessment of patients with suspected heart failure and, 2) no established criteria upon which one could make a recommendation to select those who need to have cMR following echocardiography if one adopted strategy B. The current practice is based on availability and expertise where all patients are provided by echocardiography and then dependent on the patient's post-code as well as certain personal features they may undergo a cMR which is unsatisfactory. We are aware of a Canadian study (ClinicalTrials.gov Identifier: NCT01281384) that is currently recruiting to assess the role of selective use of cMR in the diagnosis of non-ischaemic heart failure vs routine use. We believe that while this is an important study, it is not within the NHS in the UK, and is restricting the study population to those with non-ischaemic heart failure. In addition, it does not consider the option of pursuing the diagnosis using echocardiography only as a possible option.
Equality	This is relevant as the current practice is dependent on post-code and availability of the expertise rather than being evidence-based and appropriately deployed and utilised.
Study design	Prospective cohort studies investigating and reporting sensitivity, specificity, negative predictive value, positive predictive value, rate of re-classification of the diagnosis in strategies A and B and cost-effectiveness.
Feasibility	Such research could be carried out over a period of two years but requires to be carried out in the settings of both secondary and tertiary hospital settings and in both towns and cities in England and Wales to take account of the potential impact of geographic factors on the acceptability and cost-effectivenss of the different strategies. While the setting up and execution costs may be significant; the benefits of determining clear answers are significant to both the UK population and to the health communities world-wide
Other comments	N/A.
Importance	• High: the research is relevant to the recommendations in the guideline, and to the future deployment and development of NHS resources (human and structural) to deliver the care to the only population of patients with potential cardiovascular condition that is increasing in prevalence.

P.3 The impact of atrial fibrillation on the natriuretic peptide threshold for diagnosing heart failure

Research question: What is the optimal NTproBNP threshold for the diagnosis of heart failure in people with atrial fibrillation?

Why this is important:

Atrial fibrillation is a common arrhythmia in the general population, and occurs in 30% to 40% of people with heart failure. Atrial fibrillation can raise the level of serum natriuretic peptides, including NTproBNP, even in the absence of heart failure. This is complicated further in heart failure with preserved ejection fraction, in which 2 echocardiographic diagnostic criteria become unreliable (the left atrial volume and the tissue doppler imaging assessment of diastolic function). These factors contribute to the complexity of the diagnosis and have a potential impact on the usual thresholds for NTproBNP in people who have atrial fibrillation. This has been recognised in several ongoing randomised controlled trials of heart failure, which are using higher NTproBNP thresholds for the diagnosis of heart failure in people with atrial fibrillation.

Criteria for selecting high-priority research recommendations:

PICO question	Objective: To assess the optimal threshold for the NTproBNP in the diagnosis of heart failure in people with atrial fibrillation. Population: People with suspected heart failure who are in atrial fibrillation in a community or outpatient setting, in the UK. Target condition: Heart failure Statistical outcomes: Sensitivity, specificity, negative predictive value and positive predictive value.
Importance to patients or the population	Improved diagnostic accuracy and potentially reducing the workload on heart failure diagnostic clinics if the optimal threshold was found to be higher than the threshold in people who are in sinus rhythm.
Relevance to NICE guidance	Determine the optimal threshold of NTproBNP in the diagnosis of heart failure in people with atrial fibrillation.
Relevance to the NHS	Given the recognition of the factors that affect NTproBNP and the diagnosis of heart failure in people with atrial fibrillation; it would be potentially more cost-effective to provide the health care professionals and the patients with variable thresholds of a diagnostic test affected by different co-morbid condition, thus improving the accuracy of that test and reducing the workload on the over-stretched cardiac services through improving the reliability of the test in the triage of people suspected of having heart failure who have atrial fibrillation.
National priorities	This research recommendation could potentially have a significant impact on the number of people being referred for the heart failure diagnostic clinic, even though it would not necessarily lead to a reduction in the referrals of people with new atrial fibrillation for echocardiography, as all new cases of atrial fibrillation would in any case need to have echocardiography as part of their routine care.
Current evidence base	Atrial fibrillation leads to raised NTproBNP in a fashion similar to heart failure, on the basis of dilatation of the atria. We do not know the precise degree to which the rise of NTproBNP could be safely ascribed to atrial fibrillation alone. It is vital that the threshold has a good predictive value to enable triage of the people with atrial fibrillation before they are referred to heart failure clinics. Expert advice to several randomised controlled trials had resulted in the use of thresholds of NTproBNP around 900-1000 ng/l.

Equality	NA
Study design	Prospective cohort studies investigating and reporting sensitivity, specificity, negative predictive value, positive predictive value of different thresholds of NTproBNP.
Feasibility	The research could be carried out over a period of two years in the settings of both secondary and tertiary hospital settings and in both towns and cities in England and Wales.
Other comments	N/A.
Importance	• Medium: the research is relevant to the recommendations in the guideline, and to the allocation of resources to heart failure clinics in the NHS.

P.4 The impact of advanced kidney disease on the natriuretic peptide threshold for diagnosing heart failure

Research question: What are the optimal NTproBNP thresholds for diagnosing heart failure in people with stage IIIb, IV or V chronic kidney disease?

Why this is important:

Heart failure incidence and prevalence increase with age, with the rise starting at age 65 and peaking between 75 and 85. Both advancing age and heart failure are associated with a gradual and progressive decline in renal function. In addition, the progression of heart failure and some treatments for heart failure lead to progressive deterioration of renal function. A decline in renal function is associated with increased fluid retention and a rise in the level of the serum natriuretic peptides, including NTproBNP, even in the absence of heart failure. There is some evidence that the use of higher NTproBNP thresholds would improve diagnostic accuracy for heart failure in people with significant deterioration of creatinine clearance.

Criteria for selecting high-priority research recommendations:

PICO question	Objective: To assess the optimal thresholds for the NTproBNP in the diagnosis of heart failure in people with CKD IIIB, IV and V. Population: People with suspected heart failure who have advanced CKD (IIIb, V and V) in a community or outpatient setting, in the UK. Target condition: Heart failure Statistical outcomes: Sensitivity, specificity, negative predictive value and positive predictive value of one or more thresholds of NTproBNP for the various grades of advanced CKD
Importance to patients or the population	Improved diagnostic accuracy and potentially reducing the workload on the echocardiography services and the heart failure diagnostic clinics if the optimal thresholds were found to be higher than the threshold in people who have GFR better than 45 ml/min/1.73 m^2.
Relevance to NICE guidance	Determine the optimal thresholds of NTproBNP in the diagnosis of heart failure in people with advanced CKD (IIIB, IV and V).
Relevance to the NHS	Given the recognition of the factors that affect NTproBNP and the diagnosis of heart failure in people with advanced CKD; it would be potentially more cost-effective to provide the health care professionals and the patients with variable thresholds of a diagnostic test affected by different co-morbid condition, thus

	improving the accuracy of that test and reducing the workload on the over-stretched cardiac services (echocardiography and heart failure diagnostic clinics) through improving the reliability of the test in the triage of patients suspected of having heart failure who have advanced CKD.
National priorities	This research recommendation could potentially have a significant impact on the number of patients being referred for the heart failure diagnostic clinics.
Current evidence base	Advanced CKD leads to raised NTproBNP due to interference with its clearance as well as through fluid retention. We do not know the precise degree to which the rise of NTproBNP could be safely ascribed to advanced CKD alone. It is vital that the thresholds have good predictive value to enable triage of these people with advanced CKD before they are referred to heart failure clinics.
Equality	NA
Study design	Prospective cohort studies investigating and reporting sensitivity, specificity, negative predictive value, positive predictive value of different thresholds of NTproBNP.
Feasibility	The research could be carried out over a period of two years in the settings of both secondary and tertiary hospital settings and in both towns and cities in England and Wales.
Other comments	N/A.
Importance	• High: the research is relevant to the recommendations in the guideline, and to the allocation of resources to echocardiography services and heart failure clinics in the NHS.

P.5 Should the currently used natriuretic peptide threshold for the diagnosis of heart failure recommended by NICE be lowered to the threshold chosen by the European Society of Cardiology

Research question: Which is more cost effective threshold for NTproBNP for the diagnosis of heart failure in people with suspected heart failure: 400 ng/l or 125 ng/l?

Why this is important:

The European Society of Cardiology lowered the NTproBNP threshold for the diagnosis of heart failure to 125 ng/l to ensure the highest specificity is guaranteed and thus no patient is missed. The NICE guidelines chose a threshold of 400 ng/l on the basis of cost-effectiveness and accepting a diagnostic accuracy of 75%. There have been some studies which tried to address this dilemma, none of which were large and they have all suffered methodological issues and some issues with selection bias. It would be important to have a large trial that is designed to minimise selection bias.

Criteria for selecting high-priority research recommendations:

PICO question	Objective: To assess the optimal threshold for the NTproBNP in the diagnosis of heart failure. Population: People with suspected heart failure in a community or outpatient setting, in the UK. Target condition: Heart failure Statistical outcomes: Sensitivity, specificity, negative predictive value and positive predictive value of the two thresholds of NTproBNP

Importance to patients or the population	Those who propose using the lower threshold argue that using this threshold will ensure that no one with heart failure would ever be missed. However, the lower the NTproBNP the higher the incidence of no evidence of heart failure.Those who support maintaining the NICE proposed NTproBNP threshold argue that not only is there increasing number of patients with no heart failure, but the patients with lower NTproBNP have lower risks of hospitalisation and mortality. The use of these low thresholds could be less cost-effective and could potentially overwhelm the echocardiography and heart failure clinics.
Relevance to NICE guidance	The evidence could potentially change a major diagnostic guideline recommendation by NICE if the lower threshold was supported.
Relevance to the NHS	Lowering the threshold will have a profound effect on the number of people being referred to echocardiography and the heart failure diagnostic clinics. This would have a considerable effect on the resource needed to provide these services.
National priorities	This research recommendation could potentially have a significant impact on the number of people being referred for echocardiography and to the heart failure diagnostic clinics if the ESC threshold was adopted.
Current evidence base	There are no large trials in the field. There is a DANISH registry and three small sized studies since the year 2000 looking at the impact of lowering the threshold of NTproBNP for the diagnosis of heart failure. These results have their weaknesses and it would be vital if the new research was undertaken to conclude categorically which threshold is the more cost-effective in this field.
Equality	NA
Study design	Prospective cohort study investigating and reporting sensitivity, specificity, negative predictive value, positive predictive value of the two thresholds of NTproBNP.
Feasibility	The research could be carried out over a period of one year in the settings of both secondary and tertiary hospital settings and in both towns and cities in England and Wales.
Other comments	N/A.
Importance	High: the research is relevant to the recommendations in the guideline, and to the allocation of resources to echocardiography services and heart failure clinics in the NHS.

P.6 Risk tools for predicting non-sudden death in heart failure

Research question: How accurate are prognostic risk tools in predicting 1-year mortality from heart failure at specific clinically relevant thresholds (for example, sensitivity, specificity, negative predictive value and positive predictive value at a threshold of 50% risk of mortality at 1 year)?

Why this is important:

There are a number of validated prognostic risk tools for heart failure but most do not report sensitivity and specificity at clinically relevant thresholds. This information is crucial to enable accurate prediction of a person's risk of mortality. The ability to accurately predict a person's prognosis would allow clearer communication and timely referral to other services such as palliative care. Inaccurate prediction has the potential to lead to significant psychological harm and increased morbidity.

Criteria for selecting high-priority research recommendations:

PICO question	Objective: To determine which prognostic risk tools are the most accurate at predicting patient mortality, to support decisions about involvement of palliative care services and the use of palliative care processes. Population: People with heart failure in a community or outpatient setting, in the UK. Risk tool: Validated risk tools identified in the literature Target condition: Mortality (all-cause at up to 1 year) Statistical outcomes: Sensitivity, specificity, negative predictive value, positive predictive value, predicted risk versus observed risk (calibration), reclassification These outcomes should be reported at clinically relevant thresholds of predicted mortality.
Importance to patients or the population	Greater predictability over an individual's likely trajectory would allow individuals to plan their care and lives better and aid overall decision making.
Relevance to NICE guidance	Prognostic tools could be utilised to guide referral to palliative care services.
Relevance to the NHS	If a risk tool was found to have high sensitivity or specificity at a clinically relevant threshold it could be implemented to support the referral process to palliative care services, potentially decreasing the number of unnecessary referrals and increasing the number of appropriate referrals.
National priorities	N/A
Current evidence base	Current validated prognostic tools fail to report both sensitivity and specificity at clinically relevant thresholds, this information is vital in order to have confidence in the accuracy of a tool in predicting mortality within a specified timeframe.
Equality	N/A
Study design	Prospective cohort studies investigating and reporting sensitivity, specificity, negative predictive value, positive predictive value, predicted risk versus observed risk (calibration) and reclassification at clinically relevant thresholds of predicted mortality at 1 year.
Feasibility	Such research could be carried out in a realistic timescale and at an acceptable cost.
Other comments	N/A
Importance	• Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates.

Appendix Q: NICE technical team

Name	Role
Nichole Taske	Guideline Lead
Philip Alderson	Clinical Advisor
Joshua Pink	Technical Lead
Bernadette Li	Health Economist
Ben Doak	Guideline Commissioning Manager
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Appendix R: Previous NICE chronic heart failure guidelines

Chronic heart failure 2010, CG108: https://www.nice.org.uk/guidance/cg108/evidence/full-guideline-pdf-136060525

Chronic heart failure 2003, CG5: https://www.nice.org.uk/guidance/cg108/evidence/full-guideline-appendix-m-part-one-copy-of-full-version-of-cg5-pdf-136060531

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