

Chronic heart failure in adults

Clinical protocol for pharmacological therapy for
heart failure with reduced left ventricular
ejection fraction

Protocol

Clinical review protocol

November 2024

Final

Developed by NICE

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and, where appropriate, their carer or guardian.

Local commissioners and providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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Appendices

Appendix A: Review protocol

Review protocol for first-line pharmacological treatment of chronic heart failure with reduced left ventricular ejection fraction

ID	Field	Content
1.	Review title	First-line pharmacological treatment of chronic heart failure with reduced left ventricular ejection fraction (HFrEF).
2.	Review question	<p>Is it clinically- and cost-effective to use a combination of some of the following first-line pharmacological interventions in adults with chronic heart failure with reduced left ventricular ejection fraction:</p> <ul style="list-style-type: none"> • ACE inhibitor • angiotensin-receptor blocker • angiotensin receptor neprilysin inhibitor • beta blocker • mineralocorticoid receptor antagonist • sodium glucose cotransporter 2 inhibitor?
3.	Objective	The current recommendations in NG106 do not reflect all treatment options now available to patients with HFrEF, and the recommendations on sequential introduction of therapeutic agents are no longer in line with ESC guidelines or UK clinical practice. Appropriate sequencing, or the appropriateness of introducing multiple pharmacological agents at treatment initiation, has not been assessed in an evidence review during the previous updates. Therefore, the aim of this review is to update the recommendations on first-line pharmacological management for people with chronic heart failure and reduced ejection fraction.
4.	Searches	<p>Key papers:</p> <p>HFrEF</p> <ul style="list-style-type: none"> - PARADIGM-HF (McMurray 2014) - STRONG HF (Mebazaa Alexander, Lancet 7 Nov 2022)

		<p>The following databases will be searched:</p> <ul style="list-style-type: none"> • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos <p>Searches will be restricted by:</p> <ul style="list-style-type: none"> • Date limitations – from date of searches in CG5, 2003 • English language studies • Human studies <p>Other searches:</p> <ul style="list-style-type: none"> • Inclusion lists of relevant systematic reviews <p>The full search strategies will be published in the final review.</p> <p>Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).</p> <p>The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant.</p>
5.	Condition or domain being studied	Chronic heart failure with reduced ejection fraction
6.	Population	<p>Inclusion: Adults diagnosed with heart failure due to left ventricular dysfunction with reduced ejection fraction.</p> <p>Studies including an indirect population (for example mixed HFrEF and HFpEF) will only be included if ≥80% match the protocol criteria.</p> <p>Ongoing treatment after discharge for an acute episode of heart failure will be included.</p> <p>Exclusion:</p>

		<ul style="list-style-type: none"> • Children • Acute heart failure in hospital • Heart failure with preserved EF (normal EF, diastolic dysfunction) • Heart failure due to right heart dysfunction (e.g., pre-capillary pulmonary hypertension and primary right ventricular cardiomyopathies) • High output heart failure • Adult congenital heart disease • Primary heart valve disease • Acute MI (within 3 months of the event) • Isolated pulmonary hypertension • Treatment with chemotherapy
7.	Intervention	<p>Inclusion</p> <p>Pharmacological agents as first-line treatment in combination with each other or with standard background therapy including diuretics when indicated:</p> <ul style="list-style-type: none"> • Angiotensin converting enzyme (ACE) inhibitor • Angiotensin receptor-neprilysin inhibitor (ARNI; Sacubitril-Valsartan) • Angiotensin receptor antagonist / blocker (ARB) • Beta-adrenergic antagonist/blocker • Mineralocorticoid receptor antagonist • SGLT2 inhibitor (dapagliflozin or empagliflozin) • Combinations of the above (e.g. ACE-I/ARB/ARNI + BB + MRA+ SGLT2i); including different initiation strategies <p>At least 50% of the intervention group must be receiving more than one of the drugs listed above (either as the randomised intervention or as part of background treatment).</p> <p>First-line refers to the group of pharmacological agents that are considered when initially reviewing the patient. Studies that assess the listed interventions, but do not introduce them as first-line treatment (e.g., only after optimisation of other interventions) will be downgraded for intervention indirectness.</p> <p>Mode of delivery: oral.</p> <p>Analysis groupings: a class effect will be assumed.</p>

		<p>Background/concomitant treatment: studies in which participants are also receiving other pharmacological agents as background therapy (balanced between the randomised groups) will be included. This may include, for example, diuretics, statins, anticoagulants, and anti-arrhythmics.</p> <p>Studies will be included, but downgraded for indirectness if >20% of participants are also receiving therapies initiated by a specialist as part of their 'standard care' (e.g., ivabradine, hydralazine-nitrate, vericiguat)</p> <p>Exclusion</p> <ul style="list-style-type: none"> • Calcium channel blockers (because they are not used in current practice and have a do not use recommendation). • Medicines to manage oedema (except as background treatment), for example: <ul style="list-style-type: none"> ○ loop diuretics ○ thiazide diuretics • The following therapies (except as background treatment): <ul style="list-style-type: none"> ○ Digoxin ○ Ivabradine ○ Hydralazine-Nitrate ○ Omecamtiv mecarbil ○ Vericiguat • Medicines to manage comorbidities (except as part of background treatment): <ul style="list-style-type: none"> ○ Anticoagulants ○ Anti-arrhythmics
8.	Comparator	<ul style="list-style-type: none"> • Different approaches to initiation (e.g., sequential introduction with up-titration of each agent in turn vs more rapid introduction of all initial treatments). • Other active treatments in combination with each other or with standard background therapy: <ul style="list-style-type: none"> ○ Angiotensin converting enzyme (ACE) inhibitor ○ Angiotensin receptor-neprilysin inhibitor (ARNI; Sacubitril-Valsartan) ○ Angiotensin receptor antagonist / blocker (ARB) ○ Beta-adrenergic antagonist/blocker ○ Mineralocorticoid receptor antagonist ○ SGLT2 inhibitor (dapagliflozin or empagliflozin) • Placebo + usual CHF care or usual CHF care alone

		At least 50% of the control group must be receiving more than one of the drugs listed above (either as the randomised comparator or as part of background treatment). This was because trials comparing any intervention with monotherapy or placebo alone are not relevant for this population for whom current practice includes a minimum of dual therapy (ACEI + BB). Therefore, such trials will be excluded from this update although they were considered in previous versions of the guideline.
9.	Types of study to be included	<p>Inclusion:</p> <ul style="list-style-type: none"> • RCTs • Published systematic reviews of RCTs • Published network meta-analyses (NMAs) and individual participant data meta-analyses (IPDs). <p>Exclusion:</p> <ul style="list-style-type: none"> • Cross-over RCTs • Non-randomised studies <p>Note: data from a parallel project using real world data may also inform committee discussions.</p>
10.	Other exclusion criteria	<ul style="list-style-type: none"> • Non-English language studies. • Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	This review will partially update NICE guideline NG106.
12.	Primary outcomes (critical outcomes)	<p>All outcomes are considered equally important for decision making and therefore have all been rated as critical:</p> <ul style="list-style-type: none"> • All-cause mortality (time-to-event) • CV mortality (time-to-event) • Health-related quality of life (Minnesota Living With Heart Failure (MLWHF), the Kansas City Cardiomyopathy Questionnaire (KCCQ), or any validated score (continuous – change score preferred over final value) • Unplanned hospitalisation or visits (HF-related) (time-to-event; including repeat events when reported) <ul style="list-style-type: none"> ○ all cause unplanned hospitalisation or visits will be included if HF-related is not reported in a study, but this will be downgraded for outcome indirectness <p>Adverse events (recorded as the number of people with at least one event, not the total number of events)</p> <ul style="list-style-type: none"> • Withdrawal due to drug-related adverse events (dichotomous) • Acute kidney injury – serum creatinine rise of $\geq 50\%$ over ≤ 7 days (dichotomous) • Hyponatraemia – serum sodium concentration < 135 mmol/L (dichotomous) • Hyperkalaemia – serum potassium concentration ≥ 5.5 mmol/L (dichotomous) • Falls – number of participants with at least one event (not total number of events) (dichotomous)

		<p>Time points for analysis: 12 months (pool all times ≥ 3 months, taking the closest to 12 months follow-up time from each study if multiple time points are reported)</p> <p>Exclude if follow-up <3 months</p> <p>The COMET database was searched for relevant core outcome sets and one consensus document published in 2013 was identified, which was used to inform the GC discussions on protocol outcomes (https://onlinelibrary.wiley.com/doi/epdf/10.1093/eurjhf/hft095).</p> <p>Indirect outcome definitions</p> <ul style="list-style-type: none"> • If continuous data are not available, dichotomous outcome data for quality of life scales will be accepted but downgraded for outcome indirectness. For KCCQ this should be based on the threshold of an improvement of 5 points, which is the accepted MID. Only one threshold will be reported per study. • Adverse events that are similar to the protocol definitions will be considered for inclusion and, if sufficiently similar, will be included but downgraded for outcome indirectness.
13.	Data extraction (selection and coding)	<p>EndNote will be used for reference management, sifting, citations and bibliographies.</p> <p>All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated.</p> <p>10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.</p> <p>The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above.</p> <p>A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4).</p> <p>10% of all evidence reviews are quality assured by a senior research fellow. This includes checking:</p> <ul style="list-style-type: none"> • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments <p>Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.</p>

14.	Risk of bias (quality) assessment	<p>Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual.</p> <ul style="list-style-type: none"> • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0)
15.	Strategy for data synthesis	<p>Where available, outcome data from new studies will be meta-analysed with corresponding data already included in NG106.</p> <ul style="list-style-type: none"> • For analysis, interventions/comparisons will be grouped based on both the randomised and background treatment used by trial participants. To account for concomitant treatments, a protocol intervention will be included as part of the combination treatment if more than 50% of the participants were receiving it. • Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. • For time-to-event outcomes, if sufficient information is provided, hazard ratios will be reported but dichotomous data will also be extracted. Only one measure will be considered for decision making. This will be agreed with the committee taking into account the proportion of studies that report sufficient data to calculate the risk ratio and the hazard ratio, in order to maximise the available pooled data. If there are differences in effect estimates between the two measures, potential reasons for this will be considered in the interpretation of the evidence. • Heterogeneity between the studies in effect measures will be assessed using the I² statistic and visually inspected. An I² value greater than 40% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias will be considered with the guideline committee, and if suspected will be tested for when there are more than 5 studies for that outcome. • The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the ‘Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox’ developed by the international GRADE working group http://www.gradeworkinggroup.org/ • Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. • WinBUGS will be used for network meta-analysis, if possible and useful given the data identified.
16.	Analysis of sub-groups	<p>Stratified analyses will be carried out for the following subgroups if prespecified analyses are available from included studies investigating SGLT2 inhibitors as the randomised intervention (regardless of heterogeneity):</p>

		<ul style="list-style-type: none"> • Presence or absence of type 2 diabetes. <p>Analyses will be undertaken to determine if there are subgroup differences between those with and without type 2 diabetes for outcomes relevant to this review protocol. Indirectly relevant outcomes (e.g., composite endpoints combining two protocol outcomes) will be considered for inclusion if there is insufficient data from directly relevant outcomes.</p> <p>Subgroups that will be investigated if heterogeneity is present:</p> <ul style="list-style-type: none"> • Renal function (Abnormal (EGFR < 30mL/min); Normal (EGFR 30-60mL/min; >60mL/min)) • Age (18-75 years; Over 75 years) • Ethnicity (Afro-Caribbean; south Asian; Caucasian; other) 		
17.	Type and method of review	<input checked="" type="checkbox"/>	Intervention	
		<input type="checkbox"/>	Diagnostic	
		<input type="checkbox"/>	Prognostic	
		<input type="checkbox"/>	Qualitative	
		<input type="checkbox"/>	Epidemiologic	
		<input type="checkbox"/>	Service Delivery	
		<input type="checkbox"/>	Other (please specify)	
18.	Language	English		
19.	Country	England		
20.	Anticipated or actual start date	February 2024		
21.	Anticipated completion date	April 2025		
22.		Review stage	Started	Completed

	Stage of review at time of this submission	Preliminary searches	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
		Piloting of the study selection process	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
		Formal screening of search results against eligibility criteria	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
		Data extraction	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
		Risk of bias (quality) assessment	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
		Data analysis	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
23.	Named contact	Named contact Guideline Development Team NGC Named contact e-mail chfiatreatment@nice.org.uk Organisational affiliation of the review National Institute for Health and Care Excellence (NICE)		
24.	Review team members	From NICE: Dr Sharon Swain Mrs Eleanor Samarasekera Mr David Wonderling Ms Lisa Miles Ms Annette Chalker Ms Sade Naku Ms Jemma Deane Mr Daniel Davies		

25.	Funding sources/sponsor	Development of this systematic review is being funded by NICE.	
26.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
27.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual . Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10405	
28.	Other registration details	NA	
29.	Reference/URL for published protocol	https://www.nice.org.uk/guidance/indevelopment/gid-ng10405/documents	
30.	Dissemination plans	<p>NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:</p> <ul style="list-style-type: none"> • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE. 	
31.	Keywords	Heart failure; pharmacological; four pillars; ACE inhibitors; sacubitril valsartan; beta-blockers; mineralocorticoid receptor antagonists; SGLT2 inhibitors.	
32.	Details of existing review of same topic by same authors	NA	
33.	Current review status	<input checked="" type="checkbox"/>	Ongoing
		<input type="checkbox"/>	Completed but not published

		<input type="checkbox"/>	Completed and published
		<input type="checkbox"/>	Completed, published and being updated
		<input type="checkbox"/>	Discontinued
34.	Additional information	NA	
35.	Details of final publication	www.nice.org.uk	