NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Specification for manufacturer/sponsor submission of evidence

IVABRADINE FOR THE TREATMENT OF CHRONIC HEART FAILURE

Servier Laboratories Ltd

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List of abbreviations

AA	Aldosterone antagonist
ACEi	Angiotensin-converting enzyme inhibitor
AE	Adverse event
AF	Atrial fibrillation
ALAT	alanine amino transferase
ARB	Angiotensin receptor blocker
ARR	Absolute risk reduction
ASAT	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
ANZCTR	Australia New Zealand Clinical Trials Registry
bd	Twice daily
BHF	British Heart Foundation
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
ca.	*circa*
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CEAC	Cost effectiveness acceptability curve
CEAF	Cost effectiveness acceptability frontier
CG108	Clinical Guideline 108
CHD	Coronary heart disease
CHF	Chronic heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
COPD	Chronic Obstructive Pulmonary Disease
CRT	Cardiac resynchronisation therapy
CRT-D	Cardiac resynchronisation therapy - defibrillator
CRT-P	Cardiac resynchronisation therapy - pacing
CSR	Clinical Study Report
CV	Cardiovascular
CYP3A4	Cytochrome P450 subtype 3A4
DBP	Diastolic blood pressure
DPMQ	Dispensed price for maximum quantity
DRG	Diagnostic related groups
EF	Ejection fraction
eCRF	Electronic Casel Report Form
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQ-5D	EuroQol 5 Dimensions questionnaire

EQ VAS	EuroQol Visual Analogue Scale
ESC	European Society of Cardiology
EVC	Endpoint Validation Committee
GP	General Practitioner
GPRN	General Practice Research Network
GPwSI	General Practitioner with Special Interest
FAS	Full analysis set
HES	Hospital episode statistics
HIV	Human immunodeficiency virus
ICD	Implantable cardioverter defibrillator
ICER	Incremental cost-effectiveness ratio
ITT	Intention to Treat
IV	Intravenous
ESC	European Society of Cardiology
HF	Heart failure
HRG	Healthcare resource groups
HRQL	Health-related quality of life
HR	Hazard ratio
KCCQ	Kansas City Cardiomyopathy Questionnaire
LOCF	Last observation carried forward
LoS	Length of stay
LY	Life years
LYG	Life years gained
LVEF	Left-ventricular ejection fraction
LVESVI	Left-ventricular end-systolic volume index
LVSD	Left-ventricular systolic dysfunction
MI	Myocardial infarction
mg	Milligram
NHS	National Health Service
NIHR	National Institute for Health Research
NICE	National Institute for Health and Clinical Excellence
NNT	Number needed to treat
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
OMT	Optimised medical therapy
PbR	Payment by results
PCI	Percutaneous coronary intervention
PH	Proportional hazard
PI	Product Information
PRO-SHIfT	Patient reported outcomes sub-study
PSA	Probabalistic sensitivity analysis
PSE	Pre-specified event
PSS	Personal social services
PSSRU	Personal Social Services Research Unit
PSUR	Periodic Safety Update Report

PY	Patient years
%PY	Annual incidence rate
Q	Quartile
QALM	Quality adjusted life months
QALY	Quality adjusted life year
QoL	Quality of Life
QS	Quality standard
RCT	Randomised controlled trial
RRR	Relative risk reduction
RS	Randomised set
RS_{BBDOSE}	Patients of the randomised set receiving at least half of target daily dose of β-blockers at randomisation
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SHIfT	Systolic Heart Failure with the If Inhibitor Ivabradine trial
SOC	System organ class
SMC	Scottish Medicines Consortium
SPC	Summary of Product Characteristics
SVTA	Supra-ventricular tachyarrhythmia
td	Target dose
TIA	Transient ischaemic attack
TGA	Therapeutic Goods Administration
TTO	Time Trade Off
vs	*versus*

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Executive summary

Background

Heart failure (HF) is a complex syndrome characterised by symptoms such as breathlessness, fatigue and fluid retention. It is prevalent in 1 - 2% of the UK population and approximately two-fifths of patients have heart failure associated with left-ventricular systolic function (LVSD). Despite the range of existing treatments which serve to reduce important outcomes such as mortality and hospitalisation, prognosis remains poor. Mortality in heart failure patients ranges between 10-50% per year depending on severity, and the cost burden of heart failure on the NHS is significant, estimated to be over £600 million annually. (National Heart Failure Audit, 2011 (4)). A considerable proportion of costs relate to hospital admissions. (see Section 2.1)

Heart rate is now established as a predictor of outcomes in patients with heart failure due to LVSD. Beta-blocker trials show that, for every five bpm reduction in heart rate achieved, an 18% reduction in all-cause mortality is observed. (McAlister 2009 (5)) The placebo arm of the SHIfT trial also demonstrated a clear link between baseline heart rate and outcomes.(Böhm 2010 (6)) In light of the overwhelming evidence that beta-blockers reduce morbidity and mortality in patients with systolic heart failure, Servier support that these therapies should be used first line and up-titrated as far as possible (as per NICE CG108(7)). However, an unmet need exists in patients whose heart rate remains elevated. This may even occur in patients on target dose beta-blockade, but more usually when patients are either contraindicated to beta-blockers or unable to tolerate target dosages. (see Sections 2.1 and 5.10)

Ivabradine represents a new class of therapy, may be considered an innovation in the management of heart failure (Section 3.2 and 5.10.2) and has the potential to save lives (Section 5.5).

The Technology

The UK approved name: ivabradine (brand name, Procoralan®)

Marketing status: Marketing authorisation *via* the European Centralised Procedure was amended to include the relevant indication for ivabradine on 9th February 2012.

Principal mechanism of action of ivabradine: Ivabradine is a pure heart rate lowering agent and represents the first in a new class of agents that selectively and specifically inhibit the cardiac pacemaker I_f current, which in turn controls the spontaneous diastolic depolarisation in the sinus node that regulates heart rate. The cardiac effects are specific to the sinus node with no effect on intra-atrial, atrioventricular or intraventricular conduction times, nor on myocardial contractility or ventricular repolarisation. Reduction in heart rate on ivabradine is dose-dependent; at usual recommended doses heart rate reduction is *ca*. 10 bpm at rest and during exercise. This leads to a reduction in cardiac workload and myocardial oxygen consumption, which could be of particular importance in heart failure for example,

where attenuating the effect of energy starvation of the myocardium may be linked to improved cardiovascular outcomes. (see Section 1.2)

The formulation(s), strength(s), pack size(s), maximum quantity(ies), anticipated frequency of any repeat courses of treatment and acquisition cost Film-coated tablets containing 5 mg or 7.5 mg ivabradine are supplied in packs of 56 tablets (28 days) at an acquisition cost of £40.17. The 5 mg tablet may be divided into equal halves. The usual recommended starting dose of ivabradine is 5 mg twice daily. After two weeks of treatment the dose can be increased to 7.5 mg twice daily if resting heart rate is above 60 bpm, or decreased to 2.5 mg twice daily if resting heart rate is below 50 bpm. Repeat courses are not relevant for this chronic therapy. (see Section 1.10)

The indication(s) and any restriction(s): *Ivabradine is indicated in chronic heart failure NYHA II to IV class with systolic dysfunction, in patients in sinus rhythm and whose heart rate is ≥ 75 bpm, in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated.* (Section 1.5)

Ivabradine is a prescription only medicine to be used in accordance with contraindications and precautions listed in the Summary of Product Characteristics (SPC). (see Section 1.10 and Appendix 1).

The recommended course of treatment: Ivabradine is a chronic therapy for heart failure and is expected to be used for the lifetime of patients with heart failure who meet the licensed criteria.

The main comparator(s)

The only relevant comparator identified is standard treatment without ivabradine. (see Section 2.6). This may be justified in recognising that the pivotal study (SHIfT) was designed to assess the benefit of ivabradine on top of standard therapy, including beta-blockers, which had been optimised according to firm guidance in the study protocol and electronic case record form. Despite clear instructions for the up-titration of beta-blockers, only 26% of patients reached target dose beta-blockade. However, as discussed in Sections 2.6 and 5.10.4, this is somewhat better than doses achieved in UK clinical practice today and may be rationalised when considering the specific patient profile of relevance to the licensed indication and decision problem. The principal reason cited in SHIfT for under-usage of beta-blockers was tolerability, particularly hypotension (44%) and fatigue (32%).

Key Clinical Evidence

The key clinical evidence for ivabradine comes from a randomised, double-blind, placebo-controlled trial that included 6,505 patients with symptomatic chronic heart failure and a left-ventricular ejection fraction (LVEF) of 35% or lower and in sinus rhythm with heart rates of 70 bpm or higher (SHIfT, Swedberg 2010 (8)) (see Section 5.3). The trial population received recommended background treatment according to guidelines for chronic heart failure. (CG108 (7)) Results of the SHIfT Patient

Reported Outcomes sub-study are also available (Ekman et al. (2011) (2); see Section 5.5). This investigated health-related quality of life in a representative sample of 5,038 patients from the main trial population. An additional paper reported further analyses of SHIfT trial data, investigating the association between heart rate and prespecified outcomes. (Böhm 2010(6)). Safety data are also available for the SHIfT study (see Section 5.9).

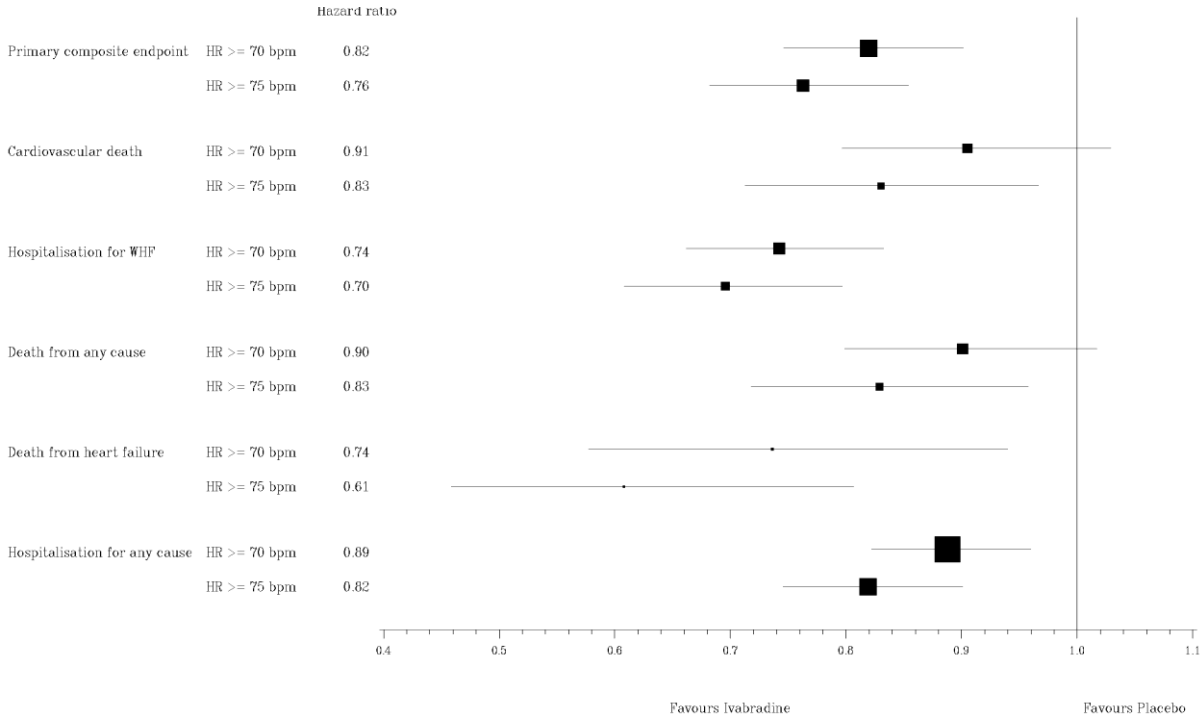
The main clinical results of the randomised controlled trials (RCTs) and any relevant non-RCT evidence

In SHIfT the addition of ivabradine to optimised standard therapy resulted in a significant reduction of 18% in the primary composite endpoint of hospitalisation due to worsening heart failure or cardiovascular mortality, *vs* placebo. This result was driven more by the rate of hospitalisation for worsening heart failure than by the rate of cardiovascular death. SHIfT results in general were driven by the cause-specific endpoints of hospitalisation for heart failure (HR 0.74, 95% CI 0.66-0.83) and heart failure death (HR 0.74, 95% CI 0.58-0.94). Despite a trend to benefit, the reduction in cardiovascular mortality was not significant in the overall population. However the trial demonstrated that patients with higher heart rates at baseline derived greater benefit (Section 5.5). On this basis, and at the request of the EMA, Servier re-analysed SHIfT data to determine the heart rate threshold over which the total mortality benefit was clear. A heart rate of 75 bpm was identified as a threshold beyond which the cardiovascular mortality and all-cause mortality benefits of ivabradine were unequivocal (HR = 0.83, 95% CI 0.71-0.97) and (HR = 0.83, 95% CI 0.72-0.96) respectively. The EMA therefore amended the marketing authorisation to include a specific group of HF patients with baseline heart rate of 75 bpm or above. The concentration in effect from the ≥70 bpm trial population to the ≥75 bpm licensed population can be seen in Figure 1 for a range of secondary endpoints. (see Section 5.5)

Analysis of the SHIfT data by Swedberg 2012 (in press) (1) suggests that the efficacy of ivabradine is modified by baseline heart rate, but not by beta-blocker dose. The apparent reduced efficacy in patients who receive higher doses of beta-blockade may be explained at least in part by the lower baseline heart rate in these patients. (see Section 5.5). Analysis of the placebo arm of the SHIfT trial by Böhm et al. (6) confirmed that high heart rate is a risk factor in heart failure, with a 3% increase in the risk of primary composite endpoint events with every beat increase in baseline heart rate. (see Sections 5.5 and 5.10.4)

The SHIfT- Patient Reported Outcomes sub-study showed, using the KCCQ disease-specific quality of life instrument, that the addition of ivabradine to recommended evidence based treatments for heart failure led to improved health status for patients compared to standard care. ((2)Section 5.5) A mixed regression model consistent with the NICE reference case and using EQ-5D Index Scores was also performed. This again showed ivabradine to be associated with a statistically significant increase in patient QoL. (see Section 6.4.3)

Figure 1: Forest plot comparison of primary and secondary outcomes: main trial population (≥70 bpm, N=6505) and licensed population (≥75 bpm, N=4150)



In the licensed SHIfT population (heart rate ≥75 bpm) the safety profile was favourable, with similar incidences of adverse events, serious adverse events and death compared to the overall SHIfT population. For the overall trial population, more bradycardia (4.6%) and visual symptoms such as phosphenes an blurred vision (3.3%) occurred on ivabradine than on placebo; however, they were unlikely to lead to treatment withdrawal. Atrial fibrillation was also reported more frequently with ivabradine than with placebo (8.3% *vs* 6.7%), but was not associated with an increased occurrence of cerebrovascular accidents and had no impact on the beneficial effect of ivabradine on cardiovascular outcomes. Overall, ivabradine was well tolerated in SHIfT. (see Section 5.9)

Type of economic evaluation and justification for the approach used:

An Excel-based cost-utility model was developed in line with the 'Guide to the methods of technology appraisal'(9). A systematic literature search identified 20 relevant cost-effectiveness models in a HF population. Of these, nine studies of pharmaceutical interventions used a simple area under the curve approach or Markov cohort analysis, often a simple two-state approach. [McKenna et al, 2010, Taylor et al. 2009, Rosen et al. 2010, Boersma et al. 2006, Colombo et al. 2008, Mark et al. 2006, McMurray et al. 2006, Pourvourville et al. 2008, Szucs et al. 2006 (10-17)]. A two-state Markov cohort model has been adopted (health states alive, dead) as it offers a simple, flexible framework, is consistent with previous studies and was deemed appropriate to address the decision problem. (see Section 6.2.3)

Pivotal assumptions underlying the model/analysis (discussed further in Section 6.3.8):

- Mortality, hospitalisation and quality of life capture the most relevant outcomes for therapy in heart failure; and ivabradine has a positive effect on all three.
- For the base case it is assumed the treatment effect for ivabradine plus standard care on the aforementioned outcomes has been modelled to continue in the post-trial period until ivabradine therapy is ceased (see Section 5.10.4 for long term maintenance of the effect of ivabradine)
- No discontinuations other than due to death are included in the model
- CV death has been modelled from a risk equation developed using SHIFT trial data, and non-CV death using interim UK life table data
- QoL has been modelled using patient baseline characteristics, the severity of disease over time (NYHA class), the occurrence of serious adverse events (hospitalisations) and treatment group. Any disutility associated with treatment related adverse events is assumed to be captured by the treatment covariate.
- Standard care therapy use in SHIfT is believed to reflect UK treatment patterns and has been modelled accordingly.

Cost effectiveness results

The base case model indicated that in patients with a heart rate ≥75 bpm the incremental cost-effectiveness ratio (ICER) for ivabradine plus standard care *versus* standard care alone in SHIfT is £8,498 per QALY saved over an average patient lifetime, well below the NICE threshold (£20,000 per QALY) (9).

Base case cost-effectiveness results:

	Ivabradine plus standard care	**Standard care**
Technology acquisition cost	£3,902	£642
Other costs (follow up and hospitalisations)	£7,920	£8,804
Total costs	£11,822	£9,446
Difference in total costs	-	**£2,376**
LYG	5.86	5.61
LYG difference	-	0.25
QALYs	4.27	3.99
QALY difference	-	**0.28**
ICER	-	**£8,498 per QALY**
LYG, life years gained; QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio		

One way sensitivity analyses indicated results were robust to alternative plausible assumptions. In general, analyses suggested that the estimated ICER was conservative with most scenarios generating more favourable results. The ICER was more sensitive to the relative treatment effect of ivabradine than the underlying risk of mortality or hospitalisation and analyses indicated some sensitivity to changes in the hazard ratio for CV mortality. The model results were robust to changes in other assumptions including the underlying risk of mortality and alternative data sources for hospitalisation costs and QoL weights.

The probabilistic sensitivity analysis indicated that ivabradine plus standard care would be expected to be over 95% likely to be optimal, when compared with standard care alone. Ivabradine remained highly cost-effective in patients treated with target dose beta blockade (£10,374 per QALY). The ICER for the theoretical patient population designed to be representative of a UK CHF population (receiving at least half target dose beta-blockade) was also highly cost-effective using existing NICE threshold values (£9,185 per QALY).

Estimated budget impact

The estimated annual budget impact for the NHS in England and Wales, in the first five years following the introduction of ivabradine for the treatment of patients with chronic heart failure and impaired systolic function is estimated at £1.7m in year 1 rising to £11.9m in year 5. Taking into account resource use saving, the net estimated annual budget impact for the NHS in England & Wales in year 1 is £1.2m, rising to £8.4m in year 5. (see Section 7)

Conclusion

Ivabradine has the potential to provide substantial benefits to patients with systolic heart failure when used on top of the current standard of care, providing the beta-blocker has been up-titrated to the maximum tolerated level and resting heart rate remains high. Cost-effectiveness estimates are driven by an important reduction in HF mortality and a substantial reduction in hospitalisations, and the associated costs of care and improvements in quality of life. The economic model indicates that ivabradine is highly likely to be cost-effective in a UK setting for the licensed population with baseline heart rate ≥75 bpm, suggesting that ivabradine offers the NHS a valuable new therapy for heart failure patients.

Section A – Decision problem

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the NICE document 'Guide to the single technology appraisal (STA) process' – www.nice.org.uk). A (draft) summary of product characteristics (SPC) for pharmaceuticals or information for use (IFU) for devices, a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report (EPAR)), and a (draft) technical manual for devices should be provided (see section 9.1, appendix 1).

1 Description of technology under assessment

Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Procoralan (ivabradine)

Therapeutic class: I_f channel inhibitor; ATC code C01EB17

What is the principal mechanism of action of the technology?

Ivabradine is a pure heart rate lowering agent, acting by selective and specific inhibition of the cardiac pacemaker I_f current that controls the spontaneous diastolic depolarisation in the sinus node and regulates heart rate. The cardiac effects are specific to the sinus node with no effect on intra-atrial, atrioventricular or intraventricular conduction times, nor on myocardial contractility or ventricular repolarisation.

The main pharmacodynamic property of ivabradine in humans is a specific dose dependent reduction in heart rate. At usual recommended doses, heart rate reduction is approximately 10 bpm at rest and during exercise. This leads to a reduction in cardiac workload and myocardial oxygen consumption (SPC 2012, Appendix 1, Section 9.1). This could be of particular importance in chronic heart failure for example, where attenuating the effect of energy starvation of the myocardium may be linked to improved cardiovascular outcomes (6;8;8;18).

Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Yes, the marketing authorisation via the European Centralised Procedure was amended to include the relevant indication on 9th February 2012.

Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the licence).

There are no special conditions attached to the marketing authorisation.

Prior to the publication of the EPAR, the CHMP Type II variation assessment report identified three central questions in the evaluation of the Ivabradine and outcomes in chronic heart failure (SHIfT) study: (19)

1. What was the effect of baseline heart rate on outcomes
2. What was the effect of beta-blocker dose on outcomes
3. Was the use of beta-blockers in SHIfT optimal

The SHIfT study recruited patients with a heart rate of ≥70 bpm and showed a significant benefit of ivabradine on the primary endpoint of cardiovascular death and hospitalisation due to worsening heart failure (HR 0.82, 95% CI 0.75-0.90) and hospitalisation for worsening heart failure (HR 0.74, 95% CI 0.66-0.83), but cardiovascular deaths were not significantly reduced (HR 0.91, 95% CI 0.80-1.03). In the Lancet publication it was noted that baseline heart rate was observed to modify treatment effect. In order to identify the patients in whom the mortality benefit of ivabradine was clear, the CHMP asked the manufacturer to re-analyse the SHIfT data. The manufacturer subsequently identified that 75 bpm was a threshold of interest. In this cohort (n=4150) the effect of ivabradine on all-cause mortality (HR 0.83, 95% CI 0.72-0.96), cardiovascular mortality (HR 0.83, 95% CI 0.71-0.97) and hospitalisation for worsening heart failure (HR 0.70, 95% CI 0.61-0.80) was clearly established. On this basis it was proposed and subsequently accepted that the indication be modified to patients with a baseline heart rate ≥75 bpm instead of ≥70 bpm.

With respect to the dose of beta-blocker, the CHMP noted that the beneficial effect of ivabradine was attenuated in patients who were on target beta-blocker dose. However there was a trend towards benefit in the small group of patients on target beta-blocker dose and with a baseline heart rate of ≥75 bpm (n=938) with respect to hospitalisation for worsening heart failure (HR 0.79, 95% CI 0.56-1.10) and death from heart failure (HR 0.69, 95% CI 0.31-1.56). Therefore the CHMP decided to grant the licence in patients with a baseline heart rate of ≥75 bpm with no stipulation regarding the dose of beta-blocker used.

Regarding the optimal use of beta-blockers, the CHMP noted that during the study investigators were explicitly asked to treat patients with optimal doses of beta-blockers and that this was supported by the study protocol and eCRF. The CHMP therefore accepted that the study design promoted optimal beta-blockade, even

though only 26% of patients attained target dose of beta-blockers in the trial. Investigators had to document the reason(s) why any patient did not tolerate up-titration to target dose; specifically Hypotension (44%), Fatigue (32%), Dyspnoea (14%), Dizziness (13%), Cardiac de-compensation (9%) and Bradycardia (6%). Whilst the number of patients receiving target beta-blocker dose in SHIfT was lower than in some other chronic heart failure trials it was acknowledged by the CHMP that this could be explained by the baseline blood pressures being lower.

What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

Ivabradine is indicated in chronic heart failure NYHA II to IV class with systolic dysfunction, in patients in sinus rhythm and whose heart rate is ≥ 75 bpm, in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated.

Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

No new studies are due to report within the next 12 months

If the technology has not been launched, please supply the anticipated date of availability in the UK.

N/A - Ivabradine has been available in the UK since 2006 for the treatment of stable angina.

Does the technology have regulatory approval outside the UK? If so, please provide details.

Regulatory approval has been obtained across all European Union countries, and also in The Philippines, Thailand, Russia, Colombia and Turkey.

Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

For its indication in angina the technology has received a positive recommendation from the SMC. It is also included in the NICE stable angina guidelines 2011. For the new heart failure indication, Servier are planning to submit to the SMC on 4th June 2012 with advice expected to be published on the SMC website on 8th October 2012.

For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table 1: Unit costs of technology being appraised

Pharmaceutical formulation	Tablet
Acquisition cost (excluding VAT)	5mg x 56 tablets = £40.17 7.5mg x 56 tablets = £40.17
Method of administration	Oral
Doses	2.5mg, 5mg, 7.5mg (dose titration based on resting heart rate as defined in the SPC)
Dosing frequency	Twice daily (bd)
Average length of a course of treatment	N/A – chronic therapy
Average cost of a course of treatment	N/A
Anticipated average interval between courses of treatments	N/A
Anticipated number of repeat courses of treatments	N/A
Dose adjustments	The usual recommended starting dose is 5 mg twice daily. After two weeks of treatment the dose can be increased to 7.5 mg twice daily if resting heart rate is above 60 bpm, or decreased to 2.5 mg twice daily if resting heart rate is below 50 bpm (SPC, Appendix 1).

For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

N/A

Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

The only “investigation” required to initiate ivabradine is for the clinician to measure the resting pulse to determine that the patient has a resting heart rate ≥ 75 bpm. This measurement is described in NICE CG108 as being part of routine care (7).

Before ivabradine is considered patients should already have a diagnosis of heart failure with systolic dysfunction and their treatment should have been optimised, particularly beta-blockers and ACE inhibitors, in line with best practice outlined in NICE CG108 (7).

Is there a need for monitoring of patients over and above usual clinical practice for this technology?

Regular clinical monitoring of patients treated with ivabradine is recommended for the occurrence of AF, which should include ECG monitoring if clinically indicated (e.g. in case of exacerbated angina, palpitations, irregular pulse) (SPC 2012, Appendix 1).

What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

N/A - Patients should already be receiving standard heart failure therapies prior to the initiation of ivabradine.

2 Context

In this background section the manufacturer or sponsor should contextualise the evidence relating to the decision problem.

Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Chronic heart failure (CHF), referred to hereafter as 'heart failure' (HF), is a complex syndrome characterised by symptoms such as breathlessness, fatigue and fluid retention (National HF Audit 2011 (4)). It may be caused by either structural or functional cardiac disorders that impair the ability of the heart to work as a pump and thus support the circulation (4). The most common causes of heart failure today in the UK are ischaemic heart disease and hypertension with many patients having both.(4). Approximately two-fifths of patients have heart failure associated with LVSD (Petersen et al.2002 (18); Davies et al. 2001(20)) which manifests in a reduced LVEF, while others have heart failure with a preserved ejection fraction. Most of the evidence in the field of heart failure treatment relates to heart failure associated with LVSD (4).

The prevalence of heart failure is approximately 1-2% of the UK population; however this rises significantly with age. For example, in men aged over 75 the prevalence rises to 16%.(4) In addition, the number of patients with heart failure is set to increase due to a combination of an aging population and improved survival rates in patients with other cardiovascular diseases, especially those surviving a heart attack. (National HF Audit 2011 (4))

Despite the range of existing treatments, many of which have substantially improved outcomes in the past two decades, prognosis remains poor. Mortality in heart failure patients ranges between 10-50% per year depending on severity, and newly diagnosed patients have a 40% risk of dying within the first year following diagnosis. These survival rates are at least comparable, and possibly worse than those for breast and prostate cancer (4). Along with the poor prognosis, heart failure is a physically and emotionally debilitating condition that impacts significantly on HRQL (Green et al. 2012 (21)). This may result in financial implications for patients associated with inability to work or reduced ability to work. The impact on HRQL in heart failure patients has been shown to be greater than in other chronic conditions such as chronic lung disease, arthritis, or other cardiac conditions (18). In addition, heart failure is often associated with other co-morbidities(18); over one third of patients are thought to suffer from prolonged and severe depression (4).

Importantly, heart failure places a significant burden on the NHS. The costs to the NHS for provision of heart failure services are estimated to be over £600 million annually (National HF Audit 2011 (4)). A considerable proportion of these costs relate to hospital admissions; heart failure is one of the most common reasons for emergency medical admission, re-admission and hospital bed-day occupancy in the

UK. heart failure accounts for approximately 2% of all NHS inpatient bed-days and 5% of all emergency medical admissions to hospital (National HF Audit 2011 (4)).

Evidence now increasingly suggests that elevated heart rate is associated with increased risk of all-cause mortality, cardiovascular mortality, and development of cardiovascular disease in a number of populations including the general population, hypertensives, diabetics, patients with pre-existing coronary artery disease, and also in heart failure patients [Böhm et al 2010, Kannel et al.1987, Hjalmarson et al. 2012, Gillman et al. 2012, Palatini et al. 1999, Diaz et al. 2005, Fox et al. 2008, Kolloch et al. 2008 (22);(23);(24);(6;25-27);(28)].

Heart failure patients are often shown to have markedly elevated heart rates; this is thought to be due to compensatory neurohormonal activation resulting in an increased and persistent sympathyetic overdrive, as the heart works harder to meet the body's oxygen demands (Kjekshus and Gullestad 1999 (29)). In the short term, such compensatory mechanisms can provide some benefit to the patient. However, as the condition persists, these mechanisms may provoke further detrimental effects on the myocardium with subsequent LVSD. In addition to the increased mortality risk that this is associated with, there is also a significantly greater risk of hospitalisation (Pocock et al. 2006 (30)).

Heart rate reduction is associated with improved outcomes in heart failure (29). Indeed a principal action of beta-blockers is to attenuate the heart rate (Black 1988(31)). In large controlled clinical trials beta-blockade has been shown to reduce mortality (32). A meta-regression of 23 beta-blocker RCTs in heart failure patients indicated that, for every 5 bpm reduction in heart rate achieved (baseline to first visit post titration period), an 18% (95% CI: 6-29%) reduction in all-cause mortality was observed (McAlister et al. 2009 (5)). Furthermore it is widely accepted that beta-blockers may confer other advantages for patients with heart failure, including an anti-arrhythmic effect.

Whilst the benefits of beta-blockers are well established, a number of patients are either contraindicated to therapy or are unable to tolerate target dosages. Furthermore, despite the best attempts to up-titrate the dose of beta-blockers according to CG108 there remains a significant proportion of patients with an elevated heart rate (Komajda et al. 2003(33)). These issues together highlight an unmet need.

How many patients are assumed to be eligible? How is this figure derived?

The prevalence of definite heart failure in the UK in patients ≥45 years is 2.3% (Davies et al. 2001(20)). Cowie 1999 (34) estimates that there are 63,000 new cases of heart failure per annum . The annual mortality rate from HF is estimated to be 9% in the ECHOES study. Therefore, the net number of patients in England and Wales with definite heart failure is approximately 551,000.

Of these, it is estimated 41.3% have systolic dysfunction (Davies et al. 2001 (20)). A recent audit analysis by Cleland & Goode et al. allows us to determine that 16% of patients with heart failure due to LVSD may be considered suitable for ivabradine therapy based on the licensed indication (i.e. NYHA class II-IV, in sinus rhythm, and with resting heart rate ≥75 bpm) (35). Therefore approximately 36,000 patients in England and Wales would be eligible for ivabradine therapy (~66 per 100,000 population).

Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

Clinical Guidelines

NICE Clinical Guideline 108 (2010) (7) – on the management of chronic heart failure in adults in primary and secondary care. Recommendations on pharmacological treatment of heart failure with LVSD is summarised in section 2.4, of relevance to the licensed indication for ivabradine

Health technology Appraisals

Published: TA120 – Heart failure, Cardiac Resynchronisation (2007) (36);
TA95 – Arrhythmia, Implantable Cardioverter defibrillators (ICDs) (review) (2006) (37)

In development: Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure (review of TA95 and TA120) – expected date of publication Sep 2013 (38)

NICE Quality Standards - Chronic Heart Failure (2011) (39)

Quality Standards (QS) cover the assessment, diagnosis and management of chronic heart failure in adults:

QS 6: People with chronic heart failure are cared for by a multidisciplinary heart failure team led by a specialist and consisting of professionals with appropriate competencies from primary and secondary care, and are given a single point of contact for the team.

QS 7: People with chronic heart failure due to LVSD are offered ACE inhibitors (or ARBs licensed for heart failure if there are intolerable side effects with ACE inhibitors) and beta-blockers licensed for heart failure, which

are gradually increased up to the optimal tolerated or target dose with monitoring after each increase.

QS 9: People with stable chronic heart failure receive a clinical assessment at least every 6 months, including a review of medication and measurement of renal function.

Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

NICE Clinical Guideline 108 (2010) (7) is divided into five sections, each of which describes evidence-based guidance on best practice:

1. Diagnosing heart failure
2. Treating heart failure
3. Rehabilitation
4. Monitoring
5. Referral and approach to care

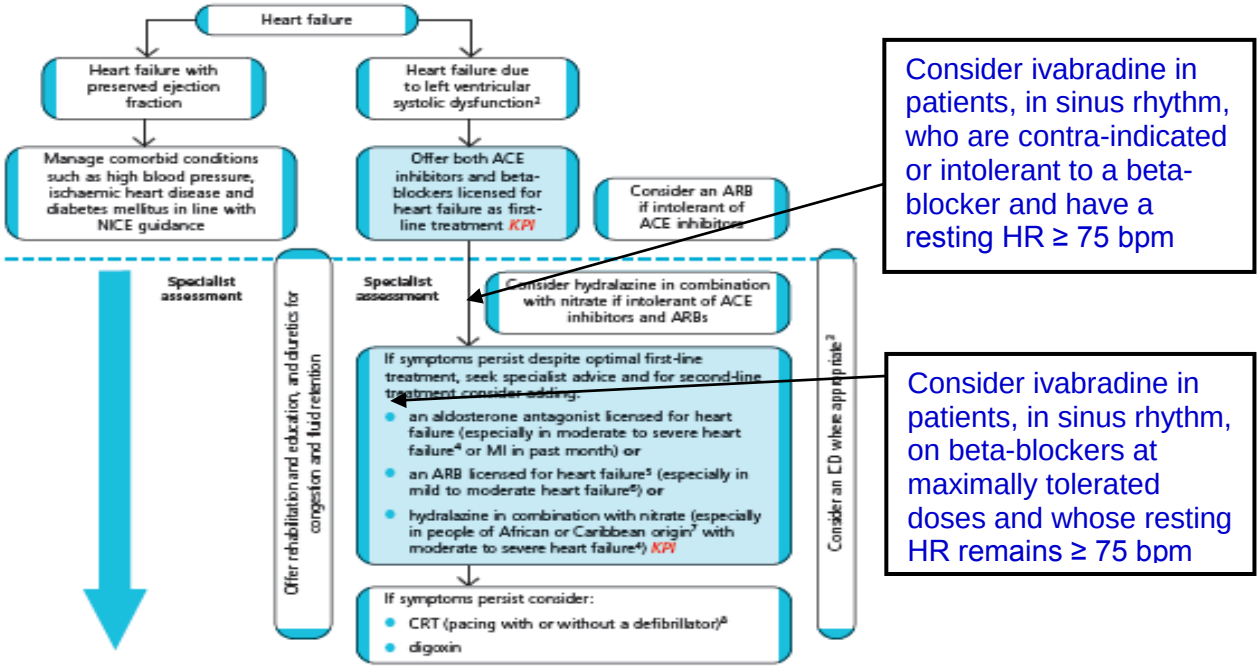
Section 2 of CG108 focuses on the care pathway and includes a pharmacological treatment algorithm for treating heart failure with LVSD (Figure 1). Servier fully supports the implementation of NICE CG108 and in particular the aggressive up-titration of beta-blockers and ACE inhibitors to target or maximum tolerated doses.

Consistent with the indication, ivabradine should be considered in heart failure due to left-ventricular systolic dysfunction, under the advice of a specialist, in the following circumstances:

1. Patients (in sinus rhythm) who are contraindicated to beta-blockers or are intolerant to these agents and have a resting HR ≥ 75 bpm

2. Patients (in sinus rhythm) on beta-blockers at maximally tolerated doses whose resting heart rate remains ≥ 75 bpm.

Figure 2: NICE CG108 treatment algorithm with suggested additions



Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

The Healthcare Commission has identified considerable variation in the prevalence of heart failure by primary care trust and that patients are frequently not receiving optimal levels of care. Access to community heart failure services or heart failure specialist nursing services is also highly variable around the UK (40)

The National Heart Failure Audit was launched in 2007 and presents key findings relating to heart failure management in England and Wales on an annual basis. Data are taken from patients discharged from hospital with a primary discharge diagnosis of heart failure. Previous reports have shown considerable variation across the country in relation to the confirmation of diagnosis and access to evidence based treatment and heart failure specialist staff. They have also shown that many patients admitted to hospitals in England, Wales and Northern Ireland were not managed fully in accordance with national and international evidence-based guidelines, and only a minority of patients with heart failure were seen, or followed up, by a specialist service. This variability appeared to have an impact on patient outcomes.(National HF Audit 2011 (4))

Despite some improvements seen in subsequent audits and the recently updated NICE Clinical guidelines for chronic heart failure, the 2010-2011 national audit report highlights some clear issues relating to current clinical practice (4):

- Mortality rates are high in the UK; 33% of patients in the 2010-2011 audit had died at the end of the follow up period. Furthermore, mortality rates in hospital are higher than in contemporary US and European registries.

- Variations in hospital admissions and readmissions are significant across the UK, ranging from 1 – 5 admissions annually.

- More pertinently, whereas the overall mean length of stay was 11 days, this can vary from between 7 days to greater than 20 days from trust to trust

- In-patient mortality rates are shown to be better for those admitted to cardiology wards (8%) compared to those in general medical wards (14%) and other wards (17%). It is noted that case-mix may account for at least some of this discrepancy.

- Mortality rates after discharge are also significantly better for those who receive cardiology follow up (18% vs 31%) and those referred to heart failure specialist nursing services (22% vs 27%) compared to those who do not.

- Although beta-blockers and ACE inhibitors are both recommended as first line treatments for all heart failure patients, prescription rates for beta-blockers are suboptimal with only 65% of patients prescribed them on discharge. However, treatment rates for ACE inhibitors/ARBs and beta-blockers are significantly better when patients are admitted to cardiology rather than general medical wards. Mortality rates with these key medical treatments, in addition to aldosterone antagonists, are substantially lower than without such therapy. In primary care, treatment rates are likely to be significantly lower.

As already stated, beta-blockers are an essential strategy for heart failure therapy, due to both the attenuation of heart rate and other beneficial mechanisms (Black 1988; Just 1996 (31;41)). They should be up-titrated to target or maximum tolerated dose to optimise outcome. However as demonstrated by the National Heart Failure Audit there are still significant numbers of patients not taking beta-blockers (4). Prescription rates for beta-blockers are suboptimal with only 65% of patients prescribed them on discharge (this figure rises to 78% for patients discharged from cardiology wards). In addition, many patients who commence beta-blockers fail to reach target doses, with hypotension, fatigue, dyspnoea or dizziness often cited as the reason (Fonarow et al. 2008; Maggioni et al. 2010 (42;43)). Treatment persistence is a further issue with as many as 50% of patients no longer taking a beta-blocker after 3 years (Setakis et al. 2009 (44)).

The NICE quality standards for chronic heart failure (2011) offer key recommendations to encourage appropriate diagnosis, assessment and management of heart failure patients. Of particular relevance to the appropriate use of beta-blockers:

- People with chronic heart failure due to LVSD are offered ACE inhibitors (or ARBs licensed for heart failure if there are intolerable side effects with ACE inhibitors) and beta-blockers licensed for heart failure, which are gradually increased up to target or maximum tolerated dose with monitoring after each increase (NICE Quality Standard: heart failure 2011 (39)).

The quality standards aim to address the variability currently seen across the UK, particularly in relation to pharmacological therapy and hospitalisations.

Please identify the main comparator(s) and justify their selection.

Standard treatment without ivabradine.

NICE define the appropriate comparator as, “routine and best practice in the NHS” (NICE Methods Guide, 2008 (9)). In the context of heart failure this consists of a range of pharmaceutical therapies including beta-blockers, the primary heart rate lowering drug. It is important to note that the SHIfT study was designed to assess the effect of ivabradine on top of the best possible care.

In order to ensure best possible care, the SHIfT protocol and eCRF were designed such that every effort was made to optimise use of established treatments in heart failure, in particular the optimal use of beta-blockers. This was acknowledged by the CHMP in their assessment report (19). Beta-blockade could only be stopped in the study for a documented reason (SHIfT study protocol, 2006 (45)). As a result of these efforts patients received care including beta-blockers (89%), ACE inhibitors and/or ARBs (91%), aldosterone antagonists (60%) and diuretics (83%) (SHIfT study, 2010 (8)). The use of these therapies in SHIfT exceeds levels of treatment observed in similar populations within UK clinical practice. Indeed the National heart failure Audit 2011 demonstrated that on discharge 65% of patients in the UK were on beta-blockers (rising to 78% from cardiology wards), 81% were taking ACEi and/or ARB, and 36% were on aldosterone antagonists (4).

With respect to the dose of beta-blocker used in SHIfT, 26% of patients received the target dose. For patients on less than the target dose, up-titration of the beta-blocker should not be considered as an appropriate comparator for reasons of tolerability. In SHIfT, despite the best efforts of the study investigators, a significant number of patients could not tolerate up-titration. Specifically, 44% of patients could not be up-titrated because of the risk of hypotension, 32% because of concerns regarding fatigue and 14% due to dyspnoea. To reinforce the concerns regarding hypotension, SHIfT patients having hypotension recorded as the reason for not achieving target dose beta-blockade were observed to have average blood pressure of 113/72 (as compared to 122/76 for patients on target dose). The issue of tolerability of beta-blockers is also reflected in numerous UK studies including the Cullington 2011 audit of a primary care heart failure clinic, which showed that after a 12 month period of follow-up to optimise therapy only 19% of patients reached target dose beta-blockade and 34% moderate dose (46).

Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

Ivabradine is generally well tolerated. Bradycardia has been reported by 3.3% of patients in clinical trials, particularly within the first 2 to 3 months of treatment initiation. 0.5% of patients experienced a severe bradycardia at or below 40 bpm (SPC 2012, Appendix 1). In the case of severe and prolonged bradycardia (for example in the case of overdose), patients should be treated symptomatically in a specialised environment. In the event of bradycardia with poor haemodynamic tolerance, symptomatic treatment including intravenous beta-stimulating medicinal products such as isoprenaline may be considered. Temporary cardiac electrical pacing may be instituted if required.

Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

Patients will already have a diagnosis of heart failure with LVSD and sinus rhythm and should be on optimised beta-blocker therapy prior to consideration for ivabradine therapy. The only action required prior to initiation is measurement of the resting pulse to determine that it is ≥ 75 bpm, and then a further consultation after two weeks to complete the ivabradine dose titration (SPC 2012, Appendix 1).

Many clinicians already record pulse rates as part of their routine practice; indeed blood pressure monitoring devices usually provide a pulse reading. One important consideration would be for the patient to have five minutes rest prior to pulse measurement in order to improve the accuracy of the reading.

For hospitalised patients initiated on ivabradine prior to discharge, up-titration is likely to be carried out as part of the routine 2-week clinical assessment from a member of the multidisciplinary heart failure team, as recommended in NICE Quality Standard 7 (Section 2.3) (39).

The SPC recommends that the treating physician should be experienced in the management of chronic heart failure so Servier anticipate that ivabradine would be initiated by either a consultant cardiologist, a primary care GPwSI (GP with special interest) or other suitably qualified member of a multidisciplinary heart failure team.

Therefore the only anticipated additional costs to the NHS would be as follows:

1 The acquisition cost of the drug; £40.17 for 28 days / 56 tablets (5mg and 7.5mg tablets have the same NHS cost) (MIMS 2012 (47)).

2 (Potentially) an additional consultation to titrate the ivabradine dose, likely to be through a GP or specialist heart failure nurse visit.
PSSRU 2011 estimates that a consultation (including the cost of qualifications) is £36 for a GP or £25 for a specialist nurse (48).

Does the technology require additional infrastructure to be put in place?

No.

3 Equity and equality

NICE considers equity in terms of how the effects of a health technology may deliver differential benefits across the population. Evidence relevant to equity considerations may also take a variety of forms and come from different sources. These may include general-population-generated utility weightings applied in health economic analyses, societal values elicited through social survey and other methods, research into technology uptake in different population groups, evidence on differential treatment effects in different population groups, and epidemiological evidence on risks or incidence of the condition in different population groups.

Identification of equity and equalities issues

Please specify any issues relating to equity or equalities in NICE guidance, or protocols for the condition for which the technology is being used.

No issues relating to equity or equality were raised in NICE clinical guideline No.108

Are there any equity or equalities issues anticipated for the appraisal of this technology (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?

No. The issues identified in the scoping comments were the relatively young age of the population in the trial, the gender (mainly male) and the ethnicity (mainly white). The EPAR contains details of an analysis provided to the EMA by the manufacturer showing the effect of the treatment to be similar in patients under the age of 70 years as those over the age of 70 years (EPAR 2012 (49)). Section 5.1 of the SPC clearly states that the reduction of the primary endpoint in the study was observed regardless of gender (see SPC, Appendix 1). It should also be noted that the average age, gender ratio and ethnicity are similar to pivotal beta-blocker and ARB trials in heart failure (age range 58 to 64, male inclusion 79 - 80%, ethnic white 90 to 94%) (Lechat 2001; McMurray2003; Packer1996; MERIT-HF1999 (50-53)). NICE guideline recommendations for these treatments in heart failure do not specify age, gender or ethnicity restrictions.

How have the clinical and cost-effectiveness analyses addressed these issues?

N/A

(Age is explored as a potential covariate within the model risk equations and is also explored in subgroup analysis. However this isn't to address issues of equality but rather issues of generalisability of the trial population to clinical practice in the UK).

Identification of innovation issues

(note, although not formally included in this version of the template the manufacturer was advised to respond to the innovation questions in this section)

Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Ivabradine is a significant new treatment for heart failure and highly cost-effective when used in its licensed indication, compared to standard care. The cost-effectiveness ratio (£8,498 per QALY) is well below the threshold generally considered by NICE. Nevertheless this section will be used to summarise the innovative nature of the technology, providing reassurance that the base case cost-effectiveness ratio is potentially conservative.

Professor Sir Ian Kennedy's 2009 report for NICE highlighted three areas with regard to innovation (1). Servier believes that each of these applies to ivabradine in heart failure and this criterion for innovation has therefore been met.

a) Is new:

Ivabradine has been licensed by the EMA as a new treatment for the management of heart failure. Despite a variety of other treatments already available for treating the condition, the prognosis of heart failure patients remains very poor. Ivabradine represents the first new class of treatment for heart failure in over 10 years. It has a unique mechanism of action and there are no other related agents currently in clinical development for heart failure.

b) Constitutes an improvement on existing therapies:

The SHIfT trial showed that the addition of ivabradine to standard best practice treatment further improved outcomes compared to best practice alone, with an 18% reduction in the primary composite endpoint of cardiovascular death or hospitalisation for heart failure, and significant reductions in death from heart failure and hospitalisation for heart failure (2). In the subgroup with baseline heart rate ≥75bpm of relevance to the licensed indication and the NICE decision problem, the primary endpoint was reduced by 24%. Improved outcomes were also reflected in secondary endpoints, including a 17% reduction in all-cause mortality, 17% reduction in cardiovascular mortality, and 39% reduction in death from heart failure (Table 12 and Table 14, Section 5.5.1). These benefits were demonstrated on top of optimised recommended background treatment for heart failure which generally exceed levels achieved currently in clinical practice in England and Wales. These findings are consistent with the objectives of heart failure treatment outlined in NICE CG108 (3). If therapy for heart failure has been optimised in line with these recommendations, there is currently no alternative non-surgical option other than ivabradine to achieve further benefit in these patients.

c) Offers something more: a step-change in terms of outcomes for patients

[note the Kennedy report highlights that a 'step-change' relates to meeting a need recognised as important by the NHS, and furthermore that the NICE Citizen's Council (May 2009) ranked quality of life as the most highly valued innovation (1)]:

The NHS has identified heart failure as being important (3,4). The Quality and Outcomes Framework 2011/12 states, "Heart failure represents the only major cardiovascular disease with increasing prevalence and is responsible for dramatic impairment of quality of life, carries a poor prognosis for patients, and is very costly for the NHS to treat (second only to stroke)." (4) In line with this, improving quality of life is one of the objectives for heart failure treatment as defined in NICE CG108 (3). Published evidence has shown no improvement in the quality of life of patients with any current treatments (e.g. beta-blockers, ACEi, ARB, aldosterone antagonists etc), either through generic or condition-specific measures (3,5-7).

The PRO-SHIfT study (a pre-defined quality of life sub-study) showed that the addition of ivabradine to standard best practice achieved statistically significant improvements in health-related quality of life using the Kansas City Cardiomyopathy Questionnaire (8). (see Section 5.5). A mixed regression model using EQ-5D Index Scores calculated using UK population tariff values, consistent with the NICE reference case, was also performed. This also showed ivabradine to be associated with a statistically significant increase in patient QoL. (see Section 6.4.3)

In terms of both clinical outcomes and quality of life improvements, the SHIfT study clearly demonstrates that the use of ivabradine in patients with heart failure will result in improvements to patient care.

Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

The Kennedy report indicates a number of benefits potentially not captured by the QALY measure (1):

From a personal perspective, disease-specific quality of life improvements and reduced heart failure hospitalisations may impact positively on patients' dignity and independence, and lead to a reduction in the social visibility of the disease and its care. From a societal perspective, heart failure may be considered an end of life issue as it carries a very poor survival prognosis (one-year mortality rates 30-40% (3,9)) which is at least comparable with the survival rate for many cancers such as breast (10) or prostate cancer (11).

4 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the evidence submission will address.

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	Adults in sinus rhythm with symptomatic chronic heart failure (NYHA class II to IV) due to left-ventricular systolic dysfunction who have been prescribed standard optimal heart failure therapy	Adults in sinus rhythm with symptomatic chronic heart failure (NYHA class II to IV) due to left-ventricular systolic dysfunction who have been prescribed standard optimal heart failure therapy and have a resting heart rate ≥ 75 bpm.	The licensed indication has limited the population to patients with resting heart rate ≥ 75 bpm.
Intervention	Ivabradine	Ivabradine	
Comparator(s)	Standard treatment without ivabradine	Standard treatment without ivabradine	Servier intend to explore potential heterogeneity in cost-effectiveness according to beta-blocker usage, i.e. in patients at target dose or not, and in patients contra-indicated to a beta-blocker.
Outcomes	• cardiovascular mortality • all-cause mortality • hospitalisation due to heart failure • all-cause hospitalisation • adverse effects of treatment • health-related quality of life	• cardiovascular mortality • all-cause mortality • hospitalisation due to heart failure • all-cause hospitalisation • adverse effects of treatment • health-related quality of life	

Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	As per final scope A lifetime horizon has been considered in the base case and shorter time horizons have been explored in sensitivity analysis.	
Subgroups to be considered	None specified	Servier intend to assess subgroups based on both pre-specified analyses and also those which appear particularly relevant to the decision problem and the cost-effectiveness estimates. The subgroups used in the model to modify either baseline risk or the treatment effect of ivabradine will be guided by the SHIfT trial protocol.	To investigate potential heterogeneity in cost-effectiveness estimates
Special considerations, including issues related to equity or equality	None specified	None specified	

Section B – Clinical and cost effectiveness

When estimating clinical and cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal' – www.nice.org.uk). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Element of health technology assessment	**Reference case**	**Section in 'Guide to the methods of technology appraisal'**
Defining the decision problem	The scope developed by NICE	5.2.5 and 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 and 5.2.6
Perspective costs	NHS and PSS	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 and 5.2.12
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12
HRQL, health-related quality of life; NHS, National Health Service; PSS, Personal Social Services; QALY(s), quality-adjusted life year(s)		

5 Clinical evidence

Manufacturers and sponsors are requested to present clinical evidence for their technology in the following sections. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3 and 5.3.1 to 5.3.8.

Identification of studies

Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 9.2, appendix 2.

The scope for this appraisal specifies that ivabradine is appraised for the treatment of HF, compared to standard treatment without ivabradine. Therefore, a systematic review was undertaken in order to identify clinical trials evaluating the safety and efficacy of ivabradine vs placebo in HF. Servier has a number of overlapping worldwide activities relating to ivabradine in HF. As a result the clinical systematic review was carried out by Servier's Australian subsidiary in May 2011, and was subsequently updated. Full details are provided below.

An initial systematic review to identify RCTs and controlled non-RCTs evaluating the clinical effectiveness of ivabradine compared with placebo for the treatment of HF was conducted in May 2011. This systematic review was subsequently extended and updated in January 2012 to ensure all relevant studies were identified for the purposes of this submission.

In the original systematic review database searches were conducted on 3rd May 2011. They were conducted in EMBASE.com (EMBASE and Medline databases) and in the Cochrane Library. These searches were supplemented by additional searching of further sources such as the US National Institutes of Health clinical trials registry (ClinicalTrials.gov) and the Australian New Zealand Clinical Trials Registry (ANZCTR). In addition, the Servier TGA (Therapeutic Goods Administration) dossier for ivabradine was searched to identify any relevant clinical study reports. Using Boolean operators, the electronic database was searched using terms (including MeSH headings as appropriate) to identify pooled analyses, systematic reviews, meta-analyses, RCTs or controlled non-RCTs for ivabradine, including any alternative names (e.g. Procorolan, Corlentor, Coraxan, Coralan and others), *versus* placebo in patients with HF (including alternative terms for HF).

For the updated systematic review, searches were conducted on 24th January 2012 via OVID in Embase, MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) and in the Cochrane Library. As the original systematic review did not search MEDLINE(R) In-Process, the updated systematic review's search strategy

was developed to account for this, in order to identify not only studies published since 3rd May 2011, but also studies indexed since then, that may have had a publication date prior to 3rd May 2011. For full details, see Section 9.2 Appendix 2. In addition, as part of the updated systematic review, the US National Institutes of Health clinical trials registry (ClinicalTrials.gov) was searched.

Study selection

Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

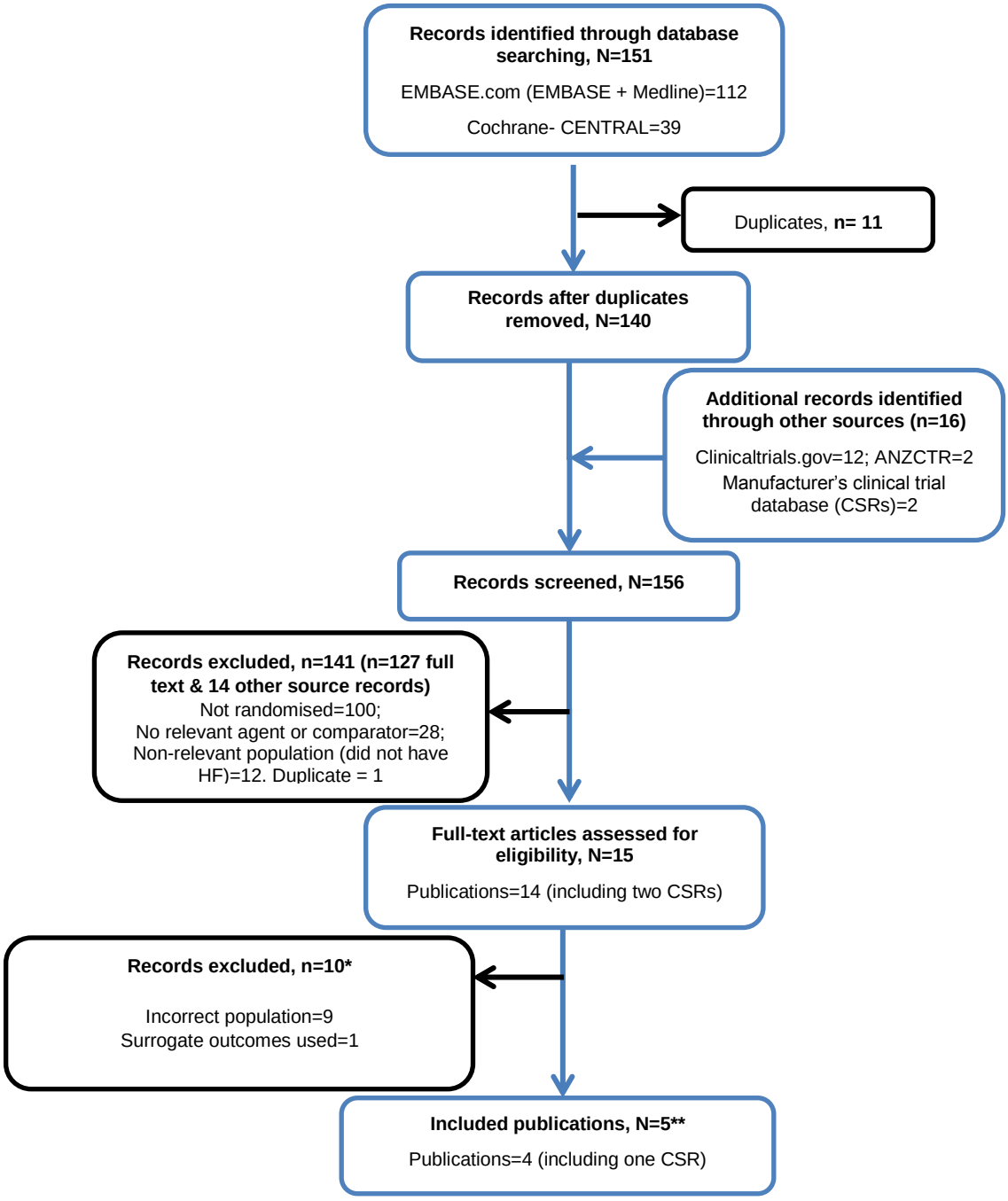
Table 2: Eligibility criteria used in the original and updated systematic review strategy

	Clinical effectiveness and adverse events
Inclusion criteria	Population – patients with systolic heart failure Interventions – ivabradine Outcomes – mortality endpoints (all-cause mortality, cardiovascular mortality, death from heart failure) and morbidity endpoints (all-cause hospital admission, hospital admission for worsening heart failure, any cardiovascular admission) Study design – randomised, double-blind controlled trials Language – none
Exclusion criteria	Population – patients without systolic heart failure, or population not consistent with Procorolan SPC Interventions –studies not including ivabradine Outcomes – surrogate outcomes (e.g. change in exercise capacity) rather than the final endpoints of mortality and morbidity Study design – no randomisation, letters, commentaries, notes, editorials, reviews or methodological papers Language restrictions – none

The search strings identified RCTs and controlled non-RCTs. Application of the selection criteria subsequently excluded any study without a randomisation step, that is, restricted studies to RCTs. Those studies excluded due to no randomisation step were reviewed to ensure no relevant non-RCTs were identified for further review (Section 5.8).

A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 5.2.4.

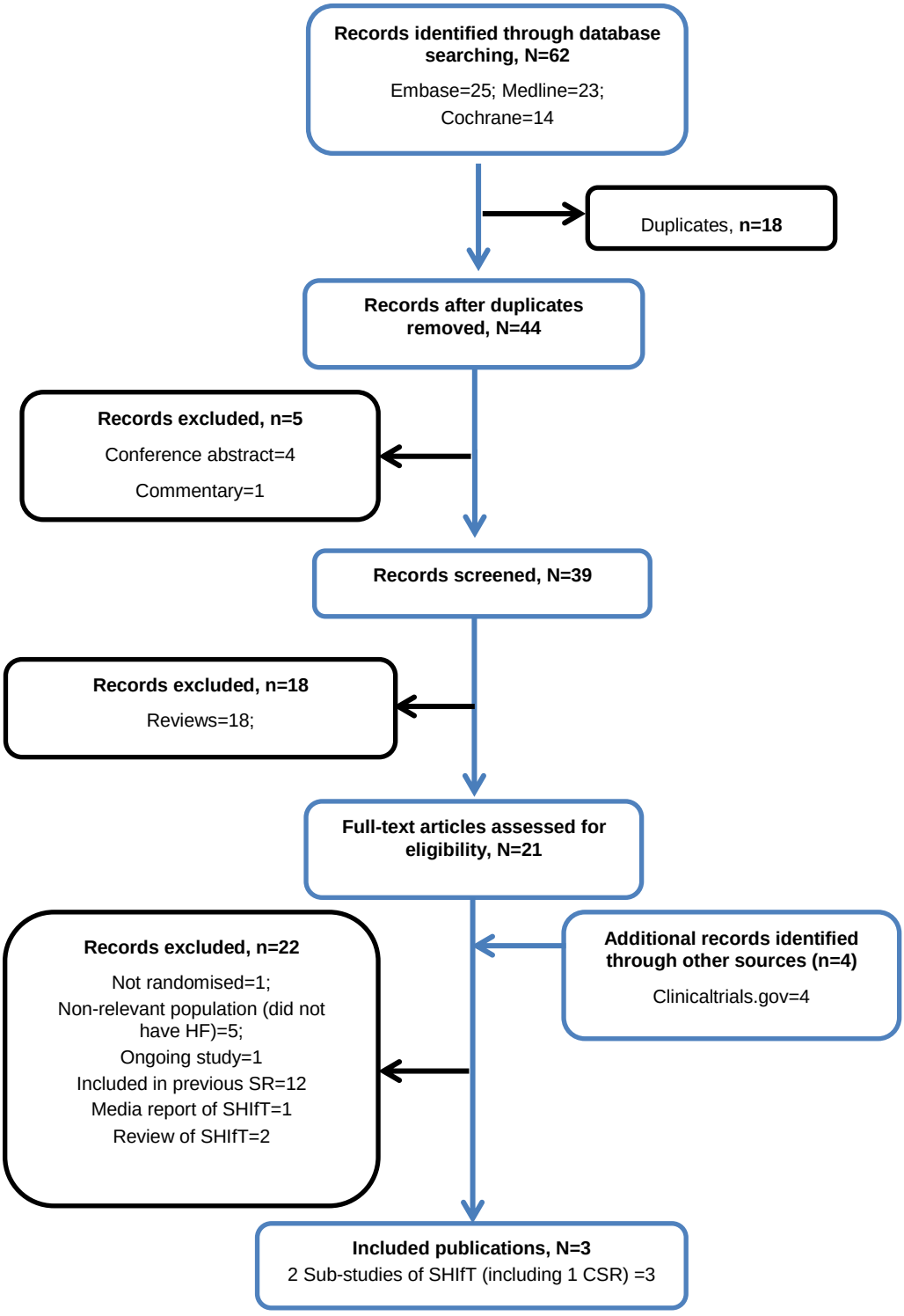
Figure 3: Flow diagram for study selection (original systematic review)



* For further details of excluded trials see Section 9.2.8, Appendix 2.
** Note, the five included publications all relate to the SHIfT trial - these are detailed in Table 3 below.

Abbreviations: ANZCTR, Australia New Zealand Clinical Trials Registry

Figure 4: Flow diagram for study selection (updated systematic review)



* Note, the three included publications all relate to the SHIfT trial - these are detailed in Table 3 below.

When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

The data presented (eight records) are based on the clinical study report and published papers for the Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial (SHIfT) study and two pre-specified sub-studies in patients with moderate to severe chronic HF and LVSD (Table 3).

The aims, study design and date of the first patient being recruited into SHIfT were published in the European Journal of Heart Failure by Swedberg et al. (2010). Results were then published in The Lancet by Swedberg et al. (2010) alongside the publication of an association between heart rate and outcomes in chronic heart failure, by Böhm et al. (2010). A SHIfT erratum was published subsequently. The related Clinical Study Report was by Komajda and Swedberg (2010).

Results of the two sub-studies were published in the European Heart Journal by Ekman et al. (2011) and Tardif (2011). In addition the SHIfT Patient Reported Outcomes sub-study is reported in the Clinical Study Report: CL3-16257-063 by Chasseny.

A further publication, Swedberg et al (2012) (in Press), was not identified in the electronic searches but is described in Section 5.5.

Table 3: Report and publications of SHIfT

Trial	Reports/publications
SHIfT	Komajda M and Swedberg K. Effects of ivabradine on cardiovascular events in patients with moderate to severe chronic heart failure and left-ventricular systolic dysfunction: SHIfT study. A three-year randomised double-blind placebo-controlled international multicentre study. 21 October 2010. Clinical Study Report: CL3-16257-063. Laboratories Servier. Published as: Swedberg et al. (2010) (54). Rationale and design of a randomized, double-blind, placebo-controlled outcome trial of ivabradine in chronic heart failure: The Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine Trial (SHIfT). European Journal of Heart Failure 12(1): 75-81. Swedberg et al. (2010). Ivabradine and outcomes in chronic heart failure (SHIfT): A randomised placebo-controlled study. The Lancet 376(9744): 875-885. Swedberg, K., M. Komajda, et al. (2010). Swedberg et al. (2010). Erratum: Ivabradine and outcomes in chronic heart failure (SHIfT): A randomised placebo-controlled study (Lancet (2010) 376 (875-885)). The Lancet 376(9757): 1988.

Trial	Reports/publications
	Böhm et al. (2010). Heart rate as a risk factor in chronic heart failure (SHIfT): The association between heart rate and outcomes in a randomised placebo-controlled trial. The Lancet 376(9744): 886-894. Chasseny O. Effects of ivabradine on cardiovascular events in patients with moderate to severe chronic heart failure and LVSD. A three-year randomised double-blind placebo controlled multicentre study. Patient Reported Outcomes Sub-study to the clinical study CL3-16257-063 Ekman I. et al (2011). Heart rate reduction with ivabradine and health related quality of life in patients with chronic heart failure: results from the SHIFT study. European Heart Journal doi:10.1093/eurheartj/ehr343 Tardif JC. et al (2011). Effects of selective heart rate reduction with ivabradine on left ventricular remodelling and function: results from the SHIFT echocardiography sub-study European Heart Journal doi:10.1093/eurheartj/ehr311 **Publications of SHIfT reported since the update search:** Swedberg et al (2012) Effects on outcomes of heart rate reduction by ivabradine in patients with CHF: is there an influence of beta blocker dose? Findings from the SHIFT- study Journal of American College of Cardiology (in press)

Complete list of relevant RCTs

Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

Table 4: List of relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
SHIfT	Ivabradine 7.5mg bd (maximum dose)	Placebo	Patients with moderate to severe chronic HF and left-ventricular systolic dysfunction	Swedberg, Komajda et al. (2010) in The Lancet plus an erratum

Full details of the study selection have been provided in Section 5.2.1 and 5.2.2. SHIfT has been identified as the only study to have directly assessed the use of ivabradine in the appropriate patient population and consequently is the only RCT that fulfils the criteria of the NICE decision problem. In addition, the EMA licence application for ivabradine in heart failure was based solely on the SHIfT study.

Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

SHIfT is the only applicable RCT.

When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

Not applicable.

List of relevant non-RCTs

Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 5.8 and key details should be presented in a table; the following is a suggested format.

No relevant non-RCTs were identified.

Summary of methodology of relevant RCTs

As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, the information should be tabulated.

Methods

Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

SHIfT has been identified in the systematic literature review as being the only study relevant to the decision problem. Information in this section relates exclusively to the methodology employed in SHIfT. Details are also provided for the SHIfT Patient Reported Outcomes sub-study.

SHIfT recruited patients with a heart rate of ≥70 bpm and showed a significant benefit of ivabradine on the primary composite endpoint of cardiovascular death or hospitalisation for worsening heart failure. However the Lancet publication identified that baseline heart rate modified the treatment effect of ivabradine. During the licensing process, the EMA therefore asked the manufacturer to identify the heart rate threshold above which the mortality benefit for ivabradine was clear. The threshold of 75 bpm or higher was identified, and the CHMP granted a licence in this population rather than the overall SHIfT population with baseline heart rate ≥70 bpm.

Key results for the main trial will be reported in Section 5.5, as well as for the specific licensed population which is directly relevant to the NICE decision problem. To guide the reader, where both populations are discussed in close proximity data and narrative relating to the main trial population is reported in black font (baseline heart rate ≥70 bpm) and the licensed population in blue.

Table 5: Summary of methodology of the SHIfT trial

Location	37 countries with 625 centres (number per country): Argentina (48), Australia (5), Austria (1), Belgium (13), Brazil (23), Bulgaria (20), Canada (10), Chile (9), China / Hong Kong (48), Czech Republic (24), Denmark (14), Estonia (4), Finland (4), France (17), Germany (29), Greece (9), Hungary (28), India (12), Ireland (4), Italy (19), Korea (16), Latvia (8), Lithuania (8), Malaysia (3), The Netherlands (26), Norway (5), Poland (41), Portugal (6), Romania (25), Russia (47), Slovakia (9), Slovenia (6), Spain (12), Sweden (17), Turkey (7), Ukraine (42), United Kingdom (6).
Design	This was a randomised, double blind, placebo-controlled, multi-centre, international, event-driven, morbidity-mortality study, with two parallel and balanced treatment arms. Randomisation was stratified on beta-blocker intake (yes/no) and centre at time of randomisation.
Duration of study	The active double-blind treatment period (ivabradine *versus* placebo) lasted from 12 months to 36 months, extended by Amendments No. 5 and 6 up to a maximal duration of 52 months
Method of randomisation	Randomisation was balanced, non-adaptive, stratified on centre and beta-blocker intake (yes/no) at time of randomisation and performed by telephone randomisation using an Interactive Randomisation Service (IRS). Eligible patients were allocated to receive ivabradine or placebo in addition to treatments appropriate to their HF, with particular emphasis on background treatment with a beta-blocker. Randomisation blocks (of size 4) were randomly and dynamically assigned to the centres in order to respect the stratification on the two pre-defined factors.
Method of blinding (care provider, patient and outcome assessor)	Double-blind (provider, patient). The endpoint validation committee was also blind to treatment group and baseline heart rate.
Intervention(s) (n = 3241) and comparator(s) (n =3264)	Oral ivabradine, twice daily (bd). All patients were prescribed the 5 mg bd. dose (ivabradine or matching placebo) at Day 0. Then, the dose was either maintained, up-titrated to the target dose of 7.5 mg bd., or

	down-titrated to 2.5 mg bd. depending on resting heart rate and tolerability.
Primary outcomes (including scoring methods and timings of assessments)	Primary composite endpoint: • First event of cardiovascular death (including death from unknown cause) or hospitalisation for worsening HF.
Secondary outcomes (including scoring methods and timings of assessments)	Secondary endpoints: • The primary composite endpoint in patients receiving at least half of the target daily dose of beta-blockers at randomisation (RSBBdose; specified in Amendment No. 5). • Hospitalisation for worsening HF. • Cardiovascular death (including death from unknown cause). • Death from any cause. • Death from heart failure. • Hospitalisation for any cause. • Unplanned hospitalisation for any cause. • Hospitalisation for cardiovascular reason (including hospitalisation for undetermined cause). • Unplanned hospitalisation for cardiovascular reason. • Secondary composite endpoint: First event among cardiovascular death (including death from unknown cause), hospitalisation for non-fatal MI or hospitalisation for worsening HF.
Duration of follow-up	The active double-blind treatment period (ivabradine *versus* placebo) lasted from 12 months to 36 months, extended to a maximal duration of 52 months

Participants

Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

Selection of the patient population

Eligible patients were men or women aged 18 years and older who were in sinus rhythm and had a resting heart rate of 70 bpm or higher, as measured on 12-lead electrocardiography (ECG) after at least 5 minute's rest on two consecutive visits before randomisation, with stable symptomatic chronic heart failure of 4 or more weeks duration, a previous admission to hospital for worsening heart failure within the previous 12 months, and a left-ventricular ejection fraction of 35% or lower. Any cause of heart failure was allowed apart from congenital heart disease or primary severe valvular disease. Patients needed to be on optimal stable background treatment for HF for at least four weeks prior to inclusion

Main exclusion criteria were unstable condition within the previous 4 weeks, recent (<2 months) myocardial infarction, ventricular or atrioventricular pacing operative for 40% or more of the day, atrial fibrillation or flutter, and symptomatic hypotension. Other inclusion and exclusion criteria together with design details have been described previously by Swedberg 2010 (54), and are described in the SHIfT CSR p.44-46.

The NICE decision problem defines a population consistent with the licensed indication for ivabradine; specifically, 63.8% of patients in SHIfT with a heart rate of 75 bpm or more.

Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

Baseline demographics and disease characteristics (main trial population and licensed population)

The baseline demographics and disease characteristics for the main SHIfT population (RS) and the licensed population (heart rate ≥ 75 bpm at baseline) are summarised in Table 6. No relevant between-group differences were observed for these parameters. Further, there were no notable differences in baseline demographics or disease characteristics between the main trial population and the licensed population.

Table 6: Baseline demographic characteristics, history of HF and other medical histories at baseline (main trial population and licensed population)

Background therapy	**Heart rate ≥70 bpm at baseline (N = 6,505)**		Heart rate ≥75 bpm at baseline (N = 4,150)	
	Ivabradine N = 3,241	**Placebo N = 3,264**	Ivabradine N = 2,052	Placebo N = 2,098
Age (years)				
Mean ± SD	60.7 ± 11.2	60.1 ± 11.5	59.7 ± 11.23	59.5 ± 11.71
Median (range)	61 (19; 89)	60 (19; 92)	60 (52; 68)	60 (52; 68)
Gender n (%)				
Male	2462 (76.0)	2508 (76.8)	1570 (76.5)	1617 (77.1)
Ethnic origins n (%)				
Caucasian	2879 (88.8)	2892 (88.6)	[redacted]	[redacted]
Asian	268 (8.3)	264 (8.1)		
Black	32 (1.0)	43 (1.3)		
Other	62 (1.9)	65 (2.0)		
Height (cm)				
n	3240	3264	[redacted]	[redacted]
Mean ± SD	169.6 ± 8.8	169.6 ± 8.8		
Median (range)	170 (135; 197)	170 (109[a]; 198)		
Weight (kg)				
Mean ± SD	80.9 ± 17.2	80.7 ± 17.1	[redacted]	[redacted]
Median (range)	80 (27; 159)	79 (29; 170)		
Body mass index (kg/m2)				
n	3240	3264	2052	2098
Mean ± SD	28.0 ± 5.1	28.0 ± 5.0	28.1 ± 5.3	27.9 ± 5.1
Median (range)	27.4 (13.7; 51.6)	27.3 (15.1; 59.5)	27.4 (24.4; 31.2)	27.2 (24.4 ; 30.7)
Heart rate (bpm)				
n	3240	3261	2052	2098
Mean ± SD	79.7 ± 9.5	80.1 ± 9.8	84.3±9.1	84.6±9.4
Median (range)	77 (48; 130)	77 (58; 142)	81 (75; 130)	82 (75; 142)
Sitting SBP (mmHg)				
Mean ± SD	122.0 ± 16.1	121.4 ± 15.9	121.6	121.2
Median (range)	120 (76; 179)	120 (78; 180)	120 (76; 179)	120 (78; 180)
Sitting DBP (mmHg)				
Mean ± SD	75.7 ± 9.6	75.6 ± 9.4	75.8	75.7
Median (range)	77 (42; 110)	76 (40; 120)	78 (42; 110)	76 (40; 120)
eGFR (creatinine clearance) (ml/min/1.73m2)				
n	3233	3252	[redacted]	[redacted]
Mean ± SD	74.6 ± 22.9	74.8 ± 23.1	75.7 ± 23.5	75.5 ± 23.1
Median (range)	73 (23; 263)	73 (17; 331)		
Smoking habits n (%)				
Yes	541 (16.7)	577 (17.7)	381 (18.6)	402 (19.2)
Previous	1355 (41.8)	1364 (41.8)	847 (40.9)	857 (40.9)
Never	1345 (41.5)	1323 (40.5)	824 (40.2)	839 (40.0)
Alcohol consumption n (%)				

Yes	988 (30.5)	940 (28.8)	[redacted]	[redacted]
Previous	628 (19.4)	648 (19.9)	[redacted]	[redacted]
Never	1625 (50.1)	1676 (51.4)	[redacted]	[redacted]
Chronic heart failure				
Duration since HF diagnosis (years) Mean ± SD	3.5 ± 4.2	3.5 ± 4.2	3.5 ± 4.1	3.4 ± 4.0
Primary cause of HF n (%)				
Ischaemic	2215 (68.3)	2203 (67.5)	1359 (66.2)	1363 (65.0)
Non-ischaemic	1026 (31.7)	1061 (32.5)	693 (33.8)	735 (35.0)
Documented hosp'n for worsening HF in pre-vious 12 months, n (%) Yes	42[a] (1.3)[b]	37 (1.1)[b]	[redacted]	[redacted]
No	3199 (98.7)	3227 (98.9)	[redacted]	[redacted]
NYHA class				
Class II, n (%)	1585 (48.9)	1584 (48.5)	977 (47.6)	975 (46.5)
Class III, n (%)	1605 (49.5)	1618 (49.6)	1035 (50.4)	1076 (51.3)
Class IV, n (%)	50 (1.5)	61 (1.9)	40 (1.6)	47 (2.2)
LVEF (%)				
Mean ± SD	29.0 ± 5.1	29.0 ± 5.2	28.7 ± 5.18	28.54 ± 5.27
Median (range)	30.0 (9; 39)	30.0 (7; 37)	30.0 (9; 39)	30.0 (7; 36)
Other medical histories, n (%)				
Coronary artery disease	2361 (72.9)	2371 (72.6)	[redacted]	[redacted]
Hypertension	2162 (66.7)	2152 (65.9)	1333 (65.0)	1349 (64.3)
Myocardial infarction	1829 (56.4)	1837 (56.3)	1124 (54.8)	1138 (54.2)
Diabetes	973 (30.0)	1006 (30.8)	638 (31.1)	665 (31.7)
Atrial fibrillation and/or	263 (8.1)	259 (7.9)	154 (7.5)	162 (7.7)
flutter	228 (7.0)	295 (9.0)	141 (6.9)	189 (9.0)
Stroke	218 (6.7)	202 (6.2)	122 (6.0)	121 (5.8)
Renal failure				

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SD, standard deviation; Q, quartile
Notes: a Patient with bilateral amputation of lower extremities
Source: SHIfT CSR Table (10.4.1.1) 1 p89, p304, p308, p310

Background therapy at randomisation and during the study

Study treatments were added to an existing and stable background therapy for heart failure that was considered by the investigator in charge of the patient as being optimal, and had been unchanged with respect to both heart failure medications and the dosages of such medication for at least 4 weeks. Patients in SHIfT were treated with recommended background therapies (ACEi/ARB 91%, diuretics 84%, beta-blocker 89% and aldosterone antagonists 61%), and dosing levels are very similar between the main trial and licensed populations. Further details are provided in Table 94, Appendix 9.15.1.4.

The context of background therapy in SHIfT is also discussed further in Section 5.10.4. One conclusion is that doses of beta-blocker achieved in SHIfT are at least as good as current UK clinical practice (NICE CG108, Swedberg 2010, Komajda 2003,

National Heart Failure Audit Report 2011 (4;7;8;33)). Further, during the licensing process the CHMP questioned whether patients in SHIfT were optimally treated, especially with regard to beta-blocker dosing. They concluded that Servier provided sufficient justification that all possible effort had been made to ascertain that patients were on maximally tolerated beta-blocker dose (EPAR 2012 (49)). Specific attention was paid to this in the trial oversight as documented in the eCRF and protocol.

Continuation of appropriate background therapy throughout the SHIfT trial is another consideration. The optimised HF background treatments at baseline were maintained following the introduction of ivabradine and continued throughout the study (no relevant between-group differences were observed). Furthermore, no discernible difference was observed in levels of dosing between the main trial and licensed populations (see Table 95, Appendix 9.15.1.4).

These data indicate the high potential for consistent beta-blocker dosing being maintained after the introduction of ivabradine to heart failure patients, i.e. physicians did not down-titrate the dose of beta-blocker in patients even when the heart rate was lowered by ivabradine. The benefits observed in the active arm of the trial may therefore be attributed to ivabradine therapy. Further details on therapy post-randomisation are provided in Table 95, Appendix 15.

Outcomes

Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life, and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.

Objectives of the SHIfT Study

The primary objective of the SHIfT trial was to demonstrate the superiority of ivabradine over placebo in the reduction of CV mortality or hospitalisation for worsening heart failure (composite endpoint), in patients with symptoms of heart failure, a reduced LVEF, sinus rhythm, and receiving optimised recommended background therapy for this disease.

The secondary objectives were to assess the effects of ivabradine compared to placebo on:

- Death from HF and overall mortality, morbidity, functional capacity and clinical symptoms of HF in both the RS (Randomised Set) and in patients receiving at least half of the target daily dose of beta-blockers at randomisation (RSBBdose) analysis sets.
- The primary composite endpoint in the RSBBdose (specified in Amendment No. 5).

Other objectives were to assess in specific sub-studies in selected centres the effects of ivabradine on known predictors of prognosis in HF (left-ventricular remodelling, plasma NT-proBNP concentration and heart rate variability) and health-related quality of life. A pharmacokinetic sub-study was also carried out. Of these, the NT-proBNP and pharmacokinetic sub-studies are not deemed to be of relevance to the decision problem are not discussed further.

An independent Endpoint Validation Committee (EVC), blinded to treatment group and baseline heart rate, adjudicated the clinical pre-specified events (PSEs) occurring in the study population. Each event was adjudicated by two EVC members, who reviewed impartially, independently and in parallel, documentation supporting the events reported by investigators. The two adjudication results were evaluated for concordance. In the case of a disagreement, a third EVS member independently reviewed the file without knowledge of the first two results. The results of these adjudications were used for the efficacy analyses.

Outcome measures of the SHIfT study

The outcome measures in SHIfT are presented in Table 7. The following additional information is provided in Section 9.15.1.2 and 9.15.1.3. Appendix 15:

1. Description of the individual components of the primary composite outcome
2. Description of secondary outcomes

Table 7: Summary of outcome measures in SHIfT

Primary outcome(s) and measures	Reliability/ validity/ current use in clinical practice
First event of CV death (including death from unknown cause) or hospitalisation for worsening HF.	Well established endpoint in HF trials relevant to clinical practice (see aims of HF management in NICE CG108). The preferred endpoint from an EMA perspective would have included all-cause mortality.
Secondary outcome(s) and measures	Reliability/ validity/ current use in clinical practice
Primary composite endpoint in the group of patients taking at least half of the recommended target dose beta-blocker at randomisation	As for primary outcome. In addition, the use of beta-blockers in HF has demonstrated benefits on both mortality and morbidity endpoints therefore it is important to assess the effects of ivabradine in addition to beta-blockade
Death from any cause	Well established endpoint, relevant to clinical practice
Cardiovascular death (including death from any cause)	Well established endpoint, relevant to clinical practice
Death from HF	Well established endpoint, relevant to clinical practice
Hospital admission for worsening HF	Well established endpoint, relevant to clinical practice (see definition below)
Hospitalisation for any cause	Well established endpoint, relevant to clinical practice
Unplanned hospitalisation for any cause	Well established endpoint, relevant to clinical practice
Hospitalisation for CV reason (including hospitalisation for undetermined cause)	Well established endpoint, relevant to clinical practice
Unplanned hospitalisation for CV reason	Well established endpoint, relevant to clinical practice
Secondary composite endpoint: First event of CV death (including death from unknown cause) hospitalisation for non-fatal MI or hospitalisation for worsening HF.	Well established endpoint, relevant to clinical practice
Other efficacy criteria	

Heart rate	Heart rate is a risk factor for outcomes in HF. As Ivabradine is a drug that specifically lowers heart rate this is a valid assessment
NHYA classification	Well established assessment of functional capacity of a person with heart failure
Global assessments	Patient and physician perception of overall impact of heart failure on the individual patient: increasingly used in randomised trials of new therapies in heart failure

Note: All criteria are expressed as the time to first event, defined as the duration between the date of randomisation and the date of the first occurrence of this event.

All endpoints that occurred until the patients' termination visit or the 31 March 2010 (if the termination visit of the patient took place after this date) were considered in efficacy analyses. If the studied event did not occur during the study, a censorship process was applied. Patient's follow-up was censored by the earliest of its termination visit, date of death (when death or nature of death was not considered as the studied event), lost to follow-up date, date of withdrawal from the study, heart transplantation date or 31 March 2010.

Outcomes utilised in the economic model

The economic model uses the outcomes of all-cause hospitalisation and cardiovascular mortality in the base case. This approach has been discussed and justified in Section 6.3.1. Cause-specific outcomes are also explored in sensitivity.

Defining hospitalisation for worsening heart failure

As the SHIfT primary endpoint was primarily driven by hospitalisation for worsening heart failure it is worth noting that this was defined appropriately. To satisfy this outcome patients had to fulfil four pre-specified criteria (outlined in Section 9.15.1.2 Appendix 15), adjudicated by an independent endpoint evaluation committee (EVC) blinded to treatment group and baseline heart rate. As part of the cost-effectiveness modelling we effectively explored methods to address the potential variability and relevance of the input to the UK setting, settling on a conservative approach (Section 6.10.3).

Patient reported outcomes sub-study (PRO-SHIfT): Health-related quality of life

The main objective of this sub-study was to evaluate the effects of ivabradine compared to placebo on HRQL in patients with HF and LVSD. The target population consisted of all patients who consented to participate, from all countries in which translations of the study questionnaires were available (35 out of 37 countries). The population were therefore a subset of the main study.

One generic and one disease-specific health status measure was used to evaluate HRQL as well as symptom perception over time:

- Generic: EuroQol 5 Dimensions (EQ-5D) questionnaire (55)

- Disease-specific: Kansas City Cardiomyopathy Questionnaire (KCCQ) (56)

The EQ-5D and KCCQ questionnaires were completed by the patients at baseline, then at four months, 12 months, 24 months and at termination visits. The endpoints were:

- EQ-5D Index Score
- EQ-5D Visual Analogue Scale (EQ VAS) of the EQ-5D questionnaire - assessed from 0 (worst health state) to 100 (highest status).
- Descriptive system for each of the 5 dimensions of the EQ-5D
- Clinical summary score (previously functional status score) of the KCCQ
- Overall summary score of the KCCQ
- Other domain scores of the KCCQ

Statistical analysis and definition of study groups

State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

SHIfT: Hypothesis objective

To demonstrate the superiority of ivabradine over placebo in the reduction of cardiovascular mortality or hospitalisations for worsening heart failure (primary composite endpoint).

Statistical analysis

All survival analyses were done on a time-to-first event basis with an intention-to-treat principle. Cox's proportional hazards model including a factor for randomised treatment group and adjusted for baseline beta-blocker intake (yes or no) was used to estimate the treatment effect, 95% CI, and associated p value. The proportionality of hazard was checked by addition of an interaction between log (time) and randomised treatment to the Cox model.

Time-to-event curves were estimated with the Kaplan-Meier method. All survival analyses were done on adjudicated endpoints for the entire population and for the subgroup with at least 50% of the target daily dose of a beta-blocker (Details of the SHIfT trial analysis sets are provided in Section 9.15.1.1 Appendix 15.). The number

of patients who would need to be treated for one year to prevent one primary endpoint event was calculated as the inverse of the difference between treatment groups of the estimated probability of having an event at one year in the Kaplan-Meier curves. Treatment effects and 95% CIs were calculated in pre-specified subgroups from Cox models containing treatment effect, baseline beta-blocker status, and subgroup status. P-values for interaction between randomised treatment and subgroup status were also provided by addition of treatment by subgroup interaction to the model.

Sample size, power calculation

On the assumption of an average yearly incidence of the primary composite endpoint of 14% in the placebo group, a treatment effect for ivabradine of 15% relative risk reduction and a significance level of 0.05, 1600 first events were needed to provide 90% power. With an expected mean follow-up of 2.25 years, this assumption required randomisation of 6500 patients. Further details of the sample-size calculation are contained in the SHIfT CSR.

It was estimated that the patients receiving beta-blocker treatment with at least 50% of the target daily dose at baseline would represent roughly 47% of the overall population. With the same risk assumptions as for the overall population, this proportion would result in about 633 events, allowing detection of a relative risk reduction of 20% in favour of ivabradine with 80% power in this subpopulation.

Data management and patient withdrawals

Of the 6,505 patients, 5,315 (81.7%) completed the study: 2,663 patients (82.2%) in the ivabradine group and 2,652 (81.3%) in the placebo group. A total of 1,056 patients died before reaching study completion, 131 patients withdrew consent and 3 were lost to follow up. Of the patients lost to follow-up, 2 were in the ivabradine group and 1 in the placebo group. All analyses were based on the intention to treat principle, unless otherwise stated.

SHIfT-PRO sub-study: Objective

The main objective of this sub-study was to evaluate the effects of ivabradine compared to placebo on HRQL in patients with HF and LVSD.

Statistical analysis

The main analysis was carried out on the FAS EQ-5D population (details of the analysis sets are provided in Section 9.15.1.1 Appendix 15,). This entailed estimation of treatment effect on the change in EQ-5D VAS between baseline and last post-baseline value using an adjusted analysis: mixed linear model with change in EQ-5D VAS as the dependent variable, treatment group as independent variable, and

baseline EQ-5D VAS, beta-blocker intake at randomisation and country (random effect) as covariates. For deceased patients, EQ-5D VAS was set to zero. The main analysis was performed on all endpoints. Additional analyses were also undertaken using the EQ-5D Index Score to inform the cost-effectiveness analysis (Section 5.5 & 6.4.9).

Determination of sample size

A total of 530 subjects per group were necessary to show a difference between ivabradine and placebo on EQ-5D VAS change between baseline and last value with a power of 90%, if the effect size was 0.2, using a two-sided test with a 5% type I error rate. Taking into account the study inclusion criteria and a 10% treatment withdrawal rate per year, a total of 1,200 patients were required. However, the main objective in this sub-study was to evaluate the effects of ivabradine compared to placebo on HRQL in patients from selected countries where the questionnaires were validated. It was therefore anticipated that 4,500 would constitute an adequate sample size.

Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

SHIfT Study

Pre-defined subgroups

The treatment effect on the primary composite endpoint was also documented on pre-defined subgroups of the randomised set based on the following eight criteria:

- Age: < 65 / ≥65 years
- Gender: male/female
- Beta-blocker intake at randomisation: yes/no
- Primary cause of HF: ischaemic cause/non ischaemic cause
- NYHA class: II / III or IV
- Diabetes: yes/no
- Hypertension: yes/no
- Heart rate above and below the median, for patients in sinus rhythm: (< 77 bpm / ≥ 77 bpm)

Details of subgroup analyses undertaken

The following subgroup analyses were undertaken in both the RS and the RSBBDose analysis sets:

- Estimate of treatment effect in each level of subgroup based on an adjusted Cox proportional hazards model with beta-blocker intake at randomisation as

a covariate for each subgroup level. (Note that for the beta-blocker subgroup, the adjustment for beta-blocker intake at randomisation was not applicable).

- Descriptive analysis of the event in each level of subgroup.
- Interaction test between treatment groups and the subgroup: likelihood ratio test comparing the model including the interaction term with the model not including the interaction term.
- Plot of Kaplan-Meier curves for each level of subgroup.

Post hoc subgroups

- Patients with a baseline heart rate ≥75 bpm
    - This subgroup was identified within the licensing process. SHIfT trial results indicated that baseline heart rate modified the treatment effect of ivabradine. The EMA therefore asked the manufacturer to identify the heart rate threshold above which the mortality benefit for ivabradine was clear. An analysis reported by Böhm et al 2010 (6) identified the threshold of 75 bpm or above, and this was proposed to the CHMP who then granted a licence in this population, as opposed to the overall SHIfT trial population with baseline heart rate ≥70 bpm.
- Age ≥ 75 years
- Age ≥ 70 years

SHIfT PRO sub-study

Pre-defined subgroups

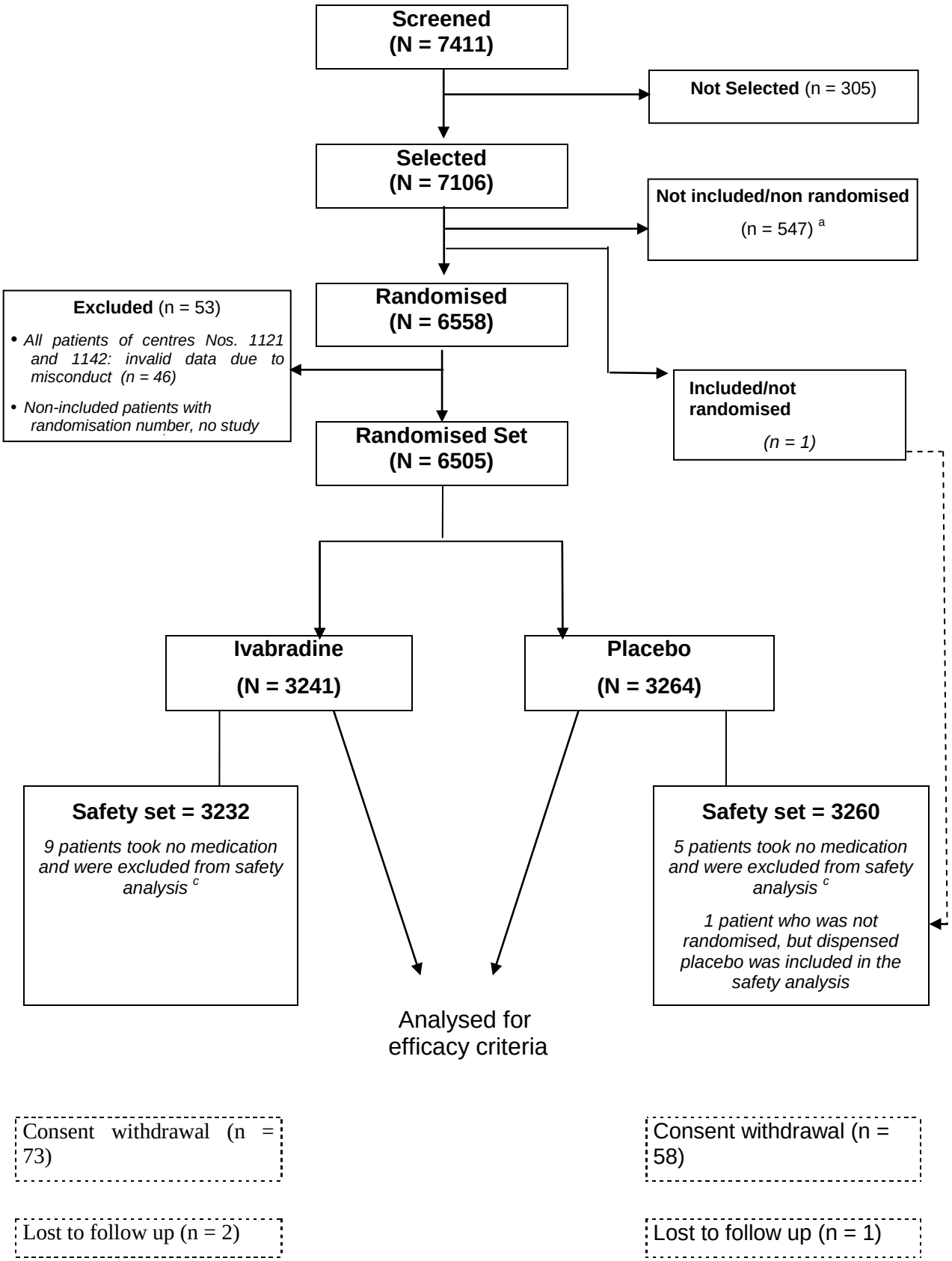
The following subgroups were evaluated for the analysis of EQ-5D and KCCQ:

- Beta-blocker intake at randomisation (yes/no)
- At least half the target dose of beta-blockers at randomisation (yes/no)
- Primary cause of HF (ischaemic, non-ischaemic)
- Gender (male, female)
- Age groups (<65/≥65 years)
- NYHA (II vs III/IV)

Participant flow

Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

Figure 5: Patient flow in SHIfT



[a] Reason for non-inclusion: at least one non-inclusion criterion (64.4%; mostly HR criterion), consent withdrawal (23.1%), adverse event (12.6%)

[b] Reason for non-inclusion: at least one non-inclusion criterion (n = 6), adverse event (n = 1)
[c] Excluded from safety analysis: 063 056 0354 00545; 063 156 4856 06791; 063 156 4862 06880; 063 428 4311 03534; 063 528 1082 02868; 063 616 1105 02831; 063 616 1136 06491; 063 705 1610 06085; 063 792 4503 06775; 063 156 4855 05951; 063 440 4423 04224; 063 620 2206 02538; 063 642 1375 02917; 063 643 1442 02807.

Critical appraisal of relevant RCTs

The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

- Was the method used to generate random allocations adequate?
- Was the allocation adequately concealed?
- Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?
- Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?
- Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?
- Is there any evidence to suggest that the authors measured more outcomes than they reported?
- Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

Please provide as an appendix a complete quality assessment for each RCT. See section 9.3, appendix 3 for a suggested format.

If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

Table 8: Quality assessment of SHIfT

Was randomisation carried out appropriately?	**YES**. Randomisation was via a central telephone randomisation service. The randomisation was balanced, non-adaptive, stratified on centre and beta-blocker intake at randomisation
Was the concealment of treatment allocation adequate?	**YES.** The allocation sequence was generated at the sponsor level through validated in-house application software; access was restricted to people responsible for study therapeutic unit's production until database lock. These people had no involvement in the rest of the trial.
Were the groups similar at the outset of the study in terms of prognostic factors?	**YES.** The randomisation was balanced, non-adaptive, stratified on centre and beta-blocker intake at randomisation. Eligible patients were allocated to receive ivabradine or placebo in addition to treatments appropriate to their HF, with particular emphasis on background treatment with a beta-blocker. Randomisation blocks (of size 4) were randomly and dynamically assigned to the centres in order to respect the stratification on the two pre-defined factors.
Were the care providers, participants and outcome assessors blind to treatment allocation?	**YES**. The study was double-blind; patients and investigators were masked to treatment allocation. The Data Monitoring Committee (DMC) was the only committee authorised to have access to comparative results on safety and efficacy data. All pre-specified events (PSE, leading to study endpoint if adjudicated) were reviewed by the Endpoint Validation Committee (EVC) who confirmed or rejected the diagnoses attached to the PSEs. This committee was blinded to the allocated study treatments as well as to baseline heart rate.
Were there any unexpected imbalances in drop-outs between groups?	**NO**. A total of 1287 patients (19.8% of the RS) prematurely discontinued the study treatment (SHIfT CSR p81 and Table (10.1) 5 p82). A slightly higher rate of study treatment withdrawal was observed in the ivabradine group: 682 patients (21.0%) in the ivabradine group vs 605 patients (18.5%) in the placebo group. The treatment withdrawals were mainly due to adverse events (64.0% of withdrawals) or non-medical reason (31.0% of withdrawals). The main between-group differences were: Events related to the mechanism of action of ivabradine; i.e., slowing of the heart rate (including the category 'heart rate < 50 bpm at the 2.5 mg b.i.d dose',

	and the adverse events, bradycardia and heart rate decreased) which led to treatment withdrawal in a total of 70 patients in the ivabradine group (2.2% of RS; 10.3% of withdrawals) vs13 in the placebo group (0.4% of RS; 2.1% of withdrawals). Episodes of 'cardiac failure' i.e. acute decompensation, which led to treatment withdrawal in 56 patients (8.2% of withdrawals) in the ivabradine group vs 65 patients (10.7% of withdrawals) in the placebo group. The use of a prohibited concomitant treatment was the main reason for permanent study drug withdrawal in a total of 39 patients (3.0% of withdrawals): 18 patients (2.6%) in the ivabradine group vs 21 patients (3.5%) in the placebo group. Non-medical reasons were mostly consent withdrawals.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	**NO**. Full details of the study (outcomes etc.) are provided within the CSR
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	**YES**. In the SHIfT study, all survival analyses based on time-to-first event were performed for all outcomes on an intention-to-treat (ITT) basis. The safety analyses were carried out on patients of the safety set; i.e., patients having taken at least one dose of study medication.
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination	

Results of the relevant RCTs

Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. **If there is more than one RCT, tabulate the responses.**

The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan-Meier plots.

For each outcome for each included RCT, the following information should be provided.

- The unit of measurement.
- The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.
- A 95% confidence interval.
- Number of participants in each group included in each analysis and whether the analysis was by ‘intention to treat’. State the results in absolute numbers when feasible.
- When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.
- Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.
- Discuss and justify definitions of any clinically important differences.
- Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.

Introduction

The SHIfT study recruited patients with a heart rate of ≥70 bpm and showed a significant benefit of ivabradine on the primary composite endpoint of cardiovascular death or hospitalisation for worsening heart failure (HR 0.82, 95% CI 0.75-0.90). Hospitalisation for worsening heart failure was significantly reduced (HR 0.74 95% CI 0.66-0.83) but, despite a trend towards benefit, the reduction in cardiovascular death did not reach statistical significance (HR 0.91 95% CI 0.80-1.03). The 2010 Lancet publication identified that baseline heart rate modified the treatment effect of ivabradine (8). In order to find the heart rate threshold beyond which the total mortality benefit was significant, the CHMP asked the manufacturer to re-analyse the SHIfT data (as described in the EPAR 2012 (49).) The manufacturer subsequently identified that 75 bpm was a threshold of interest. In this cohort (n=4150) the effect of ivabradine on all-cause mortality (HR 0.83 95% CI 0.72-0.96), cardiovascular mortality (HR 0.83 95% CI 0.71-0.97) and hospitalisation for worsening heart failure (HR 0.70 95% CI 0.61-0.80) was clearly established. On this basis it was proposed and subsequently accepted that the licence indication be modified to patients with a baseline heart rate ≥75 bpm instead of ≥70 bpm.

The NICE remit is to appraise the clinical and cost effectiveness of ivabradine within its licensed indication for the treatment of chronic heart failure. The results presented in this section therefore initially focus on the main trial population, with baseline heart rate ≥70 bpm. Primary and secondary endpoint results are also then reported for the licensed population of particular relevance to the decision problem, i.e. the SHIfT population with baseline resting heart rate of ≥75 bpm, which represents 63.8% (4150/6505) of the overall trial population; test for heterogeneity, p = 0.03. To guide the reader, where both populations are discussed in close proximity data and narrative relating to the main trial population is reported in black font (baseline heart rate ≥70 bpm) and the licensed population in blue.

Results are presented in the following order:

(A) Primary outcome:
(i) Main trial population, (ii) Pre-planned subgroups, (iii) Licensed population

(B) Secondary outcomes:
(i) Main trial population, (ii) Licensed population, (iii) Other secondary outcomes

(C) Impact of beta-blocker use in the main trial population (Swedberg in press (1))

(D) SHIfT patient reported outcomes sub-study (Ekman 2011(2))

(E) SHIfT Echocardiographic sub-study (Tardif 2011 (3) - brief summary)

(A) Primary outcome

(i) Primary outcome: Main trial population (≥70 bpm)

The incidence of the primary composite endpoint, time to first occurrence of cardiovascular death or hospitalisation for worsening heart failure, and the estimated treatment effect are presented in Table 9. Over the study period a total of 793 patients reached the primary composite endpoint in the ivabradine group *vs* 937 patients in the placebo group. The global incidence rate was thus lower in the ivabradine group (24.5%) than in the placebo group (28.7%), as was the annual incidence rate (14.5%PY *vs* 17.7%PY for 5,478 and 5,299 patient-years respectively).

Table 9: Incidence of primary outcome: main trial population (≥70 bpm)

Ivabradine n/N (%)	Placebo n/N (%)	HR[a] (95% CI)	p-value	RRR	NNT
793/3241 (24.5)	937/3264 (28.7)	0.82 (0.75, 0.90)[a] 0.82 (0.75, 0.90)[b] 0.83 (0.75, 0.91)[c]	<0.0001[a] <0.0001[b] <0.0001[c]	18% 18% 17%	24

Abbreviations: HR, hazard ratio; CI, confidence interval; RRR, relative risk reduction; NNT, number needed to treat

Notes: [a] Estimate of the HR between treatment groups based on an adjusted Cox proportional hazards model with beta-blocker intake at randomisation as a covariate
[b] Sensitivity analysis: estimate of the HR between treatment groups based on an unadjusted Cox proportional hazards model
[c] Prognostic factors analysis: estimate of the HR between treatment groups based on a Cox proportional hazards model adjusted for beta-blocker intake at randomisation, NYHA class, LVEF, aetiology of HF (ischaemic or not), age, systolic blood pressure, heart rate (in sinus rhythm) and estimated glomerular filtration rate

Source: SHIfT CSR Table (11.1.1) 1 p112, Table (11.1.1) 2 p113

The superiority of ivabradine over placebo in the reduction of the incidence of the primary endpoint was demonstrated, using a Cox proportional hazards model adjusted for beta-blocker intake at randomisation, with an estimate of the hazard ratio of 0.82 (95% CI 0.75-0.90, $p < 0.0001$), representing a highly clinically and statistically significant relative risk reduction (RRR) of 18%.

As expected, given patients generally deteriorate and are frequently hospitalised prior to death, the primary composite endpoint was more driven by the rate of hospitalisation for worsening heart failure than by the rate of cardiovascular death:

- Among the 793 patients having reached the primary composite endpoint in the ivabradine group, 63.7% of patients experienced firstly a hospitalisation for worsening heart failure.

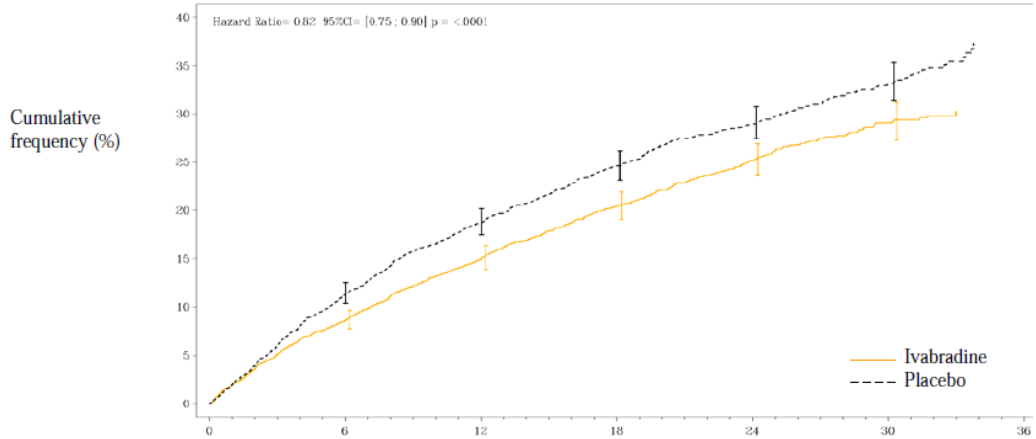
- Among the 937 patients having reached the primary composite endpoint in the placebo group, 70.4% of patients experienced firstly a hospitalisation for worsening heart failure.

The treatment effect for the components of the primary endpoint are provided with the other secondary endpoint results.

A sensitivity analysis consisted of a superiority test based on an unadjusted Cox proportional hazards model (Table 9). The results confirm those of the main analysis, with the same estimate of the HR, 95% CI and p-value of <0.0001. A further prognostic factors analysis consisted of a superiority test based on a Cox proportional hazards model adjusted for beta-blocker intake at randomisation, NYHA class, LVEF, aetiology of HF (ischaemic or not), age, systolic blood pressure, heart rate (in sinus rhythm) and estimated glomerular filtration rate (Table 9). The treatment effect observed in the prognostic factors analysis was consistent with that observed in the main analysis with an estimate of the HR of 0.83 (95% CI 0.75-0.91), the difference in favour of ivabradine (p <0.0001).

The Kaplan-Meier curves of the time to first event of the primary composite outcome for all randomised patients are presented in Figure 6. The curves visibly diverge over the first six months, indicating an early treatment effect in favour of ivabradine, and monotonously diverge thereafter. The assessment of the assumption of proportional hazards indicated constancy of effect.

Figure 6: Kaplan-Meier analysis of time to first event of primary outcome: main trial population (≥70 bpm)



Ivabradine / Placebo							
Nber of patients at risk	3241 / 3264	2928 / 2868	2600 / 2489	2173 / 2061	1191 / 1089	477 / 439	16 / 17
Cumul. nber of endpoints	-	276 / 366	477 / 604	638 / 775	745 / 876	788 / 922	793 / 937
Cumul. frequency (%)	-	8.57 / 11.27	14.93 / 18.74	20.42 / 24.58	25.17 / 28.92	29.03 / 33.15	30.26 / 37.26

In conclusion, the primary outcome of the SHIfT study was satisfied; i.e. the demonstration of the superiority of ivabradine over placebo in the reduction of cardiovascular mortality or hospitalisations for worsening heart failure, in patients

with moderate-to-severe symptoms of HF, reduced LVEF and receiving optimised recommended background therapy for heart failure.

(ii) Primary outcome: Pre-planned subgroups (Main trial population; ≥70 bpm)

Table 10 presents the incidence of the primary composite endpoint and the estimate of treatment effect in the main trial population, pre-defined according to eight baseline factors. The results are summarised in Figure 7 for the same subgroups.

The results were consistent across all subgroups with an effect in favour of ivabradine. The interaction tests all had p-values higher than 0.05, except for the subgroups on baseline heart rate less than or ≥ 77 bpm (the median heart rate) with p = 0.0288, indicating a greater effect of ivabradine in patients with higher heart rate at baseline (HR = 0.75), although the treatment effect for the subgroups on both sides of the median were in favour of ivabradine. The SHIfT results in relation to age are provided later in this section and are discussed in Section 5.10.4, and again in Section 6.10.3 with respect to cost-effectiveness.

Table 10: Primary outcome in pre-planned subgroups: main trial population (≥70 bpm)

	Ivabradine n/N (%)	Placebo n/N (%)	HR[a] (95% CI)	Interaction p-value
Age				
<65 years	407/1976 (20.6)	527/2055 (25.6)	0.76 (0.67, 0.87)	–
≥65 years	386/1265 (30.5)	410/1209 (33.9)	0.89 (0.77, 1.02)	0.099
Gender				
Men	624/2462 (25.4)	725/2508 (28.9)	0.84 (0.76, 0.94)	–
Women	169/779 (21.7)	212/756 (28.0)	0.74 (0.60, 0.91)	0.260
beta-blocker intake at randomisation				–
No	101/344 (29.4)	134/341 (39.3)	0.68 (0.52, 0.88)	0.103
Yes	692/2897 (23.9)	803/2923 (27.5)	0.85 (0.76, 0.94)	
Aetiology of HF				
Non-ischaemic	218/1026 (21.3)	296/1061 (27.9)	0.72 (0.60, 0.85)	–
Ischaemic	575/2215 (26.0)	641/2203 (29.1)	0.87 (0.78, 0.97)	0.060
NYHA class at baseline				–
Class II	300/1585 (18.9)	356/1584 (22.5)	0.81 (0.69, 0.94)	0.793
Class III or IV	493/1655 (29.8)	580/1679 (34.5)	0.83 (0.74, 0.94)	
History of diabetes				–
No	525/2268 (23.2)	611/2258 (27.1)	0.83 (0.74, 0.93)	0.861
Yes	268/973 (27.5)	326/1006 (32.4)	0.81 (0.69, 0.95)	
History of hypertension				–
No	274/1079 (25.4)	330/1112 (29.7)	0.81 (0.69, 0.95)	0.779
Yes	519/2162 (24.0)	607/2152 (28.2)	0.83 (0.74, 0.93)	
Heart rate at				

baseline				
<77[b] bpm	339/1583 (21.4)	356/1561 (22.8)	0.93 (0.80, 1.08)	–
≥77[b] bpm	454/1657 (27.4)	581/1700 (34.2)	0.75 (0.67, 0.85)	0.0288

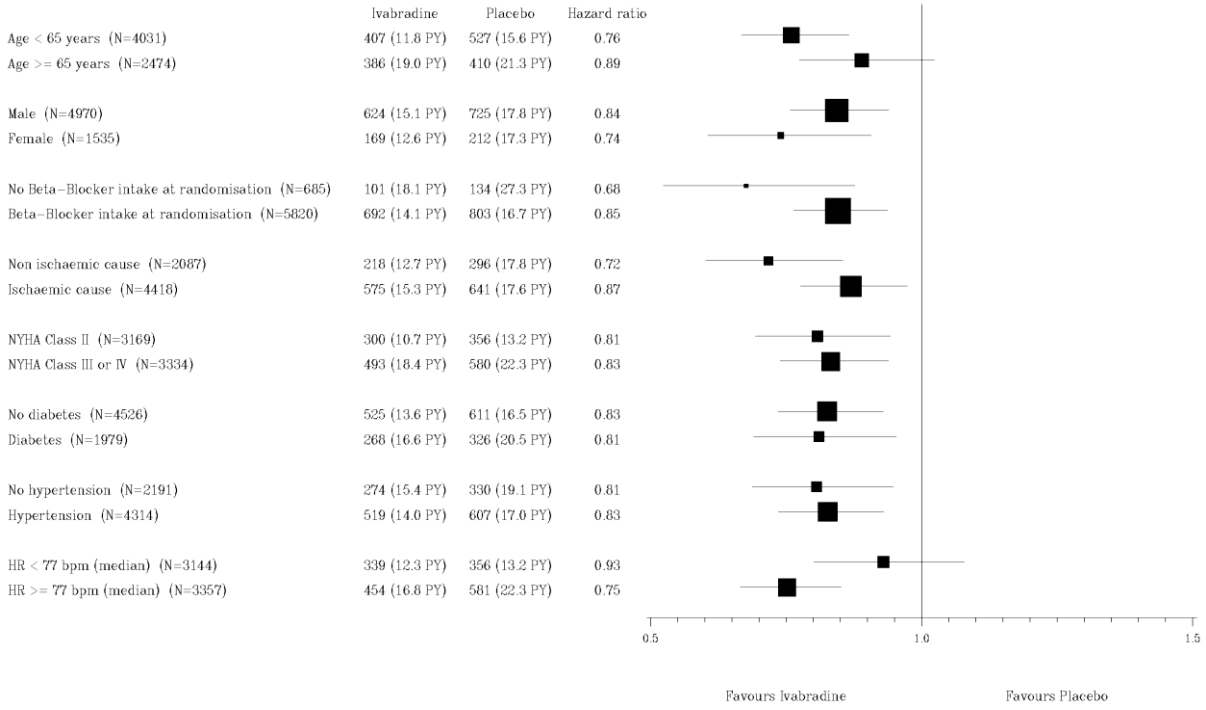
Abbreviations: HF, heart failure; NYHA, New York Heart Association; bpm, beats per minute; HR, hazard ratio

Notes: [a] Estimate of the HR between treatment groups based on an adjusted Cox proportional hazards model with beta-blocker intake at randomisation as a covariate (adjustment not applicable for beta-blocker subgroups).

[b] Median heart rate value of the randomised set.

Source: SHIfT CSR Table (11.1.1) 3 p114

Figure 7: Forest plot showing primary outcome in pre-planned subgroups: main trial population (≥70 bpm)



Note: the size of the box is proportional to the number of adjudicated events and the "whiskers" indicate the 95% confidence interval of the estimate.

Source: SHIfT CSR Figure (11.1.1) 2 p115

Primary outcome for patients on ≥50% target dose beta-blockade: main trial population (≥70 bpm)

The incidence of the primary composite endpoint for patients receiving at least 50% of target dose bet-blocker (RS_{BBdose}) are presented in Table 15. Over the study period a total of 330 patients reached the primary composite endpoint in the ivabradine group *versus* 362 patients in the placebo group. The global incidence rate was lower in the ivabradine group (20.9%) than in the placebo group (22.6%) as was the annual incidence rate (11.9%PY *vs* 13.3%PY for 2,778 and 2,721 patient-years respectively). The point estimate for the primary endpoint hazard ratio in this analysis set showed a trend towards benefit which did not reach statistical significance (HR 0.90, 95% CI 0.77-1.04). Similar results were observed with the prognostic factors analysis. As for the main trial population, the primary composite endpoint was driven more by the rate of hospitalisation for worsening HF than by the rate of CV death (63.6% of patients in the ivabradine group experienced hospitalisation for worsening heart failure first; *vs* 70.7% in the placebo group). The potential impact of beta-blocker dosing on treatment effect is discussed later in Section 5.5.

Table 11: Incidence of primary outcome: main trial population on ≥50% target dose beta-blockade (≥70 bpm)

Ivabradine n/N (%)	Placebo n/N (%)	HR[a] (95% CI)	p-value	RRR	NNT
330/1581 (20.9)	362/1600 (22.6)	0.90 (0.77, 1.04)[a] 0.92 (0.79, 1.07)[b]	0.155 0.272	10% 8%	57

Abbreviations: HR, hazard ratio; CI, confidence interval; RS_{BBDOSE}, patients of the randomised set receiving at least half of target daily dose of beta-blockers at randomisation; RRR, relative risk reduction, NNT, number needed to treat

Notes: [a] Estimate of the HR between treatment groups based on an unadjusted Cox proportional hazards model

[b] Prognostic factors analysis: estimate of the HR between treatment groups based on a Cox proportional hazards model adjusted for beta-blocker intake at randomisation, NYHA class, LVEF, aetiology of HF (ischaemic or not), age, systolic blood pressure, heart rate (in sinus rhythm) and estimated glomerular filtration rate

Source: SHIfT CSR p115, Table (11.1.2) 1 p116

(iii) Primary outcome: Licensed population (≥75 bpm)

(note, the 'licensed population' is synonymous with the population defined in the NICE decision problem)

We have seen above that baseline heart rate is observed to modify the treatment effect of ivabradine (Table 10). Unsurprising therefore, the subgroup of patients with baseline heart rate at or above 75 bpm shows the incidence of primary composite endpoint (first event of cardiovascular death or hospitalisation for worsening heart failure) to be significantly lower in the ivabradine group than in the placebo group (26.6% vs 32.8% respectively, n = 4150), corresponding to a 6.2% absolute risk reduction (NNT = 16) (Table 12). The hazard ratio revealed a clinically and statistically significant 24% RRR in favour of ivabradine (HR 0.76, 95% CI 0.68-0.85, p<0.0001).

Table 12: Incidence of primary composite outcome: licensed population (≥75 bpm)

Ivabradine n/N (%)	Placebo n/N (%)	HRa (95% CI)	p-value	RRR	NNT
545/2052 (26.6)	688/2098 (32.8)	0.76 (0.68 - 0.85)	<0.0001	24%	16

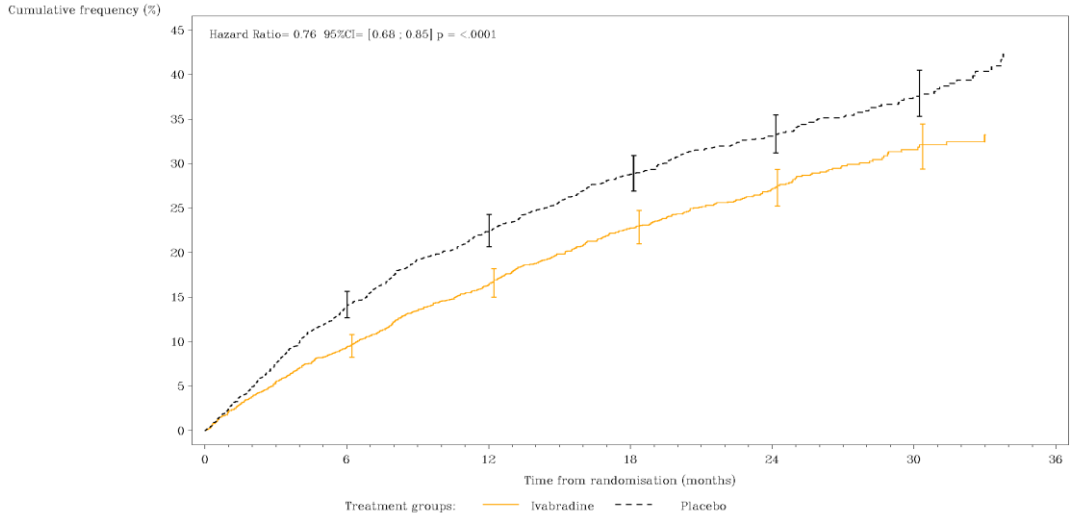
Abbreviations: HR, hazard ratio; CI, confidence interval; RRR, relative risk reduction; bpm, beats per minute, NNT, number needed to treat

Notes: a Estimate of the HR between treatment groups based on an unadjusted Cox proportional hazards model

Source EPAR (EMA 2012 (49))

The Kaplan-Meier curves for the time to first event of the primary composite outcome in patients with baseline heart rate ≥75 bpm are presented in Figure 8. The curves appear to diverge early, and a monotonous divergence is observed throughout the trial follow-up. The assessment of the assumption of proportional hazards indicated constancy of effect.

Figure 8: Kaplan-Meier analysis for time to first event of primary composite endpoint: licensed population (≥75 bpm)



Nber of patients at risk*	2052/2098	1637/1785	1614/1521	1318/1227	715/657	261/257	8/9
Cumul. nber of endpoints*	0/0	191/290	331/463	449/583	510/646	541/677	545/688
Cumul. frequency (%)*	0/0	9.37/13.9	16.37/22.37	22.74/28.8	27.11/33.08	31.57/37.59	33.23/42.42

*:Ivabradine/Placebo

(B) Secondary outcomes

(i) Secondary outcomes: Main trial population (≥70 bpm)

The results for the secondary outcomes of the SHIfT study in the main trial population are summarised in Table 13. The benefit of ivabradine in comparison to placebo in reducing death from heart failure reached statistical significance (HR 0.74 95% CI 0.58-0.94), and non-significant trends favouring ivabradine were observed for reductions in all-cause death (10%) and cardiovascular death (9%).

For hospitalisations, the treatment effect (ivabradine *vs* placebo) in the reduction of hospitalisations for any cause (11%), hospitalisations for CV reason (15%) and hospitalisations for worsening HF (26%) all reached statistical significance. Similarly, unplanned hospitalisation for any cause and unplanned hospitalisation for CV reason were also significantly reduced.

The above results were estimated using a Cox model adjusted for beta-blocker intake at randomisation, and were confirmed in sensitivity analyses (without adjustment).

Table 13: Incidence of secondary outcomes: main trial population (≥70 bpm)

	Ivabradine N = 3241 n (%)	Placebo N = 3264 n (%)	HR[a] (95% CI)	p-value	RRR	NNT
Deaths						
Death from any cause	503 (15.5)	552 (16.9)	0.90 (0.80, 1.02)	0.092	10%	72
Death for CV reason[b,c]	449 (13.9)	491 (15.0)	0.91 (0.80, 1.03)	0.128	9%	84
Death from HF	113 (3.5)	151 (4.6)	0.74 (0.58, 0.94)	0.0140	26%	88
Hospitalisations[d]						
Hospitalisation for any cause	1231 (38.0)	1356 (41.5)	0.89 (0.82, 0.96)	0.0027	11%	28
Hospitalisation for CV reason[e]	977 (30.2)	1122 (34.4)	0.85 (0.78, 0.92)	0.0002	15%	24
Hospitalisation for worsening HF[c]	514 (15.9)	672 (20.6)	0.74 (0.66, 0.83)	<0.0001	26%	21
Unplanned hospitalisation for any cause	1137 (35.1)	1264 (38.7)	0.88 (0.81, 0.95)	0.0013	12%	27
Unplanned hospitalisation for CV reason	909 (28.1)	1047 (32.1)	0.84 (0.77, 0.92)	0.0002	16%	25
Secondary composite outcome						
First event among CV death,[b] hospitalisation for non-fatal MI or hospitalisation for worsening HF	825 (25.5)	979 (30.0)	0.82 (0.74, 0.89)	<0.0001	18%	22

Abbreviations: HF, heart failure; CV, cardiovascular; RRR, relative risk reduction; MI, myocardial infarction, NNT, number needed to treat

Notes:
[a] Estimate of the HR between treatment groups based on an adjusted Cox proportional hazards model with beta-blocker intake at randomisation as a covariate
[b] Includes death from unknown cause
[c] Individual component of the primary composite outcome
[d] Patients were often hospitalised on more than one occasion and for different reasons: the first admission for each analysed reason is counted in this analysis
[e] Includes hospitalisation for undetermined cause

Source: SHIfT CSR Table (11.1.1) 1 p112, Table (11.2.1.1) 1 p118, Table (11.2.1.1) 2 p118, Table (11.2.2.1) 2 p125, Table (11.2.2.1) 3 p126, Table (11.2.3) 1 p132.

(ii) Secondary outcomes: Licensed population (≥75 bpm)

The licensed population shows a clear mortality benefit for ivabradine patients with respect to all-cause mortality and cardiovascular mortality. All secondary endpoints showed statistically significant relative risk reductions for ivabradine vs placebo (Table 14), including:

- CV death (RRR = 17%; HR = 0.83, 95% CI 0.71-0.97; p = 0.017; NNT = 39);
- Death from any cause (RRR = 17%; HR = 0.83, 95% CI 0.72-0.96; p = 0.011; NNT = 35);
- Hospitalisation for worsening HF (RRR = 30%; HR = 0.70, 95% CI 0.61-0.80; p <0.0001; NNT = 16);
- Death from HF (RRR = 39%; HR = 0.61, 95% CI 0.46-0.81; p = 0.0006; NNT = 45).

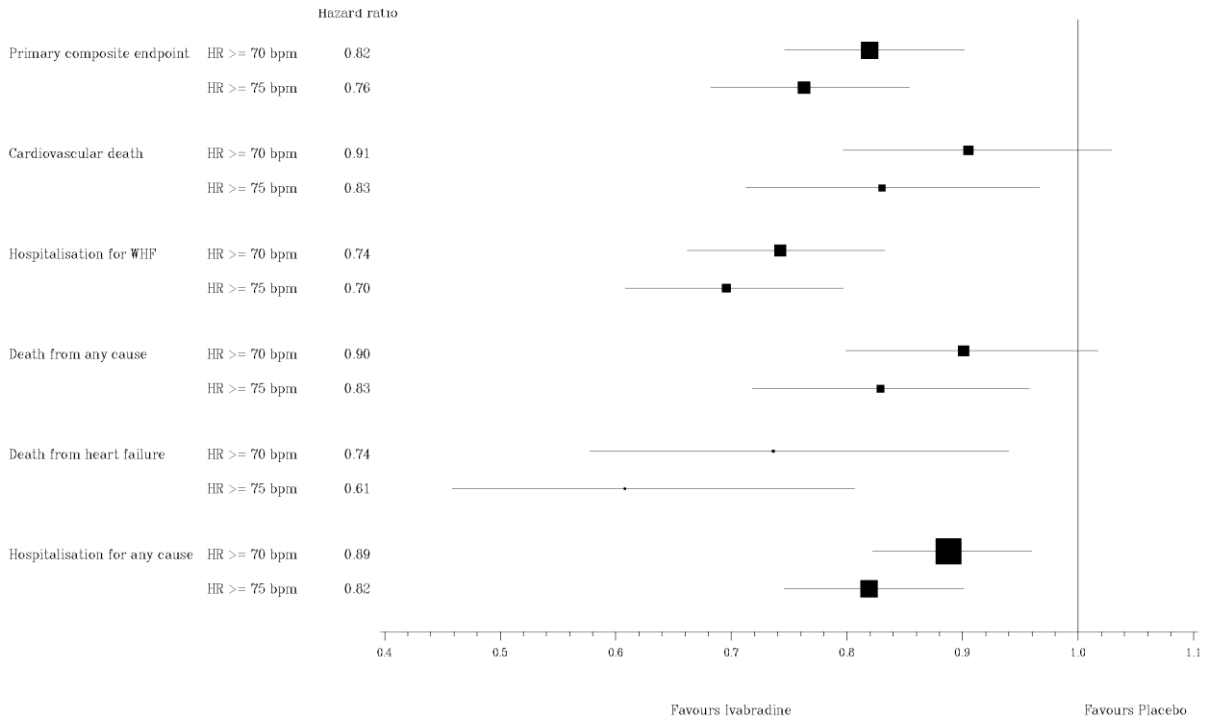
For all six endpoints, relative risk reductions appeared to be greater for the licensed population than for the main trial population. This trend can be observed in Figure 9. These results confirm that the subgroup of SHIfT trial patients with baseline heart rate ≥75 bpm show a significant improvement for all outcomes, including cardiovascular death and all-cause death.

Table 14: Secondary endpoints: licensed population (≥75 bpm)

	Ivabradine (N=2052)		Placebo (N=2098)		Hazard ratio		
	n	%	n	%	E	95% CI	p-value
Secondary endpoints							
Cardiovascular death	304	14.8	364	17.4	0.83	[0.71;0.97]	0.0166
Hospitalisation for worsening HF	363	17.7	503	24.0	0.70	[0.61;0.80]	<0.0001
Death from any cause	340	16.6	407	19.4	0.83	[0.72;0.96]	0.0109
Death from heart failure	78	3.8	126	6.0	0.61	[0.46;0.81]	0.0006
Hospitalisation for any cause	796	38.8	932	44.4	0.82	[0.75;0.90]	<0.0001
Hospitalisation for cardiovascular reason	640	31.2	779	37.1	0.79	[0.71;0.88]	<0.0001

Two-sided type I error rate : 0.05
N : number of patients at risk
NPY : number of patients-year
n : number of patients having experienced the endpoint
% : global incidence rate n/Nx100
PY : annual incidence rate number of patients having experienced the endpoint on the whole study for 1 00 patients-year at risk
E : estimate of the hazard ratio between treatment groups (Ivabradine /Placebo) based on an adjusted Cox s proportional hazards model with beta-blocker intake at randomisation as a covariate
95% CI : 95% Confidence Interval of the estimate (two-sided)
p-value : p-value from an adjusted Cox s proportional hazards model(Wald test)
Note: a sensitivity analysis based on a Cox model adjusted for prognostic factors confirmed these results

Figure 9: Forest plot comparison of primary and secondary outcomes: main trial population (≥70 bpm) and licensed population (≥75 bpm)



Note: the size of the box is proportional to the number of adjudicated events and the "whiskers" indicate the 95% CI of the estimate

(iii) Other secondary outcomes: Main trial population and licensed population

Change in heart rate

For the main trial population heart rate decreased by 15.4 bpm at Day 28 in the ivabradine group, and by 12.0 bpm at last visit (Table 15). Progression of heart rate over time is plotted in Figure 24 (Appendix 15, Section 9.15.2). A further analysis of heart rate over the trial period is presented in Section 5.10.4. This shows that the apparent 3 bpm drop-off in effect is not observed when looking only at patients who remain on therapy. Böhm et al 2010 carried out further analyses of SHIfT trial data, investigating the association between heart rate and prespecified outcomes (6). One of the findings was a direct association between heart rate achieved at 28 days and subsequent cardiac outcomes.

The drop in heart rate observed in the licensed population was higher than in the main trial population (17.4 bpm at Day 28; 14.5 bpm at last visit), consistent with a higher mean baseline heart rate in this subgroup (84 bpm) than in the overall population (80 bpm). Previous ivabradine trials have also shown that heart rate reduces in proportion to the resting heart rate (i.e. the higher the resting heart rate the greater the decrease in heart rate associated with ivabradine treatment). This is discussed further in Böhm 2010, which reports that patients with baseline resting heart rate ≥87 bpm show a 22.5 bpm decrease in heart rate; compared with an 11.1 bpm decrease in patients with a baseline resting heart rate of 70-71 bpm (6).

Table 15: **Change in heart rate from baseline to last post-baseline visit: main trial population and licensed population**

	Heart rate ≥70 bpm at baseline (n = 6,505)		Heart rate ≥75 bpm at baseline (n = 4,150)	
	Ivabradine N = 3241 bpm ±SD	Placebo N = 3264 bpm ±SD	Ivabradine N = 2052 bpm ±SD	Placebo N = 2098 bpm ±SD
Mean baseline heart rate	79.7 ± 9.5	80.1 ± 9.8	84.3 ± 9.1	84.6 ± 9.4
Mean change in heart rate				
Day 28	-15.4 ± 10.7	-4.6 ± 10.6	-17.4 ± 11.5	-5.7 ± 11.3
Last visit	-12.0 ± 13.3	-4.1 ± 12.9	-14.5 ± 13.8	-5.8 ± 13.5

Source SHIfT CSR Table 19

New York Heart Association classification

The investigator evaluated the patient's NYHA classification at each scheduled visit from baseline to the last post-randomisation visit. The change in NYHA classification from baseline to last post-randomisation visit is described in Table 16, and shows the number of patients having an improvement in NYHA class between baseline and last post-randomisation visit to be higher in the ivabradine group.

For the main trial population, the between-group difference in patients showing an improvement was statistically significant (27.6% in the ivabradine group vs 24.0% in the placebo group, p = 0.0010, complementary Chi2 test). A similar result was observed for the licensed population.

Table 16: Change in NYHA class from baseline to last post-randomisation visit: main trial population and licensed population (SHIfT CSR Table (11.3.2) 1 p137)

NYHA classification	Heart rate ≥70 bpm at baseline (n = 6,505)		Heart rate ≥75 bpm at baseline (n = 4,150)	
	Ivabradine n (%) N = 3241	Placebo n (%) N = 3264	Ivabradine n (%) N = 2052	Placebo n (%) N = 2098
All	3216 (100.0)	3234 (100.0)	[redacted]	[redacted]
Improvement	887 (27.6)	776 (24.0)	[redacted]	[redacted]
Stability	2172 (67.5)	2265 (70.0)	[redacted]	[redacted]
Worsening	157 (4.9)	193 (6.0)	[redacted]	[redacted]

Global assessment of heart failure symptoms

Table 17 presents the number and percentage of patients by class of global assessment at the last post-randomisation visit. For the main trial population, the rate of patients having an improvement in global assessment was statistically significantly higher in the ivabradine group than in the placebo group for patient-reported assessment (71.8% vs 67.6%, p = 0.0005, complementary Chi2 test) as well as for the physician-reported assessment (61.1% vs 57.0%, p = 0.0011, complementary Chi2 test). Results for the licensed group were at least as strong on both parameters.

Table 17: Change in global assessment of heart failure symptoms class from baseline to last post-baseline visit: main trial population and licensed population

	Heart rate ≥70 bpm at baseline (n = 6,505)		Heart rate ≥75 bpm at baseline (n = 4,150)	
	Ivabradine n (%) N = 3241	Placebo n (%) N = 3264	Ivabradine n (%) N = 2052	Placebo n (%) N = 2098
Patient Global Assessment				
All	2951 (100.0)	2982 (100.0)	[redacted]	[redacted]
Improvement	2118 (71.8)	2017 (67.6)	[redacted]	[redacted]
Stability	633 (21.5)	738 (24.8)	[redacted]	[redacted]
Worsening	200 (6.8)	227 (7.6)	[redacted]	[redacted]
Physician Global Assessment				
All	3091 (100.0)	3108 (100.0)	[redacted]	[redacted]
Improvement	1888 (61.1)	1772 (57.0)	[redacted]	[redacted]
Stability	954 (30.9)	1043 (33.6)	[redacted]	[redacted]
Worsening	249 (8.1)	293 (9.4)	[redacted]	[redacted]

Source: SHIfT CSR Table (11.3.3) 1 p139,

Efficacy in older patients ≥70 years: *post hoc* analysis in the main trial population (≥70 bpm)

A *post hoc* analysis of the subpopulation of patients aged ≥70 years was requested by the CHMP. As expected the incidence of primary composite and main secondary endpoints were higher in patients aged ≥70 years than in the overall trial population. For example, the incidence of the primary composite endpoint in the placebo group was 35.1% in patients aged ≥70 years, compared with 28.7% in the overall population. Results in the ivabradine and placebo groups for the primary and main secondary study endpoints are presented in Table 18.

Table 18: Primary and secondary endpoints in patients aged ≥70 years: main trial population (≥70 bpm)

	Population aged ≥70 years (N=1500)		
	Hazard ratio		
	E	(95% CI)	p-value
Primary composite endpoint : CV death or hosp for worsening HF	[redacted]	[redacted]	[redacted]
Secondary endpoints:			
Hospitalisation for worsening HF	[redacted]	[redacted]	[redacted]
Cardiovascular death	[redacted]	[redacted]	[redacted]
All-cause mortality	[redacted]	[redacted]	[redacted]
HF death	[redacted]	[redacted]	[redacted]
All-cause hospitalisation	[redacted]	[redacted]	-
CV hospitalisation	[redacted]	[redacted]	-

(C) Impact of beta-blocker use on ivabradine efficacy: multivariable analysis in Main trial population (≥70 bpm) (Swedberg manuscript)

Further analyses have been undertaken to assess whether the beta-blocker dose at baseline impacts on the efficacy of ivabradine (Swedberg et al, in press (1;1)). A summary of these analyses are presented below.

Patients were categorised into five groups: not taking a beta-blocker, taking <25%, 25% to <50%, 50% to <100% or ≥100 of target daily doses as defined by the European Society of Cardiology guidelines (107 patients taking a beta-blocker that was not recommended in the guidelines were excluded from the analyses).

Factors associated with a lower likelihood of taking a beta-blocker were the co-morbidities of COPD or asthma, having low blood pressure, high heart rate, being older and taking amiodarone, a calcium channel blocker or digoxin. Factors associated with a relatively low likelihood of taking at least 50% of the target dose were a history of COPD, a lower blood pressure, a higher heart rate, being older, being treated with amiodarone or digoxin or not being treated with a calcium channel blocker. Beta-blockers reduce heart rate and therefore it is not unexpected that patients taking no or lower doses of beta-blockers have a higher heart rate. The mean heart rate for patients not treated with a beta-blocker was 84.2 bpm compared with 78.9 bpm for patients treated with ≥100% of the beta-blocker target dose. The trend for a reduced heart rate across the beta-blocker dose categories was statistically significant (p<0.001, see Table 1 of Swedberg manuscript (in press) (1)).

Earlier in Section 5.5 we have seen that the efficacy of ivabradine is modified by baseline heart rate, with ivabradine being more effective in patients with higher

resting heart rates. This finding is consistent with ivabradine's mechanism of action which is to reduce heart rate, and with the reduction in heart rate being greater in those with a higher baseline heart rate. Thus, when considering the impact of beta-blocker dose on ivabradine efficacy, it is important to consider the interaction between baseline heart rate and beta-blocker dose because the apparent reduction in efficacy in the patients on relatively high dose of beta-blocker may be due to these patients having lower baseline heart rates.

The results for the primary composite endpoint, and its components, by beta-blocker category are summarised in Table 19. Hazard ratios for each beta-blocker category were calculated using Cox proportional hazards models. The models contained baseline heart rate as a continuous variable and adjustment for the prognostic factors: beta-blocker intake, NYHA class, LVEF, ischaemic cause, age, systolic blood pressure, and estimated glomerular filtration rate. These prognostic factors are the same as used for the analyses presented in the CSR for SHIfT and were chosen in accordance with the European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic HF (SHIfT CSR, page 69). For each endpoint three statistical tests have been undertaken to assess the differences in ivabradine efficacy across the five beta-blocker categories. The first tests for differences in treatment effect using a general test of heterogeneity. The second tests for a trend in the treatment effect across the five beta-blocker categories. The third tests for a trend in the treatment effect whilst adjusting for the interaction between baseline heart rate and ivabradine efficacy i.e. it adjusts for ivabradine being more effective in patients with higher baseline heart rates.

For the composite and component outcomes, the relative effect of ivabradine appeared to be greater (as point estimates) in patients receiving less beta-blockade or not on beta-blockers, however the differences across the beta-blocker categories were not statistically significant (test for heterogeneity, p=0.35 for the primary outcome). The 'Test for Trend' by beta-blocker dose was also non-significant (p = 0.056) . Further, after adjusting for the interaction between baseline heart rate and the efficacy of ivabradine, the p-values increased (p=0.14 for the primary endpoint, p=0.19 for hospitalisations for worsening HF and p=0.30 for cardiovascular death).

In light of the results of their analyses, Swedberg et al. conclude,

> *"The present analysis indicates that the effects of ivabradine on the primary clinical outcome of SHIfT, and its components, were not significantly impacted by beta-blocker dose. Any borderline non-significant trends were significantly weakened by adjustment for the previously identified interaction between baseline heart rate and ivabradine treatment. This suggests that any impact of background beta-blocker treatment on the effects of ivabradine are, if anything, marginal and that the critical factor driving the benefits of ivabradine treatment is heart rate."*

Table 19: Estimates of the effects of randomised treatment by category of baseline beta-blocker category for the primary composite endpoint and its components

beta-blocker category	Ivabradine n (%)	Placebo n (%)	HR (95% CI) p-value	P(interaction) Heterogeneity	P(interaction) Trend across beta-blocker categories	P(interaction) Trend, adjusted for impact of baseline heart rate on ivabradine efficacy
Primary composite endpoint						
No beta-blocker	101 (29.4%)	134 (39.3%)	0.71 (0.55–0.93) 0.012	0.35	0.056	0.135
<25%	148 (30.8%)	171 (40.0%)	0.74 (0.59–0.92) 0.007			
25%-<50%	204 (26.2%)	260 (30.8%)	0.81 (0.68–0.98) 0.029			
50%-<100%	181 (21.6%)	212 (24.8%)	0.88 (0.72–1.07) 0.193			
≥100%	149 (20.1%)	150 (20.1%)	0.99 (0.79–1.24) 0.913			
Hospital admission for worsening HF						
No beta-blocker	65 (18.9%)	98 (28.7%)	0.62 (0.45–0.85) 0.003	0.55	0.12	0.19
<25%	99 (20.6%)	125 (29.3%)	0.68 (0.52–0.89) 0.005			
25%-<50%	131 (16.8%)	183 (21.7%)	0.74 (0.59–0.93) 0.009			
50%-<100%	124 (14.8%)	154 (18.0%)	0.83 (0.65–1.05) 0.119			
≥100%	89 (12.0%)	106 (14.2%)	0.84 (0.63–1.11) 0.223			
Cardiovascular death						
No beta-blocker	63 (18.3%)	81 (23.8%)	0.80 (0.57–1.12) 0.192	0.68	0.17	0.30
<25%	84 (17.5%)	96 (22.5%)	0.82 (0.61–1.09) 0.172			

beta-blocker category	Ivabradine n (%)	Placebo n (%)	HR (95% CI) p-value	P(interaction) Heterogeneity	P(interaction) Trend across beta-blocker categories	P(interaction) Trend, adjusted for impact of baseline heart rate on ivabradine efficacy
25%-<50%	119 (15.3%)	134 (15.9%)	0.95 (0.74–1.22) 0.696			
50%-<100%	96 (11.5%)	101 (11.8%)	0.99 (0.75–1.31) 0.930			
≥100%	80 (10.8%)	74 (9.9%)	1.08 (0.78–1.48) 0.646			

Abbreviations: CI, confidence interval; HR, hazard ratio.

Notes: All analyses are adjusted for baseline heart rate, NYHA class, LVEF, ischaemic aetiology (yes/no), age, systolic blood pressure, and estimated glomerular filtration rate.

Source: Swedberg et al, Table 4.

To summarise, these data suggest that the efficacy of ivabradine is modified by baseline heart rate, but not by beta-blocker dose. The apparent reduction in efficacy for the prespecified subgroup of patients who received ≥ 50% target daily beta-blocker doses (described in the previous section) is at least partly because these patients had lower baseline heart rates. We will explore potential heterogeneity in cost-effectiveness according to beta-blocker usage in Chapter 6 (Section 6.9.4 and 6.10.3).

(D) SHIfT-PRO (patient reported outcomes) sub-study: health-related quality of life

Although the treatment effect of ivabradine on quality of life compared with standard care is included within the SHIfT study endpoints, the true value of the EQ-5D data is to inform the modelling through the use of a regression model developed to predict patient QoL according to baseline characteristics, NYHA class, treatment and hospitalisation events (Section 6.4.10). The PRO-SHIfT sub-study (n=5038) was a representative sample of the main trial population (n=6505) (Note, the analysis sets for this study are defined in Appendix 15 section 9.15.1.1). No clinically relevant between-group differences were observed regarding demographic and clinical baseline characteristics.

EQ-5D index score

Main analysis

In this analysis the last post-baseline value is substituted by 0 for deceased patients. This is appropriate even though this approach doesn't account for any improvements in quality of life that may have occurred prior to death. The mean EQ-5D index score worsened in both treatment groups (FAS EQ-5D), with a [redacted] in favour of ivabradine [redacted], adjusted analysis). The results for the EQ-5D index score are summarised in Table 20.

Analysis of surviving patients

This analysis used the last observed value before death for the deceased patients (i.e. without setting the EQ-5D index score to 0) and combined this with the data for surviving patients. The mean EQ-5D index score improved in both treatment groups ([redacted] for ivabradine group *versus* [redacted] for placebo group), with a [redacted] between-group difference favouring ivabradine ([redacted], adjusted analysis).

Change from baseline to 12 months (as described above)

In this analysis with substitution of last post-baseline value by 0 for deceased patients, The mean EQ-5D index score value improved slightly from baseline to M12 in both groups, with [redacted].

Table 20: EQ-5D index score

	Ivabradine	**Placebo**	**Difference in change in score:[b,c] Ivabradine – placebo (± SE) 95% CI; p value**
Change from baseline to last assessment			
EQ-5D index score[a] (mean ± SD)	**N = 1925**	**N = 1926**	
Including scoring death as 0:			
Baseline	[redacted]	[redacted]	
Final	[redacted]	[redacted]	[redacted]
Δ	[redacted]	[redacted]	[redacted]
Analysis of surviving patients:			
Baseline	[redacted]	[redacted]	
Final	[redacted]	[redacted]	[redacted]
Δ	[redacted]	[redacted]	[redacted]
Change from baseline to Month 12			
EQ-5D index score[b] (mean ± SD)	**N = 1770**	**N = 1789**	
Including scoring death as 0:			
Baseline	[redacted]	[redacted]	
Final	[redacted]	[redacted]	[redacted]

Δ	[redacted]	[redacted]	[redacted]

Abbreviations: EQ VAS, EuroQol Visual Analogue Scale; Δ, change; SD, standard deviation; SE, standard error; CI, confidence interval

Notes: [a] An EQ-5D index score is converted from an EQ-5D health state by applying a formula based on the valuation of EQ-5D health states from general population samples. The EQ-5D Index Score ranges from –0.594 to 1.000.

[b] Change in score from baseline to last post-baseline value, with last-post baseline value = 0 for deceased patients

[c] Results from mixed linear model on change in EQ VAS, adjusted for baseline EQ VAS, beta-blocker intake at randomisation, and country (random effect)

Source: SHIfT Patient-Reported Outcomes sub-study

EQ-5D mixed regression model

In addition to the EQ-5D analyses pre-specified in the SHIfT PRO sub-study, a mixed model designed to estimate quality of life from data with repeated measures over time was performed using EQ-5D Index Scores calculated using UK population tariff values consistent with the NICE reference case. This indicated that over the SHIfT trial period ivabradine was associated with a significant improvement in patient QoL of [redacted] in the licensed population (Table 21). The result for the main trial population also reached statistical significance (see Sections 6.4.3 and 6.4.8).

Table 21: EQ-5D mixed regression model using UK tariff values, controlling for treatment covariate only: licensed population (≥75 bpm)

EQ-5D UK	Coef.	SE	p-value	95% CI	
Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EQ-5D VAS

Main analysis

The mean EQ-5D VAS decreased in both groups from baseline to last post-baseline value. The estimated between group difference showed a [redacted] favouring ivabradine ([redacted], adjusted analysis). The results for the EQ-5D VAS are summarised in Table 22.

Analysis of surviving patients

In this analysis, the mean EQ-5D VAS improved in both treatment groups ([redacted] for ivabradine *vs* [redacted] for placebo). The estimated between group difference was [redacted] in favour of ivabradine ([redacted], adjusted analysis).

Change from baseline to 12 months

The mean EQ-5D VAS improved between baseline and M12 in both groups, with a greater improvement in the ivabradine group than the placebo group which was [redacted] (between-group difference [redacted], adjusted analysis). It is important to note that in this analysis quality of life improves in both

groups, which contrasts with the findings of the main analysis (above). This may be explained by the minimal effect of death on this analysis as the number of deaths in the 0 to 12 month time period is lower than in the whole study.

Table 22: EQ-5D VAS

	Ivabradine	Placebo	Difference in change in score:[b,c] Ivabradine – placebo (± SE) 95% CI; p value
Change from baseline to last assessment			
EQ VAS[a] (mean ± SD) Including scoring death as 0: Baseline Final Δ Analysis of surviving patients: Baseline Final Δ	**N = 2018**	**N = 2018**	
Change from baseline to Month 12			
EQ VAS[a] (mean ± SD) Including scoring death as 0: Baseline Final Δ	**N = 1769**	**N = 1791**	

Abbreviations: EQ VAS, EuroQol Visual Analogue Scale; Δ, change; SD, standard deviation; SE, standard error; CI, confidence interval

Notes: [a] EQ VAS contains a 20 cm vertical rating scale from 0 to 100 (with 0 for worst possible health state and 100 relative to full health).

[b] Change in score from baseline to last post-baseline value, with last-post baseline value = 0 for deceased patients

[c] Results from mixed linear model on change in EQ VAS, adjusted for baseline EQ VAS, beta-blocker intake at randomisation, and country (random effect)

Source: SHIfT Patient-Reported Outcomes sub-study

Clinical summary score of the KCCQ (previously functional status score)

Main analysis

The main analysis was performed on the FAS KCCQ population. Substitution for death consisted of setting the last post-baseline value to 0 for deceased patients. The mean KCCQ Clinical summary score decreased between baseline and last post-baseline value in both groups: the decrease was [redacted] higher for the placebo group than for the ivabradine group, with the estimated difference [redacted] in favour of ivabradine ([redacted]). The results for the KCCQ are summarised in Table 23.

Analysis of surviving patients

The mean summary score increased in both groups. The increase for ivabradine was [redacted] greater than placebo.

Change from baseline to 12 months

The mean clinical summary score value improved between baseline and M12 in the ivabradine group (Δ = 2.6), which represented a statistically significant improvement compared to placebo (2.6 ± 0.9; p=0.008).

Table 23: Clinical summary score of KCCQ

	Ivabradine	**Placebo**	**Difference in change in score:[b,c] Ivabradine – placebo (± SE) 95% CI; p value**
Change from baseline to last assessment			
Clinical summary score[a] (mean ± SD) Including scoring death as 0: Baseline Final Δ Analysis of surviving patients: Baseline Final Δ	**N = 968** [redacted]	**N = 976** [redacted]	[redacted]
Change from baseline to Month 12			
Clinical summary score[a] (mean ± SD) Including scoring death as 0: Baseline Final Δ	**N = 872** 68.9 (20.0) 71.4 (24.4) 2.6 (21.72)	**N = 882** 68.6 (20.5) 68.7 (25.5) 0.1 (21.8)	2.6 (0.9) [0.7; 4.5] p = 0.008

Abbreviations: Δ, change; SD, standard deviation; SE, standard error; CI, confidence interval; QoL, quality of life; KCCQ; Kansas city cardiomyopathy questionnaire

Notes: [a] Clinical summary score is the mean of the physical limitation and total symptom domain scores; the higher score indicates better function.

[b] Change in score from baseline to last post-baseline value, with last post-baseline value = 0 for deceased patients

[d] Results from mixed linear model on change in KCCQ clinical summary score, adjusted for baseline KCCQ clinical summary score , β-blocker intake at randomisation, and country (random effect)

Source: SHIfT Patient-Reported Outcomes sub-study

Summary

In the PRO-SHIfT sub-study the generic EQ-5D questionnaire showed only small differences in favour of ivabradine compared to placebo. Generic questionnaires can give a general view of the impact of heart failure on patients, but they are known to be less sensitive to clinically meaningful changes over time than disease-specific instruments, and are therefore less able to detect a relevant impact of treatments on patients' perceived health status. In this sub-study, the EQ-5D VAS and EQ-5D index score revealed satisfactory but limited responsiveness, and were less sensitive to a decrease in heart rate than the KCCQ. A mixed regression model designed to estimate quality of life from data with repeated measures over time was also performed, and this showed ivabradine to be associated with a [redacted] increase of [redacted] in patient QoL for the licensed population.

The treatment effect of ivabradine on patients' perceived health status as measured by the disease-specific KCCQ also showed a statistically significant improvement on clinical summary scores *vs* placebo for the main analysis, analysis of surviving patients and baseline to month 12 analysis. To provide context it is important to note that other heart failure medications have not been studied in this way so there is a limited evidence base. Dobre 2007 (57) conducted a systematic review and meta-analysis, and concluded that beta-blockers do not impair quality of life but do not improve it. Similar effects have been found with ACE inhibitors and ARBs (Wong 2004 (58); Majani 2005 (59)).

In conclusion, the PRO-SHIfT sub-study showed that the addition of ivabradine to recommended evidence based treatments for heart failure led to improved health status for patients compared to standard care.

(E) SHIfT Echocardiographic sub-study

The pre-specified SHIfT echocardiographic sub-study evaluated the effects of ivabradine on left-ventricular (LV) remodelling in heart failure. The study is not considered to be very relevant to the decision problem and is thus only described briefly.

The primary endpoint of the sub-study was the change in the LV end-systolic volume index (LVESVI) from baseline to 8 months. This showed that treatment with ivabradine for 8 months was associated with a significant reduction in LVESVI *vs* placebo (27.0+16.3 *vs* 20.9+17.1 mL/m2, estimate (SE) 25.8 (1.6), 95% CI 28.8 to 22.7, P< 0.001).

The results indicate a reversal of cardiac remodelling with ivabradine, with significant reductions in LV volumes and an increase in LVEF over 8 months of treatment. These changes were consistent in the pre-specified subgroups, irrespective of baseline LVEF, beta-blocker intake, and aetiology of HF. Moreover, these results occurred despite treatment with beta-blockers and ACE inhibitors and/or ARBs, each used in more than 90% of patients.

In conclusion, heart rate reduction with ivabradine reverses LV remodelling in patients with HF and LV systolic dysfunction. Treatment with ivabradine is associated with marked reductions in LV volumes and a significant improvement in LVEF, therefore suggesting that it is modifying disease progression in patients with HF.

Meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

The following steps should be used as a minimum when presenting a meta-analysis.

Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.
Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).
Provide an adequate description of the methods of statistical combination and justify their choice.
Undertake sensitivity analysis when appropriate.

- Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).

Not applicable

If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

Not applicable

If any of the relevant RCTs listed in response to section 5.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.

Indirect and mixed treatment comparisons

Data from head-to-head RCTs should be presented in the reference-case analysis, if available. If data from head-to-head RCTs are not available, indirect treatment comparison methods should be used. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.13 to 5.3.22.

Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 9.4, appendix 4.

Not applicable

Please follow the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 9.5, appendix 5, a complete quality assessment for each comparator RCT identified.

Not applicable

Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

Not applicable

For the selected trials, provide a summary of the data used in the analysis.

Not applicable

Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

Not applicable

Please present the results of the analysis.

Not applicable

Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

Not applicable

If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

Not applicable

Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

Not applicable

Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3.2.8 to 3.2.10.

If non-RCT evidence is considered (see section 5.2.7), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.6 and 9.7, appendices 6 and 7.

100 studies without a randomisation step were identified during first pass of the search outlined in Section 5.1. A subsequent review of these studies revealed no non-randomised trials relevant to the decision problem.

Adverse events

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials

may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.8 and 9.9, appendices 8 and 9.

N/A - The search strategy outlined in section 5.2 identified that only the SHIfT study was applicable to the decision problem for the use of ivabradine in heart failure. SHIfT is primarily an efficacy study, however is an important source of safety data.

Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

Safety data is presented in the following order:

- **Summary: main trial (≥70 bpm) and licensed population (≥75 bpm)**
- **Detailed analysis of safety: main trial population (≥70 bpm):**
  - (i) Adverse events leading to treatment withdrawal
  - (ii) Serious adverse events
- Also reported in Appendix 9.15.3:
  - (iii) All clinical events
  - (iv) Clinical events related to heart failure
  - (v) Severe adverse events
  - (vi) Treatment–related adverse events
  - (vii) Deaths

This section begins with a summary of the adverse event profile for the main trial and licensed populations. There are no notable differences between the two, indeed the SPC states that the safety profile of the licensed population (≥75 bpm) is in line with that for the overall trial population. For this reason, more detailed findings are subsequently reported only for the main trial population of SHIfT.

Safety set definition

The Safety Set comprised of all patients who took at least one dose of the study product (6,492 patients: 3,232 in the ivabradine group and 3,260 in the placebo group). A total of 14 randomised patients were not included because they did not take any study medication (nine in the ivabradine group and five in the placebo group). One additional patient who received the study drug (placebo) without being randomised was included in the safety set.

All safety analyses presented in this section relate to adverse events (AEs) in the Safety Set which were performed on treatment' (i.e. all AEs that occurred between the first study drug intake and last intake + two days).

Summary of safety: main trial population (≥70 bpm) and licensed population (≥70 bpm)

A summary of the main forms of adverse event is provided in Table 24. There was no difference in the rate of adverse effects of ivabradine in the ≥70 and ≥75 bpm groups. A higher prevalence of symptomatic bradycardia was observed on ivabradine vs placebo, but there was no difference between the ≥70 and ≥75 bpm groups. Atrial fibrillation and visual symptoms were also more frequent in the ivabradine group than in the placebo group, but again no difference was observed between the main trial and licensed populations. Adverse events leading to drug withdrawals on ivabradine were 14.4% in the main trial population (≥70 bpm) and 14.7% in the licensed population. This suggests that the tolerability of ivabradine is not limited by baseline heart rate. Even at lower heart rates, adverse events leading to withdrawals do not

appear to be enhanced. Withdrawal rates for symptomatic adverse events were low in both populations (3%).

In patients with baseline heart rate ≥75 bpm the safety profile was favourable, with similar incidences of adverse events, serious adverse events and death compared to the overall population, and similar differences *vs* placebo. There was no specific signal resulting from raising the threshold of baseline heart rate up to 75 bpm.

Table 24: Summary of adverse event 'on treatment': main trial population (≥70 bpm) and licensed population (≥75 bpm)

	Heart rate at baseline ≥70 bpm			Heart rate at baseline ≥75 bpm		
	Ivabradine (N=3232)	**Placebo N=3260)**	**Rel. risk (95% CI)**	**Ivabradine (N=2046)**	**Placebo N=2095)**	**Rel. risk (95% CI)**
All emergent adverse events	2414 (74.7%)	2392 (73.4%)	1.02 (0.99, 1.05)	1554 (76.0%)	1607 (76.7%)	0.99 (0.96, 1.02)
All **serious** emergent adverse events	1369 (42.4%)	1481 (45.4%)	0.93 (0.88, 0.99)	892 (43.6%)	1020 (48.7%)	0.90 (0.84, 0.96)
All EAEs leading to **drug withdrawal**	467 (14.4%)	416 (12.8%)	1.13 (1.00, 1.28)	300 (14.7%)	295 (14.1%)	1.04 (0.90, 1.21)
Selected emergent adverse events						
• Cardiac failure	701 (21.7%)	846 (26.0%)	0.84 (0.77, 0.91)	487 (23.8%)	609 (29.1%)	0.82 (0.74, 0.91)
• Symptomatic bradycardia	148 (4.6%)	28 (0.9%)	5.33 (3.57, 7.96)	84 (4.1%)	14 (0.7%)	6.14 (3.50, 10.78)
• Asymptomatic bradycardia	181 (5.6%)	45 (1.4%)	4.06 (2.94, 5.60)	98 (4.8%)	25 (1.2%)	4.01 (2.60, 6.20)
• Atrial fibrillation	267 (8.3%)	217 (6.7%)	1.24 (1.04, 1.47)	161 (7.9%)	143 (6.8%)	1.15 (0.93, 1.43)
• Phosphenes	89 (2.8%)	16 (0.5%)	5.61 (3.30, 9.53)	57 (2.8%)	11 (0.5%)	5.31 (2.79, 10.09)
• Blurred vision	17 (0.5%)	7 (0.2%)	2.45 (1.02, 5.90)	11 (0.5%)	7 (0.3%%)	1.61 (0.62, 4.14)

(i) Adverse events leading to treatment withdrawal

The analysis of AEs leading to treatment withdrawal by SOC is summarised in Table 25**.** For the preferred terms associated with each SOC, see the SHIfT CSR Table (12.1.2.3) 4, p158. The rate of withdrawal from adverse events was numerically higher in the ivabradine arm but did not reach statistical significance (Swedberg 2010 (8)).

Regarding the more frequent known adverse events associated with ivabradine treatment, withdrawal rates were (ivabradine *vs* placebo): Symptomatic bradycardia (0.6% *vs* 0.2%), Phosphenes (transient enhanced brightness in a limited area of the visual field) (0.2% *vs* 0.1%) and Ventricular extrasystoles (0.2% *vs* 0.2%).

Table 25: Adverse events 'on treatment' leading to treatment withdrawal by system organ class (at least five patients in either group) (safety set)

System organ class	Ivabradine N = 3232 n (%)	Placebo N = 3260 n (%)
All	**467 (14.4)**	**416 (12.8)**
Cardiac disorders	303 (9.4)	270 (8.3)
Investigations	34 (1.1)	11 (0.3)
Nervous system disorders	26 (0.8)	38 (1.2)
Gastrointestinal disorders	21 (0.7)	20 (0.6)
Infections and infestations	10 (0.3)	11 (0.3)
Eye disorders	10 (0.3)	6 (0.2)
Surgical and medical procedures	11 (0.3)	7 (0.2)
Neoplasms benign, malignant and unspecified	9 (0.3)	11 (0.3)
General disorders and administration site conditions	9 (0.3)	6 (0.2)
Vascular disorders	5 (0.2)	4 (0.1)
Renal and urinary disorders	5 (0.2)	3 (0.1)
Injury, poisoning and procedural complications	5 (0.2)	2 (0.1)
Skin and subcutaneous tissue disorders	4 (0.1)	8 (0.3)
Respiratory, thoracic and mediastinal disorders	2 (0.1)	8 (0.3)

Source: SHIfT CSR Table (12.1.2.3) 4 p158

(ii) Serious adverse events

The analysis of patients having at least one serious adverse event (SAE) 'on treatment' by SOC is summarised in Table 26. For the preferred terms associated with each SOC, see the SHIfT CSR Table (12.2.1.2) 1, p164. The analogous table for SAEs 'during the study' (i.e. after first intake of study drug until database closure) by SOC is reported in the SHIfT CSR, Table (12.2.1.1) 1, p163.

A total of 2850 patients (43.9%) experienced at least one SAE, with slightly lower frequencies in the ivabradine group. The main between-group difference was due to the lower rate of cardiac failures in the ivabradine group than in the placebo group:

15.7% *vs* 20.4%. The main preferred terms that were reported at higher frequencies in the ivabradine group than in the placebo group were Atrial fibrillation (3.9% *vs* 3.3%), Coronary arteriogram (0.7% *vs* 0.4%) and Bradycardia (0.5% *vs* 0.1%). Serious AEs in the safety set that led to drug withdrawal were reported in 270 patients (8.4%) in the ivabradine group *vs* 279 patients (8.6%) in the placebo group.

Table 26: Serious adverse events 'on treatment' by system organ class (at least five patients in either group) (safety set)

System organ class	Ivabradine N = 3232 n (%)	Placebo N = 3260 n (%)
All	**1369 (42.4)**	**1481 (45.4)**
Cardiac disorders	853 (26.4)	939 (28.8)
General disorders and administration site conditions	201 (6.2)	198 (6.1)
Infections and infestations	178 (5.5)	198 (6.1)
Nervous system disorders	110 (3.4)	154 (4.7)
Respiratory, thoracic and mediastinal disorders	90 (2.8)	113 (3.5)
Surgical and medical procedures	82 (2.5)	95 (2.9)
Gastrointestinal disorders	70 (2.2)	87 (2.7)
Vascular disorders	68 (2.1)	75 (2.3)
Investigations	65 (2.0)	62 (1.9)
Neoplasms benign, malignant and unspecified	64 (2.0)	56 (1.7)
Injury, poisoning and procedural complications	54 (1.7)	63 (1.9)
Metabolism and nutrition disorders	42 (1.3)	52 (1.6)
Renal and urinary disorders	40 (1.2)	32 (1.0)
Hepatobiliary disorders	26 (0.8)	36 (1.1)
Musculoskeletal and connective tissue disorders	23 (0.7)	29 (0.9)
Eye disorders	17 (0.5)	13 (0.4)
Blood and lymphatic system disorders	10 (0.3)	15 (0.5)
Psychiatric disorders	9 (0.3)	9 (0.3)
Reproductive system and breast disorders	7 (0.2)	9 (0.3)
Skin and subcutaneous tissue disorders	4 (0.1)	8 (0.3)

Source: SHIfT CSR Table (12.2.1.2) 1 p164

Give a brief overview of the safety of the technology in relation to the decision problem.

The efficacy and safety of ivabradine has been evaluated in a number of phase II and phase III trials in both CAD and HF, recruiting over 13,000 patients. All studies have shown ivabradine to be well tolerated. In the SHIfT study, with 6,505 randomised heart failure patients with LV systolic dysfunction, the overall incidence of AEs was similar in the ivabradine (74.7%) and placebo (73.4%) groups. In the licensed population of relevance to the decision problem (baseline heart rate ≥75 bpm) the safety profile was favourable, with similar incidences of adverse events, serious adverse events and death compared to the overall SHIfT population, and similar differences *versus* placebo. There was no specific signal resulting from raising the threshold of baseline heart rate to 75 bpm, and no evidence of delayed, rare or unexpected adverse events with ivabradine in the treatment of HF.

In the main SHIfT trial population the most frequent AE was cardiac failure, as one would expect in heart failure, and this was reported in fewer patients in the ivabradine group. In line with previous trials, ivabradine was associated with more bradycardia and visual symptoms than the placebo group however this was unlikely to lead to treatment withdrawal. Atrial fibrillation was reported more frequently with ivabradine than with placebo but was not associated with an increased occurrence of cerebro-vascular accidents and had no impact on the beneficial effect of ivabradine on cardiovascular outcomes. Fatal events were less frequent in the ivabradine group than the placebo group, as were other serious AEs.

Further, results indicate that the tolerability of ivabradine is not limited by baseline heart rate. Adverse events leading to drug withdrawals on ivabradine were 14.4% in the main trial population (≥70 bpm) and 14.7% in the licensed population indicating that, even at lower heart rates, adverse events leading to withdrawals are not significantly enhanced. Withdrawal rates for symptomatic adverse events (3%) remained low in both heart rate populations.

Overall, taking into account the specific nature of the heart failure population, the safety profile of ivabradine in the SHIfT study was favourable and was consistent with previous studies in the clinical development programme. There is no evidence for delayed, rare or unexpected AEs with ivabradine nor any pharmacological, biological or clinical basis to suspect that such events may be anticipated.

Interpretation of clinical evidence

Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

The evidence base to support the use of ivabradine is derived from the SHIfT study which demonstrated the superiority of ivabradine *vs* placebo in HF patients with low ejection fraction and in sinus rhythm, on top of optimised recommended treatment. There is overwhelming evidence that beta-blockers reduce morbidity and mortality in such patients, and these first line therapies should be assertively up-titrated to target, or maximum tolerated dose in the case of intolerance, prior to considering ivabradine. In line with the indication, ivabradine should be used in patients with systolic heart failure, in sinus rhythm, who are:

1. contraindicated to beta-blockers or are intolerant to these agents and have a resting heart rate ≥75 bpm
2. receiving beta-blockers at maximally tolerated doses and whose resting heart rate remains ≥75 bpm

Clinical benefit

In the whole population of the SHIfT study the magnitude of benefit was statistically significantly better than placebo, with an 18% reduction in risk for the primary composite outcome of time to first event of cardiovascular death or hospitalisation for worsening heart failure (HR 0.76, 95% CI 0.68-0.85, p<0.0001) (Table 9). The NNT for the primary endpoint was estimated to be 24.

In the subgroup with a baseline heart rate ≥75bpm, which is relevant to the licensed indication and the NICE decision problem, the incidence of the primary composite endpoint was statistically significantly lower in the ivabradine group than in the placebo group (26.6% *vs* 32.8% respectively; HR 0.76, 95% CI 0.68-0.85, p <0.0001) (Table 12). Importantly, this subgroup showed a statistically significant benefit for ivabradine with respect to all-cause mortality, CV mortality and death from HF: RRR = 17% for death from any cause (HR = 0.83, 95% CI 0.72-0.96, p = 0.011); 17% for CV death (HR 0.83, 95% CI 0.71-0.97, p = 0.017); and 39% for death from HF (HR 0.61, 95% CI 0.46-0.81, p = 0.0006). Furthermore, the absolute risk reduction for all-cause death corresponds to an NNT of 35, thus for every 35 patients treated with ivabradine one life will be saved.

These benefits were demonstrated on top of optimised recommended background treatment for HF which generally exceeds levels achieved currently in clinical practice in England and Wales. This indicates that the addition of ivabradine to the treatment regime for heart failure would impact positively on the aims identified in NICE CG108, namely improved mortality, reduced hospitalisations and better quality of life.

Safety

The AEs observed in ivabradine-treated patients within the SHIfT trial presented no new signal to the known safety profile (Section 5.9). The majority of events were those that can be expected in this population or were previously described as drug-related events that manifest in the first few months of treatment (e.g. bradycardia and phosphenes). Ivabradine treatment was associated with similar rates of AEs and a slightly lower frequency of serious AEs compared to placebo. In patients with baseline heart rate ≥75 bpm the safety profile was favourable, with similar incidences of AEs, SAEs and death compared to the overall population, and similar differences *vs* placebo. No specific signal resulted from raising the baseline heart rate threshold from 70 to 75 bpm.

Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

Ivabradine represents the first new class of treatment for heart failure in over 10 years. The SHIfT study has provided conclusive evidence that elevated heart rate is a clear risk factor that needs to be addressed to prevent mortality and morbidity endpoints in patients with heart failure.

Strengths

Well-designed RCT

The SHIfT study was a well-designed and conducted multicentre, double blind, randomised RCT targeting patients with heart failure which met its primary endpoint. The trial recruited 6,505 patients with stable symptomatic heart failure and evaluated the effects of ivabradine in addition to standard therapy which are reflective of the recommendations in NICE CG108 and the ESC heart failure guidelines (Section 5.10.4).

Consistency with published literature

The results of the SHIfT study are consistent with published literature which suggests that an elevated resting heart rate is a risk factor for excess mortality and morbidity in the general population and in heart failure patients (Fox et al. 2008; McAlister et al. 2009; Metra et al. 2005; Pocock et al. 2006 (27);(60);(5);(30)). A meta-regression of 23 beta-blocker RCTs in heart failure patients indicated that, for every five bpm reduction in heart rate achieved (baseline to first visit post titration period), an 18% (95% CI: 6-29%) reduction in all-cause mortality was observed (McAlister et al. 2009 (5)). Analyses of in-patient data from other large randomised controlled trials (RCTs) in HF patients have also shown strong associations between heart rate and death. The CHARM trial of candesartan in heart failure estimated that, for every 10 bpm. increase, the risk of all-cause mortality increased by 8% (Pocock et al. 2006 (30)). There is also evidence that a heart rate above a target value increases the risk of mortality. The COMET trial of carvedilol in HF showed that heart rate above the

median value achieved at 4 months (68 bpm) predicted subsequent increased mortality (relative risk 1.33; 95% CI 1.15–1.54, p< 0.0001). (Metra et al. 2005 (60)).

Safety

Ivabradine has been licensed in the UK since 2006 for the treatment of chronic stable angina. The licence was extended in 2009 to include the 'combination with beta-blockers in patients inadequately controlled with an optimal beta-blocker dose and whose heart rate is >60 bpm'. Ivabradine has been shown to be generally well tolerated both in clinical trials and clinical practice. Ivabradine has been studied in clinical trials involving nearly 14,000 participants. The most common adverse reactions with ivabradine are luminous phenomena (phosphenes) and bradycardia, which are dose dependent and related to the pharmacological effect of the medicinal product. Other common adverse reactions are listed within the SPC.

Limitations

Analysis of SHIfT in patients with baseline heart rate ≥75 bpm

Servier acknowledge that the most robust analysis of the SHIfT trial is the ITT analysis of the overall trial population. Following the study, it was apparent that baseline heart rate modifies the treatment effect of ivabradine. In order to identify the patients in whom the mortality benefit of ivabradine was clear, the CHMP asked Servier to re-analyse the SHIfT data (EPAR 2012 (49)). It was subsequently identified that 75 bpm was a threshold of interest. In this cohort (n=4,150) the effect of ivabradine on all-cause mortality (HR 0.83, 95% CI 0.72-0.96), cardiovascular mortality (HR 0.83, 95% CI 0.71-0.97) and hospitalisation for worsening heart failure (HR 0.70, 95% CI 0.61-0.80) was clearly established. On this basis the CHMP granted a licence indication for the treatment of HF in patients with a resting heart rate ≥75 bpm. Analysis of this subgroup of the SHIfT trial is therefore of direct relevance to the NICE decision problem and has been presented in Section 5.5.

Number of patients recruited from the UK

Recruitment of patients into the SHIfT trial from the UK was low. This is consistent with a number of other major outcome trials such as the CHARM 2003 trial (50) and ATMOSPHERE 2011 (61). It is important to note that the UK is a poor recruiter, which may be related to the challenges of gaining study approval within the UK. This has been recognised as a problem by the National institute for Health Research, with one of its current performance improvement targets being to increase recruitment to commercial studies. It is hoped that a strong focus on recruitment 'to time and to target' will increase the recruitment of UK patients into clinical trials in the future.

As indicated throughout this submission document, the patients in SHIfT are relevant to the patients with heart failure seen in the UK. The demographic characteristics are similar to those of heart failure patients in the UK, except that the average age is lower, as found in most clinical trials in heart failure and discussed further in Section

5.10.4. In addition, they were receiving optimised background therapy for heart failure which is consistent with the best practice seen currently in the UK.

Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

The SHIfT study includes 63.8% (4150/6505) of patients with the demographic profile applicable to the NICE decision problem (adults in sinus rhythm with symptomatic chronic heart failure, NYHA class II to IV, due to left-ventricular systolic dysfunction who have been prescribed standard optimal heart failure therapy). The evidence base is reflective of current practice in England and Wales in terms of background therapy and routine monitoring.

The outcomes measured in the SHIfT study are consistent with the EMA Guideline on clinical investigation of medicinal products for the treatment of heart failure [CPMP/EWP/235/95 Rev. 1]. The primary and secondary outcomes, combined with the pre-specified patient reported outcomes sub-study, together cover all of the outcomes listed within the final scope for this appraisal.

NICE CG108 states that medical therapy for heart failure has two aims (7):

1. Improving the patients' morbidity: by reducing the patient's symptoms, improving their exercise tolerance, reducing their hospitalisation rate and improving their quality of life.
2. Improving the patients prognosis, through the reduction of all-cause mortality or their heart failure-related mortality.

The SHIfT study is consistent with these aims and the licensed relevant subgroup demonstrated statistically significant outcomes associated with ivabradine in addition to optimised recommended background treatment, on the hard endpoints of mortality, morbidity and safety specified in the decision problem.

Furthermore, the benefits in the subpopulation with baseline heart rate ≥75 bpm were consistent across the subgroups that were pre-specified for the overall trial population:

- Age: < 65 / ≥ 65 years.
- Gender: male/female.
- Beta-blocker intake at randomisation: yes/no.
- Primary cause of HF: ischaemic cause/non ischaemic cause.
- NYHA class: II / III *vs* IV.
- Diabetes: yes/no.
- Hypertension: yes/no

The evidence for ivabradine derived from the SHIfT study is therefore relevant to the decision problem and provides data on tangible benefits that will be realised by patients in heart failure.

Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

Use of the technology in the trial

There are two issues of interest with respect to how the technology was used in the trial when considering its usage in UK clinical practice; 1) The initiation of ivabradine and 2) Length of ivabradine treatment in the trial

1) Initiation of ivabradine

Within the SHIfT trial the initiation of ivabradine (or matching placebo) was undertaken under the care of a specialist heart failure team. The starting dose was 5 mg twice daily and SPC recommendations on dose titration were adhered to thereafter. For the purpose of this technology appraisal the manufacturer similarly proposes that, for patients fulfilling the criteria of the licence, ivabradine is initiated under the advice of a multidisciplinary heart failure team (NICE QS 6, see Section 2.3 (39)), which involves professionals from both primary and secondary care and is usually led by a consultant cardiologist.

2) Duration of ivabradine treatment and maintenance of benefit

The SHIfT trial has a median follow-up of 22.9 months. However for chronic diseases such as heart failure patients are expected to continue facing an elevated risk of major clinical events for the remainder of their lifetime. The SHIfT heart rate paper (Böhm 2010 (6)) shows that the magnitude of heart rate reduction is directly associated with cardiac outcomes. One might therefore equate the duration of treatment effect to the duration of heart rate reduction. During the study follow up period those remaining on therapy demonstrated a consistent reduction in heart rate of approximately 10 bpm compared with placebo (Table 27), indicating that at least over the course of the study heart rate reduction is maintained with ivabradine.

Table 27: Heart rate reductions in SHIfT patients on treatment

	Ivabradine		Placebo		Ivabradine-placebo difference E (SE) bpm
	N	HR lowering *vs* baseline (mean +/- SD) bpm	N	HR lowering *vs* baseline (mean +/- SD) bpm	
Baseline	3241	-	3264	-	-
D28	3113	-15.51 ± 10.67	3149	-4.63 ± 10.59	-10.99 (0.25)
M12	2587	-14.62 ± 11.86	2664	-5.12 ± 11.94	-9.54 (0.31)
M24	1592	-14.08 ± 11.85	1617	-5.12 ± 12.36	-8.98 (0.39)
M36	142	-14.01 ± 13.55	167	-4.25 ± 14.24	-11.04 (1.42)

In order to assess the longer term heart rate efficacy of ivabradine it is useful to review data from the seven year extension study for patients with Angina – the CL3-16257-044 trial. This is a multi-centre, open-label, non-comparative, phase III study, designed as an extension of three one-year, phase III ivabradine studies. The study follows patients over a seven-year treatment period. Of the 557 included patients, 61% completed three years of follow-up, 58% completed five years and 40% completed seven years of follow-up. Consistent with patients being treated with ivabradine for up to one year prior to entry into the study, mean heart rate decreased only slightly over the first 12 months of the extension period and then remained [redacted] during the remaining six years of follow up. Table 28 summarises mean heart rates over the seven-year follow-up period.

Table 28: Mean heart rate over seven-year angina study CL3-16257-044

	N	Heart rate (mean +/- SD) bpm
Baseline for three feeder studies	[redacted]	[redacted]
044 extension study:		
M00	[redacted]	[redacted]
D15	[redacted]	[redacted]
M6	[redacted]	[redacted]
M12	[redacted]	[redacted]
M18	[redacted]	[redacted]
M24	[redacted]	[redacted]
M30	[redacted]	[redacted]
M36	[redacted]	[redacted]
M42	[redacted]	[redacted]
M48	[redacted]	[redacted]
M54	[redacted]	[redacted]
M60	[redacted]	[redacted]
M66	[redacted]	[redacted]
M72	[redacted]	[redacted]
M78	[redacted]	[redacted]
M84	[redacted]	[redacted]

Given the heart rate lowering effect of ivabradine and the associated outcome benefits are expected to continue in the long term, the base case approach adopted for the economic model assumes the relative treatment effect of ivabradine to continue in the post-trial period (Section 6.3.7). More conservative assumptions of a shorter duration of therapy and a reducing treatment effect are explored in sensitivity.

Generalisability of SHIfT to UK clinical practice

Considering the generalisability of the SHIfT study to routine clinical practice in the UK, there are two principal issues to consider; 1) Patient characteristics, and 2) Background therapies

1) Patient characteristics

There are four potential issues with respect to the patients included in SHIfT, some of which were raised in comments on the draft scope for this appraisal. These are discussed below:

a) Age

The mean age of patients in SHIfT was 60 years. The National Heart Failure Audit 2008-2009 (Cleland 2011 (62)) demonstrated that the average age of patients in the UK discharged with heart failure and an ejection fraction less than 40% is 76 years. A recent analysis of patients in Hull which more closely match the SHIfT patient profile showed a median age of 69 years (Cleland 2012 unpublished (35)). Whilst there is therefore an obvious age difference between SHIfT patients and UK patients with HF and systolic dysfunction, it is recognised that clinical studies in heart failure tend to recruit younger patients. Indeed Table 100 (Appendix 16), illustrates that the average age of patients recruited in SHIfT is similar to many other landmark trials in this disease area. To therefore question the relevance of SHIfT to UK clinical practice on the basis of age may also cast some doubt over the strong evidence base supporting the use of beta-blockers and other heart failure therapies.

However in order to provide reassurance as to the benefit of ivabradine in older patients, a specific analysis of SHIfT patients aged ≥70 years was requested by the CHMP. In this cohort a 16% relative risk reduction (HR 0.84, 95% CI 0.70-1.00, p=0.0478) of the primary endpoint was observed, and the secondary endpoints of cardiovascular death (23%), death from worsening heart failure (49%) and hospitalisation for worsening heart failure (20%) were all significantly reduced (Section 5.5). In terms of safety, patients aged ≥70 years had a similar incidence of emergent adverse events and serious adverse events in both treatment groups and no specific or unexpected safety concerns were observed.

Additional age-related analyses are discussed in Section 6.10.3 in relation to cost-effectiveness, recognising that beyond any possible modification of treatment effect the baseline risk of patients increases with age.

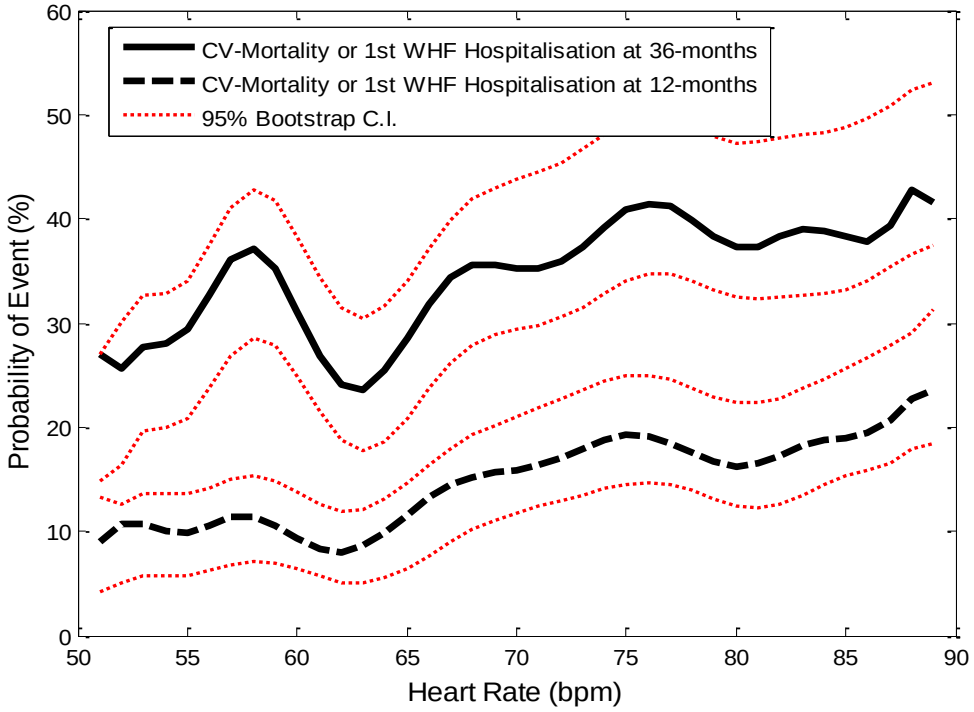
b) Baseline risk

Resting heart rate is another patient characteristic which affects baseline risk, as recognised for example in randomised trial data for beta-blockers (McAllister 2009 (5)) and ivabradine (Böhm 2010; Swedberg 2010 (6;8)). A new complementary analysis of clinical audit data, not yet published, has now been carried out on a population of 1,554 patients from Hull with similar characteristics to SHIfT patients (sinus rhythm and heart failure due to LVSD), using heart rate as a continuous variable (Cleland 2012 (35)). A plot of the probability of a SHIfT primary endpoint event according to achieved heart rate at 4 months (Figure 10) shows that higher heart rates are strongly associated with worse outcomes. This analysis suggests that patients with heart rates in the range 60 - 65 bpm appear to be at lowest risk. (Results from a published analysis on this same database are also discussed later in this section in the context of background therapies).

One might consider how the primary endpoint event rate in the SHIfT placebo arm compares with observation of UK clinical practice. The Hull audit analysis shows one-year mortality rates to be somewhat higher than the SHIfT placebo data (all-cause mortality 16.2% *vs* 9.3% respectively; and CV mortality 13.5% *vs* 8.3% respectively).

The difference might be attributed to a) the SHIfT trial population is younger and has fewer co morbidities; and b) background therapies are slightly better in the trial cohort than in clinical practice. Once again, the modelling explores this issue further by considering the scenario of a 'typical UK heart failure patient' profile (Section 6.10.3).

Figure 10: Moving average plot of the probability of an event (CV mortality or 1st WHF hospitalisation) according to achieved heart rate at 4-months in patients in sinus rhythm



c) Gender

76% of patients with a heart rate ≥75 bpm in the SHIfT study were male, this compares to 57% in the National Heart Failure Audit 2008-2009 (Cleland 2011 (62)). However if the patients in the Audit most similar to those included in SHIfT (i.e. under the age of 75 with and ejection fraction <40) are isolated out then 72% of the patients were male. Indeed it is well accepted that patients with systolic dysfunction tend to be younger and male, whilst those with diastolic function tend to be older and female. Irrespective, Section 5.1 of the SPC clearly states that the reduction of the primary endpoint in the study was observed regardless of gender (test for heterogeneity, p = 0.260) therefore the results of SHIfT can confidently be applied to UK patients regardless of gender.

d) Ethnicity

SHIfT recruited patients predominately from Europe and Asia. Whilst recruitment in Eastern Europe was higher than in Central and Western Europe, there is no biologically plausible reason why ivabradine should work differently in different ethnic groups. Further, other trials in heart failure have shown similar proportions of white

participants to SHIfT (90–94% *vs* 89% respectively). The results of SHIfT are therefore applicable to any heart failure population, including the UK.

Finally, with regards to patient characteristics it should be noted that for other heart failure treatments, such as ACE inhibitors and beta-blockers, NICE guideline recommendations do not specify age, gender or ethnicity restrictions.

2) Background therapies

Patients in the SHIfT study were treated in accordance with good clinical practice. Indeed the SHIfT protocol and eCRF were designed such that every effort was made to optimise use of established treatments in heart failure. As a result the majority of patients received care including beta-blockers (89%), ACE inhibitors and/or ARBs (91%), aldosterone antagonists (60%) and diuretics (84%). Table 29 compares NICE recommended background therapy usage in the SHIfT trial to the National HF Audit and two British clinical practice audits of patients with HF and LVSD. This demonstrates that patients in SHIfT were well treated in line with NICE CG108. GP prescribing data for the UK shows that 63% of patients with a primary diagnosis of HF are receiving beta-blockers (CSD Jan 2012 (63)), a similar level to that seen on discharge from hospital in the National HF Audit.

Table 29: Comparison of background therapies between SHIfT and UK clinical practice

	SHIfT Baseline	**National HF Audit** on discharge from hospital	**HOOPS (Lowrie (64))** Baseline (yr 1 for intervention group)	**Hull Audit (Cullington (46))** Baseline (4 months)	**Hull Audit (Cleland (35))** 'SHIfT-like' patients[2]
Beta-blocker	89%	65% (78%)[1]	62% (64%)	58% (81%)	67%
ACEi/ARB	91%	81%	86% (85%)	79% (90%)	90%
Diuretic	84%	86%	61% (NR)	74% (77%)	86%
Aldosterone antagonists	60%	36%	5% (NR)	25% (29%)	47%
Cardiac glycosides	22%	NR	14% (NR)	18% (19%)	17%

[1] If discharged from a cardiology ward

[2] Patients with LVEF≤35%, heart rate ≥70 bpm, NYHA class II-IV, in sinus rhythm and following therapy optimisation

Abbreviations: NR not recorded

When considering beta-blocker therapy in SHIfT and its applicability to clinical practice in the UK it is important, given the relationship between beta-blocker dose, heart rate reduction and outcomes, to not only consider the number of patients on beta-blockers in the study but also the dose used. A published analysis of a community heart failure clinic in Hull (Cullington 2011) aimed to quantify the proportion of patients with heart failure and LVSD attending the clinic who might be suitable for ivabradine therapy. The audit also recorded beta-blocker dosages at baseline (following referral to the clinic), at 4 months and 12 months. After the

baseline visit patients either returned to the clinic for medication titration or received follow-up from their GP who had been given detailed advice on titration. Table 30 shows the dosages of beta-blockade achieved at 4 and 12 months.

The National Heart Failure Audit collects data on 54% of all patients discharged from hospital in the UK with a primary diagnosis of heart failure. Table 30 shows the levels of beta-blocker dosing achieved on discharge from hospital. Patients have had limited opportunity for dose optimisation, hence only 1 – 2 % are on target dose. Of 112 hospitals in the audit with data on beta-blocker dosing, only 9% managed to discharge a majority of patients on at least half of the target dose.

Table 30: Beta-blocker dosage in UK audits: a community heart failure clinic; and on discharge from hospital

Beta-blocker dose	**SHIfT** Baseline	**Hull Audit (Cullington 2011 (46))**			**National HF Audit (2011) (65)**[1] <75 yrs, on discharge from hospital		
		Baseline (n=2211)	**4 months (n=1309)**	**12 months (n= 910)**	**All patients (n=4,615)**	**Tertiary centres (n=1,127)**	**Cardiology care (n=3,141)**
None	11%	42%	19%	14%	28%	16%	18%
Low dose	40%	29%	40%	36%	44%	45%	48%
Moderate dose	26%	23%	27%	34%	27%	37%	32%
Target dose	23%	7%	13%	19%	1%	2%	2%

[1] percentages as a proportion of patients who have beta-blocker dose recorded (*ca.* one third)

Definition of beta-blocker dose (expressed as % of target dose):

SHIfT, National HF Audit: Low 1-49%, Moderate 50-99%, Target 100%

Hull Audit for bisoprolol, carvedilol, nebivolol, atenolol and timolol: Low 1-49%, Moderate 50-99%, Target 100%

Hull Audit for metoprolol, propranolol, sotolol: Low 1-24%, Moderate 25%-99%, Target 100%

Hull Audit for celiprolol: Low 50%, Moderate 75%, Target 100%

A third UK analysis (Setakis et al. 2009 (44)) investigated beta-blocker doses in over 12,000 patients with a first ever diagnosis of CHD (angina, heart failure, previous MI) using the UK General Practice Research Database (GPRD). 715 patients with a heart failure diagnosis had beta-blocker dose information available 12 months after initiating therapy. Of those, 57% were on low dose, 26% moderate, and 17% on target dose beta-blockade. These studies highlight that beta-blockers are often used at dosages below 50% of target dose, and that fewer than 20% of patients attain the maximum recommended dose. In the case of the Hull audit this is in spite of concerted efforts to up-titrate the beta-blocker.

In the SHIfT trial, the study protocol and eCRF were designed to ensure optimal use of all medications during the study, including beta-blockers. Despite these efforts the dose of beta-blockers achieved in SHIfT were only marginally higher than those reported by Cullington and Setakis. Specifically, 56% of SHIfT patients who were on a beta-blocker were on at least 50% of the target dose, and only 26% received the

full target dose. Reasons for underutilisation of beta-blockers in both clinical practice and in SHIfT principally relate to issues of hypotension, fatigue, dyspnoea, dizziness, cardiac decompensation and bradycardia.

On this basis it can be concluded that the use of background therapies in SHIfT, including the dose of beta-blocker, generally exceed clinical practice in the UK, giving confidence that the benefits observed in SHIfT may be expected in the broader UK heart failure population when ivabradine is used in line with the licence.

One might also consider a comparison between beta-blocker dosing in SHIfT and the landmark beta-blocker trials in heart failure. Table 100 (Appendix 16) clearly shows that levels of beta-blockade are higher than in the SHIfT study, ranging from 43% achieving target dose in CIBIS II (Simon et al. 2003 (66)) up to 75% for carvedilol in COMET (Metra et al. 2005 (67)). These studies incorporated forced beta-blocker titration and excluded contraindicated or co-morbid patients such as those with respiratory disease. The possibility of selection bias can also not be excluded (recruitment of patients predisposed to tolerate beta-blockade). Furthermore, patients could often not be maintained on the doses achieved after the titration phase and had to reduce or interrupt treatment due to intolerance during the maintenance phase (Dobre 2007 (57)). Such high beta-blocker dosing has not been replicated in clinical practice.

Concomitant prescribing of drugs which lower blood pressure such as aldosterone antagonists was also less common 15 to 20 years ago when the beta-blocker trials were performed (Table 100, Appendix 16). Consequently hypotension would have been less likely to prevent up-titration of the trial intervention (Table 31). Interestingly, baseline blood pressure in the SHIfT trial (122/76 mmHg) is similar to that of SHIfT-like patients in clinical practice today (123/73 mmHg), as defined by a group of 276 patients from Hull who have undergone therapy optimisation (Cleland 2012).

Table 31: Baseline SBP (mmHg) in SHIfT and other HF trials in the beta-blocker treated group

Trial (year)	BaselineSBP(mmHg) in BB treated group	Baseline DBP (mm Hg) in BB treated group
CIBIS II (1999)	129.2	79.4
MERIT HF (1999)	130.0	78.4
COMET (2003)	126.0.	77.0
SENIORS (2005)	138.6	80.5
SHIfT (2010)	122.0	75.7

CIBIS-II Investigators and Committees, 1999; MERIT-HF study group, 1999; Poole-Wilson, 2003; Flather, 2005

It is also worth noting that comparisons with the SHIfT study are confounded by the requirement of a heart rate ≥70 bpm for inclusion. Specifically, patients on higher beta-blocker doses are less likely to have a high heart rate and may be excluded

from the trial. This effect was evidenced in an analysis which showed the mean heart rate for SHIfT patients not treated with a beta-blocker to be 84.2 bpm, compared with 78.9 bpm for patients treated with ≥100% target dose beta-blockade (Swedberg, Section 5.5). One would expect this effect to be exaggerated when considering the ≥ 75 bpm licensed heart rate threshold.

A more contemporary RCT in heart failure (EMPHASIS, Zannad 2011 (68)), which shared the inclusion criterion in SHIfT such that patients were required to be receiving optimal and unchanged beta-blockers and dosage for at least four weeks prior to study inclusion, reported that 40% of patients were treated with ≥50% of target beta-blocker doses. This is lower than in SHIfT.

Criteria used to select eligible patients in clinical practice

The criteria used to select eligible patients in clinical practice should be the same criteria as identified in the licence. In short these are:

1) Chronic heart failure with systolic dysfunction
2) Presence of symptoms as per NYHA class II-IV
3) Sinus rhythm
4) Heart rate ≥75 bpm

For criteria 1-3 the manner in which this is determined by the clinician should be well established and accepted. Regarding heart rate, NICE CG108 considers the measurement of heart rate as part of routine care. In SHIfT, heart rate was measured by a 12 lead ECG following five minutes rest. However an ECG is not necessary to accurately measure a patient's heart rate, indeed it is widely recognised that heart rate can be accurately measured by a clinician so long as the patient has rested for five minutes beforehand (Palatini 2006 (69). Nevertheless, to adopt a conservative approach in the cost-effectiveness model the cost of an ECG has been included (Section 6.5.1).

What proportion of the evidence base is for the dose(s) given in the SPC?

100%. The titration of ivabradine in the SHIfT trial is identical to the dosing requirements in the SPC.

6 Cost effectiveness

Published cost-effectiveness evaluations

Identification of studies

Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 9.10, appendix 10.

Three literature searches were carried out to identify economic evaluations of ivabradine in chronic heart failure. The first literature search was a targeted search undertaken in year 2010. The second subsequent literature search was a comprehensive systematic literature search carried out in 2011. The third literature search was an update search carried out in 2012.

These searches were designed to identify economic evaluations of other interventions in HF as it was not anticipated that any previous studies of ivabradine in HF would be identified. These additional economic studies were used to inform model methods and provide insight into potential comparators, key clinical endpoints and model structure for the ivabradine cost-effectiveness model.

The systematic reviews comprised of an electronic database search of MEDLINE, MEDLINE in Process, EMBASE, NHS-EED, EconLit, and Cochrane databases and the following Centre for Reviews and Dissemination (CRD) databases:

- Health Economic Evaluation Database
- Database of Abstracts of Reviews and Effects
- Health Technology Assessments Database

The following inclusion criteria were applied:

- Patients with heart failure
- Cost-effectiveness analyses (reporting both costs and effects with final outcomes LYs or QALYs gained)
- Fully published studies (conference abstracts excluded)
- English language only

The search inclusion criteria was initially limited to those studies published after the year 2000, but this was subsequently restricted to studies published in the previous five years (from 2006 onwards) to include only the most recent and relevant cost-effectiveness studies.

The search identified 20 relevant cost-effectiveness models, nine studies were identified using the search of the CRD databases, a further nine studies were identified using the full electronic database search and a final two studies were identified using the full electronic database update search. The full search strategies and the Prisma flow diagrams can be found in Appendix 9.10.

Description of identified studies

Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

No economic studies of ivabradine in HF were identified. A tabulation of the cost-effectiveness analyses of other interventions in HF has been documented in Appendix 9.10, it is noted that these studies were not directly relevant to the ivabradine decision problem but were used to inform the model structure for the current cost-effectiveness analysis.

The cost-effectiveness studies of other interventions in HF patients included nine studies of cardiac devices (Aidelsburger et al. 2008, Blomstrom et al. 2008, Caro et al. 2007, Heerey et al. 2006, Linde et al. 2010, Ribeiro et al. 2009, Stecker et al. 2006, Yao et al. 2007, Perez et al. 2011(70);(71);(72);(73);(74);(75);(76);(77);(78), five studies of ACE inhibitors (Boersma et al. 2006, Pradelli et al. 2009, Taylor et al, 2009, Colombo et al. 2008, McMurray et al. 2006 (11;13-15;79)), three studies of aldosterone therapy (McKenna et al.2010, Pourvourville et al. 2008, Szucs et al. 2006 (10;80;81),one study of beta-blockade (Yao et al. 2008 (82)), one study of amiodarone (Mark et al. 2006, (17)) and one study of statins (Rosen et al. 2010(12)). The model methods of studies in pharmaceutical interventions (11/20) were considered most relevant to the ivabradine cost-effectiveness model and have been discussed further below and are summarised in Table 32.

Frameworks

The cost-effectiveness models for pharmaceutical interventions consisted of three Markov cohort analyses (McKenna et al, 2010, Taylor et al. 2009, Rosen et al. 2010, (10-12)), two patient level simulations (Yao et al. 2008, Pradelli et al. 2009 (79;82)) and six models where the model frameworks were not explicitly described and were believed to be a simple area under the curve models (or two-state Markov cohort models with health states alive and dead) (Boersma et al. 2006, Colombo et al. 2008, Mark et al. 2006, McMurray et al. 2006, Pourvourville et al. 2008, Szucs et al. 2006 (10;13-15;17;80;81).

Area under the curve models do not explicitly model transitions between states and the relationship between each endpoint is modelled to be independent (i.e. no formal

modelled association between endpoints). These models consequently offer the simplest model structure and appeared to have been adopted by the majority of cost-effectiveness studies of pharmaceutical interventions in HF. Markov cohort models estimate the proportion of patients in specific states over time but assume that transitions between states occur over a given time period using assigned transition probabilities. It is noted that a simple Markov Model with two health states (alive, dead) is synonymous with an area under the curve model with an overall survival endpoint. Patient level simulations model individual patients transitioning through health states over time. These models break the Markov property because prior event history can be 'remembered' for each modelled individual patient and are particularly useful for indications with time dependent transitions or a large number of conditional events, (83;84). A patient level simulation is computationally expensive and this type of model was not considered necessary for the ivabradine cost-effectiveness analysis. These models have not therefore been included in the discussions below, nor in Table 32, although these studies have been summarised in Section 9.10.

Comparators

The majority of time-to-event and Markov cohort studies (7/9) compared the intervention of interest to standard care therapy although Mark et al. 2006,(17) considered amiodarone *versus* an implantable ICD device. The reported definition of standard care varied, but typically patients were treated at least with ACE inhibitors, beta-blockers, aldosterone and diuretics, see Table 32.

Time horizon

The time horizon considered in the models ranged from within-trial to lifetime; 4/8 studies considered a lifetime time perspective, see Table 32.

Clinical endpoints

The area under the curve models considered a clinical endpoint of all-cause mortality (Boersma et al. 2006 Colombo et al. 2009, Mark et al. 2006, McMurray et al. 2006, Pourvourville et al. 2008(13-15;17;80)), an additional hospitalisation endpoint was included in these models to capture resource use. In four studies baseline event rates were estimated using data from the reference arm of a single clinical trial (Boersma et al. 2006, Mark et al. 2006, Pourvourville et al. 2008, Szucs et al. 2006 (13;17;80;81)), two studies applied data from three related RCTs (CHARM clinical study program, Colombo et al. 2008, McMurray et al. 2006(2; 6)).

The health states included in the three Markov cohort models included:

- Index hospitalisation, non-fatal CV event, fatal CV event, other mortality (McKenna, 2010 (10)).
- No complications (after first MI), post MI heart failure, post MI stroke, post MI subsequent MI, dead (Taylor, 2009(11)).

- Stable HF, single major event, two major events, minor events, (event specific) mortality 2010 (Rosen (12)).

Extrapolation

In both Markov Cohort studies baseline clinical event rates were estimated from RCT data extrapolated to lifetime estimates using parametric survival analysis (McKenna et al. 2010, Taylor et al. 2009 (10;11)). In two studies Pourvourville et al. 2008 (80) and Szucs et al. 2006 (81), RCT data were extrapolated to lifetime estimates using population epidemiological data. The methods used to extrapolate data in the study by Mark et al. 2006 (17) were unclear although the description provided by the author has been detailed in Table 32.

Treatment efficacy

In all studies the treatment effect was estimated using either Kaplan Meier data or a hazard ratio and applied to the baseline risk. The methods used to extrapolate the hazard ratios beyond the observed trial periods and treatment duration was poorly reported, see Table 32.

Health Related Quality of Life (HRQL)

Two studies considered HRQL (Mark et al. 2006, McKenna et al. (10;17)) applied HRQL data. Only one study used data collected from an RCT (Mark et al. 2006). In this study patient utility was estimated using a regression model constructed to predict the covariate adjusted utilities, based on the recorded time trade off (TTO) data. The study by McKenna et al. 2010 used a large previously published study which reported EQ-5D data by NYHA class (Gohler et al. 2009(85)). In both studies population utility values were downward adjusted to take into account a utility loss associated with heart failure and other CV adverse events.

Resource use

The modelled resource use included study drug use; drug costs were reported to reflect trial doses and with recognised national pricing data used to determine unit costs. Hospitalisations were considered in all studies, events were costed using two primary methods - cost per DRG event (priced using National DRG reference costs) or cost per diem (priced using the estimated length of stay for each patient, estimated from trial data, two studies reported costs by ward type (McMurray, 2006, Colombo, 2008(1;2)), see Appendix 9.10.

Other modelled resource use included background management of heart failure, management costs post CV events, physician visits, outpatient procedures, diagnostic tests and nursing home care, see Appendix 9.10.

Table 32 Summary of model methods cost-effectiveness studies of pharmaceutical interventions in HF

Author, year Country	Model framework	Time horizon	Population	Data source clinical evidence	Intervention and comparators	Baseline risk	Treatment effect
1.Boersma, 2006(13) Dutch health care perspective	Time to event	Within-trial	Patients with heart failure (NYHA II -IV) and on stable heart regimen of heart failure medication.	Val-HEFT Valsartan Heart Failure Trial	Valsartan plus standard care *versus* standard care alone **Definition of standard care** Diuretics, digitalis, statins, anticoagulants, ACE inhibitors, beta-blockers, nitrates, calcium channel blockers and aspirin.	Model endpoints: All-cause mortality and composite combined mortality and morbidity. Within-trial estimates taken from standard care arm of VAL-HEFT (mean follow up 23 months).	Within-trial estimates taken VAL-HEFT
2. Colombo, 2008(14) Italian health service (IHS)	Time to event	Within-trial	Patients with heart failure (NYHA II - IV) and left ventricular ejection fraction (3 subgroups examined in separate trials LVEF <40% not receiving an ACE inhibitor, LVEF<40% receiving an ACE inhibitor, LVEF >40%)	CHARM trial program Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity	Candesartan plus standard care vs. placebo + standard care **Definition of standard care** Digitalis glycosides, diuretics, calcium channel blockers, vasodilators, anti-arrhythmic drugs, ACE inhibitors, angiotensin II receptor blockers, lipid lowering agents and anticoagulants	Clinical endpoints: All-cause mortality. Standard care all-cause mortality estimated from CHARM (overall CHARM program) and composite CV mortality or hospitalisation for worsening heart failure (each individual trial)	The hazard ratios for all-cause mortality were estimated from CHARM overall. The hazard ratios for CV mortality and hospitalisation were estimated from each trial individually.

Author, year Country	Model framework	Time horizon	Population	Data source clinical evidence	Intervention and comparators	Baseline risk	Treatment effect
3.Mark, 2006(17) US health care provider	Time to event	Lifetime	Patients aged>18 with NHYA class II, III chronic stable heart failure and life ventricular ejection fraction <35%.	SCH-HEFT (Sudden Cardiac Death in Heart Failure Trial)	Amiodarone, placebo or implantable ICD **Definition of standard care** N/R	Clinical endpoint: all-cause mortality. The model was populated using trial data from SCH-HeFT (median follow up 45.5 months). Extrapolation of SCH-HeFT survival data was performed by modelling the hazard rate as a function of a patient's age rather than time in the model 'age based' model. Analysis of SCH-HeFT data showed that the treatment effect varied after 1.5 years of follow up. Two models were developed. Model 1: The initial 1.5. Year survival model was modelled using a Cox regression model. Model 2: The survival post 1.5 years was based on Cox regression model with left-truncated and right censored data to model the hazard of death as a function of age conditional on surviving 1.5 years and adjusted for the same covariates as model 1. The author states using the laws of conditional probabilities these 2 models were linked together to obtained a covariate specific lifetime survival prediction for each patient. The individual survival predictions were averaged together over all patients in each treatment group to produce mean predicted survival estimates for each treatment group.	The effect of treatment was modelled as a hazard ratio as a function of age and was assumed to remain constant over time.

Author, year Country	Model framework	Time horizon	Population	Data source clinical evidence	Intervention and comparators	Baseline risk	Treatment effect
4.McKenna, 2010(10) UK NHS and PSS	State transition model - Markov cohort model	Lifetime	Patients with post-MI heart failure	EPHESUS Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study	Spironolactone + standard care, eplerenone + standard care vs. standard care **Definition of standard care** Aldosterone antagonists	Clinical endpoints were time to death from CV events, death from any cause (all-cause mortality). Baseline event rates for CV death in the short term model were based on the first 3 month data observed in the EPHESUS RCT. Parametric Weibull regressions were fitted from Kaplan Meier data from EPHESUS to estimate monthly transition probabilities for time to death. The baseline CV death event rates for the long term model were obtained from the linked Scottish Morbidity Record (SMR) which records all hospitalisations and subsequent deaths in Scotland. Using probability matching IPD analysis by diagnosis code can be performed. SMR data was obtained on individuals with a first discharge from hospital between 1993 and 2003 with a principal diagnosis of heart failure and no previous diagnosis for heart failure in the 5 years prior to the index admission. For individuals with an index event, data was collected for subsequent major events (MI, stroke, angina, other HF events) to estimate the probability of a subsequent major event in patients with a prior MI. Non-CV mortality was estimated using UK population life tables (with cardiovascular deaths removed).	A Bayesian meta-analysis (indirect comparison) was performed to estimate the treatment effect for spironolactone and eplerenone to synthesize the network of evidence. The relative treatment effect for each therapy was applied to baseline event rates. Non-CV mortality was estimated from UK age/sex specific mortality rates.

Author, year Country	Model framework	Time horizon	Population	Data source clinical evidence	Intervention and comparators	Baseline risk	Treatment effect
5.McMurray 2006(15) Third party payer in France, Germany and UK (NHS)	Time to event	Within-trial	Patients with heart failure (NYHA II - IV) and left ventricular ejection fraction (3 subgroups examined in separate trials LVEF <40% not receiving an ACE inhibitor, LVEF<40% receiving an ACE inhibitor, LVEF >40%)	CHARM trial program Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity Three trial population subgroups in CHARM program. CHARM added (already treated with ACE inhibitor), CHARM alternative (not yet treated with ACE inhibitor), patients with LVEF >40 CHARM preserved.	Candesartan + standard care *versus* placebo + standard care. **Definition of standard care** Diuretic, digoxin, ACE inhibitor, beta-blocker and spirinoloctone	Clinical endpoints were time to death from CV events, death from any cause (all-cause mortality). Baseline event rates for CV death in the short term model were based on the first 3 month data observed in the EPHESUS RCT. Parametric Weibull regressions were fitted from Kaplan Meier data from EPHESUS to estimate monthly transition probabilities for time to death. The baseline CV death event rates for the long term model were obtained from the linked Scottish Morbidity Record (SMR) which records all hospitalisations and subsequent deaths in Scotland. Using probability matching IPD analysis by diagnosis code can be performed. SMR data was obtained on individuals with a first discharge from hospital between 1993 and 2003 with a principal diagnosis of heart failure and no previous diagnosis for heart failure in the 5 years prior to the index admission. For individuals with an index event, data was collected for subsequent major events (MI, stroke, angina, other HF events) to estimate the probability of a subsequent major event in patients with a prior MI. Non-CV mortality was estimated using UK population life tables (with cardiovascular deaths removed).	The hazard ratios for all-cause mortality were estimated from CHARM overall. The hazard ratios for CV mortality and hospitalisation were estimated from each trial individually.

Author, year Country	Model framework	Time horizon	Population	Data source clinical evidence	Intervention and comparators	Baseline risk	Treatment effect
6.Pourvourville, 2008(80) A partial societal perspective.	Time to event	Lifetime	Patients with heart failure NYHA class II-IV	EPHESUS Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study	Eplerenone plus standard care *versus* standard care **Definition of standard care** ACE inhibitors, angiotensin II receptor blockers, diuretics, beta-blockers, coronary reperfusion	Clinical endpoints: All-cause mortality (overall CHARM program) and composite CV mortality or hospitalisation for worsening heart failure (each individual trial)	Methods unclear although treatment efficacy estimated from EPHESUS trial data.
7. Rosen, 2010	State transition markov model	Lifetime	Patients with a history of both CHD and HF	Patient level data from Treating to New Targets(TNT) trial	Atorvastatin 80 mg/day (A80) *versus* Atorvastatin 10 mg/day (A10)	Clinical endpoint: event specific all-cause mortality Mortality estimates were derived from literature. A sensitivity analysis was also performed using, non-CVD and post-event mortality estimates from TNT trial.	Treatment effects/events rate were derived from the TNT trial and extrapolated
8.Taylor, 2009(11) UK NHS	State transition model - Markov cohort model	10 years	Post-MI patients with left ventricular systolic dysfunction, heart failure or both who are not suitable for ACE inhibitors.	VALIANT Valsartan Acute Myocardial Infarction	Valsartan *versus* placebo **Definition of standard care** N/R	Clinical endpoint: all-cause mortality. For placebo event rates were estimated from a meta-analysis of clinical trials (results pooled from AIRE, SAVE and TRACE trials). A relative risk of death for placebo *versus* valsartan was estimated by assuming that the relative ratio of ACE inhibitors *versus* placebo estimated from the meta-analysis was the same as the relative ratio of valsartan *versus* placebo.	Valsartan event rates were obtained from the VALIANT trial. Author reported that transition probabilities for 3 month cycles data were estimated by converting trial rates (over 24.7 months) using the formula P = 1- (1-P 24.7 months)^3/24.7 months. Methods to extrapolate to 10 years not reported. It was assumed that for the first cycle (3 months) patients were at a higher risk of subsequent events.

Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[1] or Philips et al. (2004)[2]. For a suggested format based on Drummond and Jefferson (1996), please see section 9.11, appendix 11.

No economic studies of ivabradine in HF were identified. A critical appraisal of other economic studies in HF has been undertaken using an adapted version of the Drummond checklist (86), see Appendix 9.10.

De novo analysis

Patients

What patient group(s) is (are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.4 and 5.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

SHIfT was a multicentre, randomised controlled trial conducted in HF patients with New York Heart Association class II, III or IV heart failure, in sinus rhythm and with left ventricular ejection fraction ≤35%. The study recruited patients with heart rate ≥70 bpm and showed a significant benefit with ivabradine on the primary composite endpoint of cardiovascular death or hospitalisation for worsening heart failure (HR 0.82, 95% CI 0.75-0.90). Hospitalisation for worsening heart failure was significantly reduced (HR 0.74 95% CI 0.66-0.83) but, despite a trend towards benefit, the reduction in cardiovascular death did not reach statistical significance (HR 0.91 95% CI 0.80-1.03). The trial publication identified that baseline heart rate modified the treatment effect of ivabradine. In order to find the heart rate threshold above which the total mortality benefit was clear, the CHMP asked the manufacturer to re-analyse the SHIfT data. The manufacturer subsequently identified that 75 bpm was a threshold of interest. In this cohort (n=4154) the effect of ivabradine on all-cause mortality (HR 0.83 95% CI 0.72-0.96), cardiovascular mortality (HR 0.83 95% CI 0.71-0.97) and hospitalisation for worsening heart failure (HR 0.70 95% CI 0.61-0.80) was clearly established. On this basis the licensed indication was granted in patients with a baseline heart rate ≥75 bpm, instead of ≥70 bpm:

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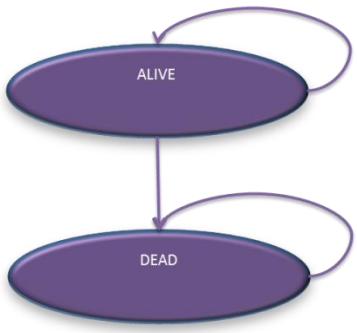
[1] Drummond MF, Jefferson TO (1996). Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.

[2] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

for use *in chronic heart failure NYHA II to IV class with systolic dysfunction, in patients in sinus rhythm and whose heart rate is ≥75 bpm, in combination with standard therapy including beta-blocker therapy, or when beta-blocker therapy is contraindicated or not tolerated*.

The modelled population is therefore consistent with the European licensed indication. The base case model considers ivabradine in combination with standard care, including beta-blocker therapy, for a subgroup of the SHIfT cohort with baseline heart rate ≥75 bpm. Other characteristics of the SHIfT trial population matched the licence (HF patients NYHA class II to IV with systolic dysfunction, in sinus rhythm).

Please provide a diagrammatical representation of the model you have chosen.



Please justify the chosen structure in line with the clinical pathway of care identified in section 2.4.

NICE CG108 states that the aim of medical therapy are (see Section 5.10.3) (7):

1. Improve the patients morbidity; by reducing symptoms, improving exercise tolerance, reducing hospitalisation and improving quality of life
2. Improving prognosis through the reduction of all-cause mortality or heart-failure related mortality

Consistent with these treatment aims the model has been constructed to take into account

- Mortality
- Hospitalisation
- Quality of life/ Symptoms

The most commonly used classification of severity of HF symptoms is the NYHA classification of functional capacity. This system assigns patients to one of four functional classes depending on patient symptoms. It is anticipated that patient QoL is likely to deteriorate as symptoms progress and patients are classified into higher NYHA classes.

A two-state Markov cohort model has been employed (health states alive, dead); this model structure was chosen since it offers a simple, flexible framework and is consistent with previous approaches taken in cost-effectiveness studies of pharmaceutical interventions in HF (see Section 6.1). The patients who remain alive in the model are distributed according to NYHA class (I, II, III and IV) in order to capture differences in quality of life (QoL) associated with the severity of heart failure. The distribution of patients in each NYHA class has been modelled to change over time and treatment type based on clinical evidence from SHIfT. Whilst the distribution of patients in each NYHA class has been captured within the ivabradine model, the proportion of surviving patients in each NYHA class are simply estimated across each time interval, and NYHA class is not modelled as a separate health state *per se.*

The model captures the rate of hospitalisations across treatment groups to take into account associated resource use and transient reductions in QoL. However, as with NYHA class, hospitalisations are not formally considered in a separate health state. Patients are modelled to receive concomitant therapies such as ACE inhibitors, beta-blockers and diuretics consistent with the clinical care pathway described in the treatment algorithm from NICE CG108, see Section 2.4.

Please define what the health states in the model are meant to capture.

The 'Alive' health state is designed to capture QoL and resource use of all patients who remain alive in the model. QoL has been modelled using patient baseline characteristics, the severity of disease over time (NYHA class), the occurrence of serious adverse events (hospitalisations) and treatment group. The resource use modelled includes standard care medication costs, serious adverse events (heart failure hospitalisations, other CV hospitalisations and non-CV hospitalisations) and general heart failure follow-up care (outpatient visits, GP visits, diagnostic tests).

The mortality endpoint captures all-cause death (heart failure death, other CV death and non-CV death).

How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

Heart failure is a complex clinical syndrome, a structural or functional cardiac disorder characterised by the inability of the heart to pump enough blood to meet the body's demands. The clinical syndrome is linked to specific symptoms (dyspnoea and fatigue) and signs (fluid retention potentially resulting in peripheral oedema and/or pulmonary congestion). Heart failure impairs QoL and can result in hospitalisation and death (Section 2.1).

The ivabradine economic analysis captures the main clinical consequences and underlying disease progression of HF by modelling mortality, heart failure severity (NYHA distribution), serious adverse events (hospitalisations) and patient QoL. The underlying risk of these key events is assumed to be captured by the standard care arm of the SHIfT trial, whilst the treatment effect of ivabradine therapy has been estimated relative to standard care alone.

The regression equations developed for mortality, hospitalisation and QoL have been based on data from the entire SHIfT cohort (patients with a baseline heart rate ≥70 bpm, n=6505) and predict outcomes according to the treatment received and patients' baseline characteristics, including baseline heart rate. The regression equations also consider variables that could potentially alter the relative treatment effect of ivabradine *versus* standard care alone (treatment effect interactions). The regression equations are consequently capable of predicting outcomes and cost-effectiveness estimates for the licensed population of patients with heart rate ≥75 bpm.

The regression equations were based on the full SHIfT population (patients with a heart rate ≥70 bpm (n=6505), in preference to developing risk equations based solely on data from patients with a baseline heart rate ≥75 bpm (n=4154). This was to avoid breaking randomisation and reducing the predictive power of the risk equations due to the smaller sample size. However, a second cost-effectiveness model was developed using only data from patients with a heart rate ≥75 bpm to demonstrate the robustness of cost-effectiveness results to other model approaches; an outline of the methods and results from this second model has been reported in the section on subgroup analyses (Section 6.9).

NYHA distribution was included in the current model because NYHA class was found to be a significant predictor of patient QoL in previous QoL studies in heart failure. Goher et al, 2009 (85) and SHIfT indicated that the distribution of patients in each NYHA class differed between treatment arms. In SHIfT, subjects treated with ivabradine plus standard care were distributed into milder NYHA classes (NYHA class I and II) compared to standard care therapy alone.

Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Table 33: Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	Lifetime (when 99% of the cohort have died)	Ivabradine has been associated with a reduction in mortality. A lifetime time horizon has consequently been used to capture the full benefit of therapy.	NICE, 2008 Swedberg, 2010
Cycle length	Monthly	The shortest cycle length considered practical given the modelled lifetime time horizon	NICE, 2008(9)
Half-cycle correction	Included	On-going costs have been half cycle corrected	NICE, 2008(9)
Were health effects measured in QALYs; if not, what was used?	Yes health effects were measured in QALYs	Ivabradine is expected to improve patient QoL and to quality adjust the life years gained due to the reduction in mortality.	NICE, 2008(9)
Discount rates for utilities and costs	3.5% discount used for costs and effects	Consistent with the NICE reference case	NICE, 2008(9)
Perspective (NHS/PSS)	NHS/PSS	Consistent with the NICE reference case	NICE, 2008(9)
NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years			

Technology

Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

The cost-effectiveness model considers ivabradine as per the current European marketing authorisation. The model estimates the cost-effectiveness of ivabradine in a HF population (NYHA class II-IV with systolic dysfunction, in patients in sinus

rhythm and whose heart rate is ≥75 bpm) in combination with standard therapy including beta-blockade.

Standard care therapy has been modelled according to SHIfT trial patterns. SHIfT data were employed because the use of NICE recommended heart failure medications in the trial, including beta-blockade, appeared greater than current UK treatment patterns, as discussed in Sections 6.2.1 and 5.10.4. SHIfT required that patients receive optimal heart failure medication prior to study commencement and consequently every effort was made by investigators to up-titrate patients to the maximum tolerated beta-blocker dose; documented reasons for lack of up-titration were consistent with well recognised clinical issues and contraindications to therapy (8). Despite all best efforts only 26% of patients in SHIFT received the target dose of beta-blocker which generally exceeded doses seen in audits of UK clinical practice (see section 5.10.4).

It could be argued that ivabradine efficacy may diminish with increased beta-blocker use. In reality, the SHIfT trial did not show a declining treatment effect once differences in baseline heart rate were taken into account (see Section 5.5.). However, in order to provide reassurance on the potential cost-effectiveness of ivabradine given varying doses of beta-blockers, two sensitivity analyses were developed in the economic model. These analyses used the SHIfT risk equations to predict outcomes for a UK population treated with different levels of beta-blockade [at least half target dose therapy (but less than target dose); and at least target dose therapy] and were designed to demonstrate the robustness of results to alternative assumptions on beta-blocker use, see Section 6.9.1.

Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators.

No treatment continuation rules or response criteria have been applied. Heart failure is a chronic, progressive disease and ivabradine plus standard care therapy is therefore assumed to commence in patients with heart rate ≥75 bpm and continue over a patient's lifetime. In the base case model 99% of patients had died by 12.4 years.

Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 5). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

Please demonstrate how the clinical data were implemented into the model.

Overview

SHIfT was considered the best source of data to model the underlying risk of clinical events in a chronic heart failure population (CV death, all-cause hospitalisation and the distribution of patients by NYHA class). The underlying risk of these events for the 'within-trial' period has been based on the standard care arm of the SHIfT study. It is noted that the primary composite endpoint used in the clinical trial (CV death or hospitalisation for worsening heart failure) was not used for the economic analysis since this did not break down survival and resource use to permit separate estimation of costs and outcomes.

Heart failure is a chronic progressive disease requiring lifelong therapy. The costs and benefits of ivabradine in HF are consequently expected to extend beyond the observed SHIfT trial period (median follow-up period of 23 months). NICE guidelines recommend that a lifetime time horizon should be considered for interventions that affect overall survival (9), consequently, the ivabradine cost-effectiveness model has been designed to capture lifetime costs and effects. However at study close only 17% of patients had died in SHIfT, thus costs and outcomes for the surviving patients in the post-study period must be inferred from observed data or estimated independently from external literature.

In the base case analysis a parametric survival model has been used to predict CV mortality for the extrapolated, post-trial period. This approach is similar to the approaches taken in two previous cost-effectiveness models of pharmaceutical interventions in HF (McKenna et al. 2010, Taylor et al. 2009 (10;11). A parametric survival model is a type of regression model that fits a mathematical function to observed survival data (time to event data) and allows survival estimates to be predicted (extrapolated) beyond observed data to predict expected mean survival. A parametric model may take into account variables which predict differences in the underlying mortality risk (i.e. patient characteristics, such as age or gender, which affect survival outcomes). The inclusion of these variables permits exploration of the mortality risk for different patient subgroups. Parametric models are, of course, characterised by the parametric distribution used, with different distributions generating distinct predictions of mean survival. In the ivabradine economic model external data have been used in sensitivity analysis.

The methods used to model mortality, hospitalisation and NYHA class are described further below.

Mortality

The underlying risk of non-CV death

The underlying risk of non-CV death has been based on age and sex adjusted UK National life table data with CV mortality removed (87). This was selected in preference to estimates of non-CV death derived from SHIfT since it provides a larger, UK-specific data source.

Underlying risk of CV mortality, within-trial period

SHIfT was considered the best source of data to model the underlying risk of CV death. The CV mortality endpoint in SHIfT included heart failure and other non-heart failure CV death. In the economic model, CV mortality has been modelled consistently with the SHIfT CV mortality endpoint, with the underlying risk of CV death modelled from the standard care arm of the study. It is noted that the model also captures heart failure deaths independently as a separate endpoint. The reason for modelling heart failure deaths and CV deaths independently is to allow sensitivity analysis of the ivabradine treatment effect on a heart failure mortality-only endpoint. However, the base case analysis model uses the total CV mortality endpoint and it is the parametric regression models developed for CV mortality that have been reported in detail below.

The risk of CV death for the within-trial period has been estimated using a parametric survival regression model based on the full SHIfT cohort (all patients ≥70 bpm). However, differences in patient baseline heart rate have been taken into account to allow results to be predicted for the licensed population with baseline heart rate ≥75 bpm.

It is recognised that in general the most reliable estimate of the patient survival in the 'within-trial' period may be obtained from the observed data, a parametric regression has been used in this study to:

- Provide the relative treatment effect of ivabradine and permit specific exploration of the interaction between treatment and baseline heart rate evidenced in SHIfT.
- Provide cost-effectiveness results relevant to the licensed indication (patients with a baseline heart rate ≥75 bpm).
- Provide an estimate of the natural history of HF (underlying baseline risk of mortality without ivabradine) and explore differences in the underlying baseline mortality risk due to patient heterogeneity and to permit subgroup analyses.
- Extrapolate SHIfT estimates beyond the SHIfT study period

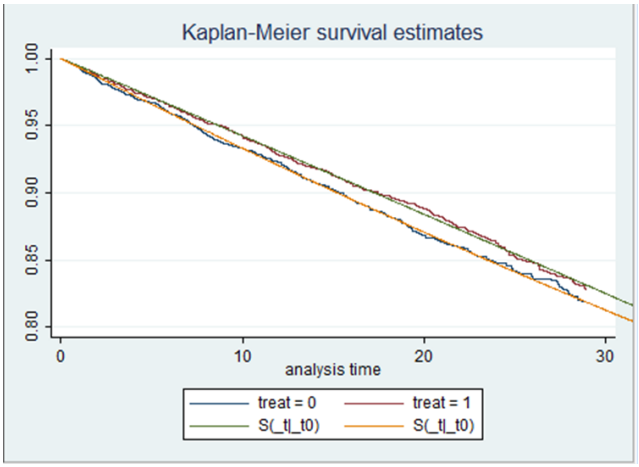
Six alternative parametric distributions were fitted to SHIfT data (exponential, Weibull, log-logistic, lognormal, Gompertz, gamma). The Gompertz distribution was considered to be the most appropriate distribution based on AIC and BIC criteria (see Table 34), a visual plot of the Kaplan Meier data *versus* the predicted curves (see

Figure 11) and the plausibility of the tail of the survival curve (88). The Gompertz model provided the most conservative estimate of patient long term survival and was consequently considered to offer a more plausible prediction than other distributions. Survival models based on the exponential and Weibull parametric distributions, the next best fitting distributions, and Kaplan Meier data, were included in the model as part of the sensitivity analyses.

Table 34 CV mortality: AIC and BIC statistics

Model	Obs	ll(null)	ll(model)	df	AIC	BIC
exponential	6505	-3630.34	-3370.16	26	6792.32	6968.61
weibull	6505	-3630.31	-3369.53	27	6793.07	6976.14
gompertz	6505	-3629.96	-3366.90	27	6787.79	6970.86
lognormal	6505	-3684.60	-3440.48	27	6934.96	7118.03
loglogistic	6505	-3632.42	-3373.61	27	6801.23	6984.30
gamma	6505	-3628.90	-3368.94	28	6793.87	6983.72

Figure 11 CV mortality: Kaplan Meier *versus* Parametric survival model (Gompertz distribution)



The CV mortality risk equation has been estimated adjusting for a series of baseline patient characteristics. The purpose of including these covariates was to generate different estimates of mortality, depending on the baseline characteristics of the population (e.g. age, sex, NYHA class). It is important to capture differences in population risk since a change in the absolute baseline risk for a given patient subgroup will generate different ICER values, even if the relative treatment effect of ivabradine is assumed to be constant for all types of patient.

The covariates considered for the analysis were derived from the SHIfT clinical study protocol, a previous HF risk equation published by Levy et al. 2006 (89), as well as clinical advice, and included:

- Baseline socio demographic and clinical characteristics (age, sex, NYHA class, HF duration, LVEF, smoking status, alcohol use, diabetes, race, BMI)
- Baseline use of heart failure medications (beta-blockers, ACE inhibitors,

aldosterone antagonists, loop diuretics (dose/kg/day), angiotensin receptor blocker, cardiac glycosides, allopurinol)

- Prior use of other cardiac therapies: cardiac resynchronisation, implantable cardiac device (ICD), conventional bradycardia-indicated pacemaker
- Medical history: prior event (myocardial infarction (MI), stroke, coronary artery disease (CAD), atrial fibrillation, renal disease, hypertension)
- Patient biological characteristics (serum sodium, potassium, creatinine clearance, cholesterol systolic blood pressure).

The continuous variables considered in the model were reviewed to confirm whether they showed evidence of a linear relationship with the dependent variable and a series of tests were undertaken to ascertain the best functional form. Initially a plot of the log coefficients was undertaken using quartile and decile cut-points to examine the linearity assumption; a plot was also created showing the series of survival curves generated using these cut points. We tested linear, quadratic and fractional polynomial functions in addition to other standard transformations including centering on the mean. In the final regression five continuous variables were centred on the mean (age, body mass index, heart rate, systolic blood pressure and sodium) and two continuous variables were ultimately treated as categorical variables (LVEF and HF duration), both categorised using quartile cut-points).

The relationship between baseline heart rate and mortality was given particular consideration. Patients were divided into baseline heart rate strata (70-74, 75-79, 80-84, ≥85 bpm), see Figure 12. The log rank test for trend across these strata indicated very strong evidence of an ordered trend (chi-square 71.65, $p<0.001$). A plot of the log coefficients for each stratum, against log time also indicated evidence of a fundamentally linear relationship, see Figure 13. A log likelihood test indicated that the risk equation for CV mortality achieved a better statistical fit of the observed data if heart rate was treated as a continuous variable in preference to a categorised variable (categories considered were based on heart rate strata as well as other potential cut-points: binary, quartile, quintile and decile cutpoints). In order to maximize the information available from the heart rate variable and, given evidence of a fundamentally linear relationship between heart rate and CV mortality, heart rate was considered as a continuous variable in the SHIfT analysis.

However, it is noted there was some evidence of a reduction in the association between heart rate and CV mortality in patients with a baseline heart rate below 75bpm, see Figure 13. The risk equation developed in the base case economic analysis has been developed using data from the entire SHIfT population (including patients with a heart rate 70-74bpm). The use of heart rate as a strictly linear, continuous estimate consequently resulted in a more conservative prediction of the increase in CV mortality associated with an increasing heart rate in the population with a heart rate ≥ 75bpm and a more conservative hazard ratio for ivabradine than observed data (due to the treatment interaction between ivabradine and heart rate). This problem could be partially solved with the use of cubic transformation of the

heart rate variable for heart rate in the CV mortality risk equation. The resulting risk equation provided a better statistical fit of the data and generated a hazard for ivabradine on CV mortality which more closely reflected observed estimates in patients with a heart rate ≥75bpm. However, this model was non-intuitive and difficult to interpret due to the cubic functional form and the associated interaction terms.

In the base case model the relationship between heart rate and CV mortality has been modeled simply and has been considered to be linear. This approach was taken to ease interpretation of the final regression equation and since this method yielded a hazard ratio that was more conservative and generated a less favourable ICER for ivabradine for the base case analysis. However, a model in which the heart rate covariate was transformed using a cubic functional form for the CV mortality risk equation has been implemented in a sensitivity analysis. The results of this model have been reported in Section 6.9.

Figure 12 Plot of survival curves by heart rate strata (CV mortality patients ≥70 bpm)

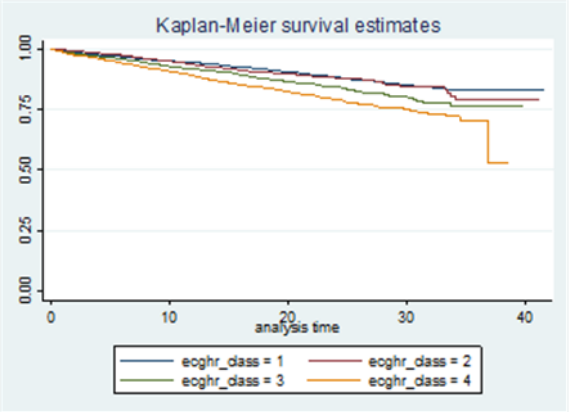
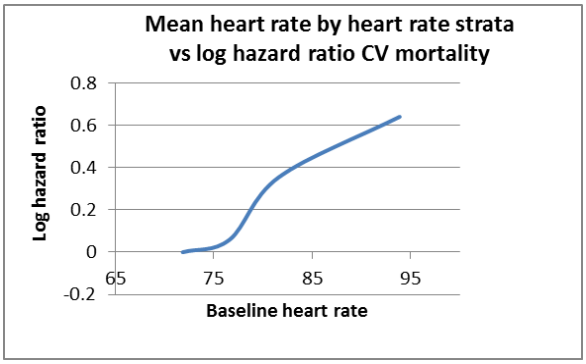


Figure 13 Plot of mean baseline heart rate against log hazard ratio (CV mortality patients ≥70 bpm)



All binary and categorical variables were reviewed to confirm whether the existing categorisations were satisfactory and to ensure there were sufficient patients in each group to permit appropriate analysis. The variable for beta-blocker use was re-grouped into four discrete categories to capture any variation in baseline risk for patients using different levels of beta-blockade:

- No beta-blocker use
- Beta blockade < half target dose
- Beta blockade ≥ half target dose < target dose
- Beta blockade ≥ target dose

The variable for tobacco use was re-grouped into 'yes/stopped' *versus* 'no' due to overlapping Kaplan Meier plots for 'yes/stopped'; other variables included in the final regression equations remained as per their original designation in SHIfT. It is noted that insufficient patients used cardiac devices (~3%) in SHIfT at baseline to include this as a potential covariate in the final analysis, whilst a large proportion (~90%) of patients used ace inhibitors/ angiotensin receptor blockers. The latter variable was retained in the final analysis.

An initial set of covariates for the HF and CV mortality risk equation were identified using backwards stepwise elimination and cross validated using forwards stepwise selection (using a p-value of <0.1). The correlation matrix for the initial model produced by the stepwise elimination process was reviewed to identify potential correlation between variables. Those variables which demonstrated evidence of possible correlation were further analysed for evidence of collinearity; the fit of the model was tested with and without the variable of interest using a loglikelihood test, and the direction and magnitude of effect for all other covariates were reviewed to determine whether the variable should be retained. If variables demonstrated evidence of collinearity, the variable which showed the strongest relationship with the outcome variable and greatest face validity was retained in the final regression model and other collinear variables were removed. The variables which showed evidence of a borderline association with CV mortality (p0.05<0.10) were tested for potential inclusion one at a time. The regression model was fitted with and without the variable of interest and the direction and magnitude of effect of all variables, in particular treatment, was reviewed alongside the log likelihood estimate. If the variable significantly improved the fit of model, or improved the estimate of effect for other relevant covariates, the variable was retained. All covariates included in the final HF and CV regression models were reviewed by a clinical expert to ascertain whether any spurious or unexpected results had been obtained and whether the direction and magnitude of effect for included variables was consistent with clinical expectations based on a knowledge of the published literature and clinical practice.

The final CV regression model is documented in Table 37 (without interaction terms) and Table 38 (with interaction terms included). It is noted that the direction of effect for some heart failure medications (e.g. aldosterone HR 1.28, 95% CI 1.11-1.48, p<0.001) was not in the direction expected (medication use was associated with

poorer outcomes). However, given that aldosterone was not recommended in a HF indication at the time of the SHIfT study it is likely that patients taking these medications were of poorer health than the average SHIfT patient, and this effect, rather than the true effect of aldosterone use, was captured. Whilst it was recognised that the variables included in the regression model may not be capturing the true effect of the medication in question, they were retained, since they were strong predictors of the outcome of interest and significantly improved the overall model fit.

Diagnostics

Cox-Snell residuals were evaluated for all selected variables included in the final adjusted regression model to check the overall model goodness of fit. The proportional hazards (PH) assumption for all included variables was tested using a plot of the Schoenfeld residuals and a test of the PH assumption, neither indicated deviation from the PH assumption for included variables. The predictive power of the final model was also tested using the Harrell's concordance measure. The final CV mortality regression model showed concordance of >70% (95% confidence interval (CI) 0.68-0.72) and was consequently considered to be good predictor of mortality (Harrell 2001(90)).

Ivabradine treatment effect on CV mortality: overview

The treatment effect on CV mortality for ivabradine plus standard care has been estimated by applying a relative treatment effect (hazard ratio) estimated from the parametric model to the underlying mortality risk estimated for the standard care group. It has been assumed that the treatment effect of ivabradine continues in the post-trial period and is equivalent to that demonstrated within the SHIfT study, see Section 6.3.7.

In further support of this assumption, the heart rate lowering effect of ivabradine has been shown to be maintained over the SHIfT trial follow-up period (median 23 months), and also over a seven-year extension period of studies of ivabradine in patients with angina (see Section 5.10.4). In sensitivity analysis alternative scenarios were considered for the treatment effect of ivabradine in the post-trial period, see Section 6.6.

The risk equations used to populate the economic model have been developed using the full patient cohort (n=6505, patients with a baseline heart rate >70 bpm). The use of the entire SHIfT cohort, rather than splitting out the data for the sub-population with a baseline heart rate ≥75bpm, was deemed appropriate to avoid breaking randomisation and to provide greater power to the analysis.

Ivabradine treatment effect on CV mortality: clinical endpoint

In the base case economic analysis ivabradine is modelled to reduce CV mortality. The ivabradine treatment effect has been modelled on CV mortality rather than HF mortality alone for the following reasons:

1. Ivabradine demonstrated a statistically significant effect on CV mortality in the licensed population (patients with heart rate ≥75 bpm)
2. Ivabradine is already licensed for other CV indications and has the potential to affect other CV mortality endpoints
3. Heart failure death is implicitly captured within the CV mortality endpoint.

In a scenario analysis the treatment effect of ivabradine has been modelled only on HF mortality with other CV death modelled as equivalent to standard care (i.e. the probability of non-heart failure CV death for ivabradine was modelled to be equivalent to standard care). This scenario analysis was undertaken to demonstrate robustness of results to other model assumptions.

Non-CV mortality was modelled to be equivalent between ivabradine plus standard care and standard care alone in all scenarios and no treatment effect has been applied for this endpoint.

Ivabradine treatment effect on CV mortality: treatment effect modification

The variables reviewed for treatment effect modification (treatment interaction terms) reflected those covariates with prior clinical evidence of potential modification of the treatment effect (age, ischaemia, beta-blocker use, heart rate (8)). The potential interaction of treatment with other baseline covariates and between baseline covariates was not considered to prevent the risk of spurious results.

The simple Cox regression analyses undertaken for the clinical section of this submission, which included terms for treatment, heart rate and the treatment interaction term (heart rate* treatment), indicated that the ivabradine treatment effect was significantly modified by baseline heart rate, (see Section 5.5). This result was reflected in the full parametric adjusted model produced for the economic model which included treatment, heart rate and other baseline covariates. The full parametric regression equations developed for the economic model, consistent with analyses undertaken for the clinical section of this submission, also suggested that after taking baseline heart rate into account there was no significant evidence that the treatment effect of ivabradine diminished with increased beta-blocker use. These equations also indicated that the primary influence on ivabradine efficacy was patient baseline heart rate.

Ivabradine treatment effect on CV mortality: Proportional Hazards (PH) assumption

It is assumed that the proportional hazards assumption is upheld for CV mortality. The PH assumption implies that the relative treatment effect of ivabradine remains consistent over the modelled time horizon and that the treatment effect of ivabradine would not be expected to change over time. The parametric distributions applied in the current model are all based on a PH assumption. The use of a PH assumption was tested using a plot of the Schoenfeld residuals and a test of the PH assumption in addition to a graphical assessment of PH assumption by plotting log time with log-log survival probability. These tests showed no evidence of violation of the PH assumption. Whilst there was some evidence of poorer correspondence of the predicted exponential curve *versus* the observed Kaplan Meier estimates after 26 months, the number at risk in SHIfT reduced from ~50% at 22 months to ~20% at 29 months. It is not clear, therefore, whether the slight reduction in the observed hazard ratio post 26 months reflects censoring, or a genuine reduction in the treatment benefit. A scenario analysis has been undertaken to test the robustness of the model results to other assumptions. In this analysis the hazard ratio of ivabradine has been modelled to return to one linearly over a specified time horizon (range considered 5-10 years).

Table 35 CV mortality: Gompertz parametric regression model ≥70 bpm (treatment covariate only)

	HR	Coefficient	SE	p-value	95% LCI	95% UCI
Treatment	0.9086	-0.0958	0.0653	0.1420	-0.2238	0.0322
Constant		-5.0165	0.0678	0.0000	-5.1493	-4.8837
Gamma		0.0035	0.0040	0.3810	-0.0043	0.0114

Table 36 CV mortality: Gompertz parametric regression model ≥75 bpm (treatment covariate only)

	HR	Coefficient	SE	p-value	95% LCI	95% UCI
Treatment	0.8359	-0.1793	0.0777	0.0210	-0.3315	-0.0270
Constant		-4.8411	0.0792	0.0000	-4.9964	-4.6858
Gamma		0.0026	0.0048	0.5870	-0.0068	0.0120

Table 37 CV mortality: Final Gompertz parametric regression model 70 bpm (treatment covariates and baseline characteristics without interaction

Description	HR	Coefficient	SE	p-value	95% LCI	95% UCI
Treatment	0.9198	-0.0836	0.0655	0.202	-0.2121	0.0449
Female	0.6891	-0.3724	0.0849	0	-0.5388	-0.206
Aldosterone	1.2842	0.2502	0.0743	0.001	0.1046	0.3957
Digitalis use	1.3239	0.2806	0.0747	0	0.1343	0.4269
Loop diuretic (dose/kg/day)	1.1222	0.1153	0.0299	0	0.0567	0.1738
Lipid medications	0.7932	-0.2317	0.0671	0.001	-0.3632	-0.1001
Systolic BP *	0.9902	-0.0099	0.0022	0	-0.0142	-0.0055
NYHA III (*vs* II)	1.303	0.2647	0.0705	0	0.1264	0.4029
NYHA III (*vs* II)	2.7582	1.0146	0.1648	0	0.6916	1.3375
HF duration ≥0.6<2 yrs *vs* <0.6 yrs	1.5155	0.4158	0.1074	0	0.2053	0.6263
HF duration ≥2<4.8 yrs *vs* <0.6 yrs	1.7417	0.5549	0.1066	0	0.346	0.7638
HF duration ≥4.8 yrs *vs* <0.6 yrs	1.9859	0.6861	0.1033	0	0.4836	0.8886
LVEF ≥26% <30% *vs* <26%	0.8625	-0.1479	0.0929	0.111	-0.33	0.0342
LVEF ≥30% <33% *vs* <26%	0.7122	-0.3394	0.0893	0	-0.5145	-0.1644
LVEF ≥33% *vs* <26%	0.5905	-0.5268	0.0921	0	-0.7073	-0.3462
Heart rate bpm*	1.0181	0.0179	0.0031	0	0.0118	0.024
Beta blocker use < half target dose (td)	0.9851	-0.0151	0.0988	0.879	-0.2086	0.1785
Beta blocker use ≥ half td< td	0.7147	-0.3359	0.1136	0.003	-0.5586	-0.1132
Beta blocker use ≥ td	0.6891	-0.3723	0.1214	0.002	-0.6103	-0.1343
Age (years)*	1.0204	0.0202	0.0032	0	0.0139	0.0264
Prior stroke	1.2779	0.2452	0.1056	0.02	0.0381	0.4522
Sodium*	0.9815	-0.0187	0.0093	0.046	-0.037	-0.0004
Potassium	1.2063	0.1875	0.0807	0.02	0.0293	0.3458
_cons	0.004	-5.5179	0.1612	0	-5.8338	-5.202
_gamma	1.0102	0.0101	0.004	0.012	0.0022	0.018

Footnotes: *LCI – lower confidence interval, UCI upper confidence interval, NYHA – New York Heart Association, LVEF – left ventricular ejection fraction, td – target dose*

**Variables centred on the mean*

Table 38 CV mortality: Final Gompertz parametric regression model 70 bpm (treatment covariates and baseline characteristics with interaction)

Description	HR	Coefficient	SE	p-value	95% LCI	95% UCI
Treatment	0.9423	-0.0594	0.0670	0.3750	-0.1907	0.0719
Female	0.6889	-0.3726	0.0849	0.0000	-0.5389	-0.2063
Aldosterone	1.2823	0.2486	0.0743	0.0010	0.1031	0.3942
Digitalis use	1.3225	0.2795	0.0747	0.0000	0.1332	0.4259
Loop diuretic (dose/kg/day)	1.1215	0.1147	0.0298	0.0000	0.0562	0.1731
Lipid medications	0.7946	-0.2299	0.0672	0.0010	-0.3616	-0.0983
Systolic BP *	0.9902	-0.0099	0.0022	0.0000	-0.0142	-0.0055
NYHA III (*vs* II)	1.3030	0.2647	0.0705	0.0000	0.1264	0.4029
NYHA III (*vs* II)	2.7614	1.0157	0.1648	0.0000	0.6928	1.3386
HF duration ≥0.6<2 yrs *vs* <0.6 yrs	1.5099	0.4120	0.1074	0.0000	0.2015	0.6225
HF duration ≥2<4.8 yrs *vs* <0.6 yrs	1.7334	0.5501	0.1066	0.0000	0.3412	0.7591
HF duration ≥4.8 yrs *vs* <0.6 yrs	1.9833	0.6848	0.1033	0.0000	0.4822	0.8873
LVEF ≥26% <30% *vs* <26%	0.8644	-0.1457	0.0929	0.1170	-0.3278	0.0364
LVEF ≥30% <33% *vs* <26%	0.7121	-0.3395	0.0893	0.0000	-0.5145	-0.1645
LVEF ≥33% *vs* <26%	0.5895	-0.5285	0.0921	0.0000	-0.7091	-0.3480
Heart rate bpm*	1.0229	0.0226	0.0040	0.0000	0.0148	0.0305
Beta blocker use < half target dose (td)	0.9908	-0.0092	0.0989	0.9260	-0.2031	0.1846
Beta blocker use ≥ half td< td	0.7148	-0.3358	0.1137	0.0030	-0.5586	-0.1130
Beta blocker use ≥ td	0.6918	-0.3684	0.1215	0.0020	-0.6066	-0.1302
Age (years)*	1.0201	0.0199	0.0032	0.0000	0.0137	0.0262
Prior stroke	1.2753	0.2432	0.1057	0.0210	0.0361	0.4503
Sodium*	0.9808	-0.0194	0.0094	0.0390	-0.0377	-0.0010
Potassium	1.2038	0.1855	0.0807	0.0220	0.0272	0.3437
Treat*heart rate	0.9893	-0.0108	0.0060	0.0710	-0.0225	0.0009
_cons	0.0040	-5.5309	0.1615	0.0000	-5.8476	-5.2143
_gamma	1.0102	0.0101	0.0040	0.0120	0.0022	0.0181

Footnotes: *LCI – lower confidence interval, UCI upper confidence interval, NYHA – New York Heart Association, LVEF – left ventricular ejection fraction, td – target dose*

**Variables centred on the mean*

NYHA class within-trial

The distribution of patients in each NYHA class over time has been estimated from a generalised ordered logistic regression (a proportional odds model) developed from SHIfT data (91). The generalised ordered logistic regression is similar to a normal logistic regression but allows for an outcome variable with more than two response categories such as the proportion of patients in each NYHA class (classes I-IV), see Table 40 and Table 41.

The regression equation was designed to predict the distribution of NYHA class and considered treatment and time covariates but did not consider other patient baseline characteristics to ease interpretation of final estimates for the economic analysis.

Table 39 Distribution of patients in each NYHA class: ordered logistic regression model

Description	Coefficient	Std. Err.	P>z	95% LCI	95% UCI
Treatment NYHA II	-0.1681	0.0922	0.0680	-0.3489	0.0126
Logmonths NYHA II	-0.6288	0.0270	0.0000	-0.6817	-0.5759
Cons NYHA II	4.5662	0.0931	0.0000	4.3838	4.7487
Treatment NYHA III	-0.0933	0.0473	0.0480	-0.1859	-0.0006
Logmonths NYHA III	-0.2106	0.0091	0.0000	-0.2284	-0.1928
Cons NYHA III	0.0305	0.0346	0.3780	-0.0373	0.0984
Treatment NYHA IV	-0.3666	0.1571	0.0200	-0.6746	-0.0586
Logmonths NYHA IV	-0.0476	0.0420	0.2570	-0.1300	0.0347
Cons NYHA IV	-3.9546	0.1248	0.0000	-4.1992	-3.7101

Table 40 Predicted proportion of patients by NYHA class: Standard care

Year	NHYA I	NHYA II	NHYA III	NHYA IV
0	0.01	0.48	0.49	0.02
1	0.05	0.57	0.36	0.02
2	0.07	0.58	0.33	0.02
3	0.08	0.58	0.32	0.02

Table 41 Predicted proportion of patients by NYHA class: Ivabradine plus standard care

Year	NHYA I	NHYA II	NHYA III	NHYA IV
0	0.01	0.50	0.47	0.01
1	0.06	0.59	0.35	0.01
2	0.08	0.59	0.31	0.01
3	0.09	0.59	0.30	0.01

Underlying rate of hospitalisations within-trial with standard care

SHIfT was considered the best source of data to model the underlying rate of all hospitalisations for HF patients. The cost-effectiveness model has been designed to capture HF hospitalisations, CV hospitalisations and all-cause hospitalisations. These endpoints were each modelled separately to allow appropriate resource use to be applied to different types of hospitalisation and to permit sensitivity analysis on the treatment effect of ivabradine (see 'Treatment effect of ivabradine on hospitalisation'). However, the all-cause hospitalisation endpoint was used for the base case economic model and is reported in detail below.

The hospitalisation regression model was developed using data from the entire study cohort (patients with a heart rate ≥70 bpm, N=6505). However, consistent with the regression equations developed for mortality, the hospitalisation risk equations adjust for patient baseline heart rate and are able to predict estimates for the licensed population with heart rate ≥75 bpm.

The rate of HF, CV and all-cause hospitalisation per person month has been estimated using Poisson regression models with robust estimates of the variance (data was clustered on patient id to take into account the variance associated with each individual patient (92)). The rate of hospitalisation has been converted into a monthly transition probability for use in the final economic model. A negative binomial model was considered as an alternative to the Poisson model. A negative binomial model can be used given evidence of over-dispersion in a Poisson analysis (i.e. greater variability in the number of hospitalisations than expected) (91). Statistical analyses of SHIfT data suggested some evidence of over-dispersion; however, a negative binomial model produced higher estimates for the rate of hospitalisation than observed in SHIfT, and this model would consequently favour ivabradine and was therefore not employed in the final model.

The Poisson regression model has been estimated adjusting for treatment and other baseline variables considered to be potential predictors of hospitalisation rates. The variables considered were consistent with the covariates examined in the clinical analyses (see Section 6.3) plus geographical region (Western, Eastern European, Latin America and Asia).

The covariates included in an initial regression model were identified using both forward and backwards stepwise elimination (using a p-value of <0.1). The methods used to select covariates for the final regression model were comparable to the mortality risk equations: covariates were reviewed for collinearity, and variables with evidence for borderline significant association with the outcome variable were reviewed individually for potential inclusion (see previous description of CV mortality methods). All covariates included in the final model were reviewed by a clinical expert; the final regression model for all-cause hospitalisations has been reported in Table 42.

Treatment effect of ivabradine on hospitalisations

The effect of ivabradine plus standard care on the rate of hospitalisations has been estimated relative to the rate with standard care alone using a rate ratio derived from the Poisson regression model. The treatment effect has been modelled on all-cause hospitalisation rather than just CV or HF hospitalisations for the following reasons:

- SHIfT demonstrated that ivabradine had a significant effect on all-cause hospitalisation in the main study population (patients with a baseline heart rate ≥70 bpm)
- SHIfT demonstrated that the significant effect on all-cause hospitalisation was maintained in the licensed population of interest to this economic evaluation (patients with a baseline heart rate ≥75 bpm)
- Heart failure and CV hospitalisations are implicitly captured within the all-cause hospitalisation endpoint (Swedberg et al. 2010 (8)).

However, it is noted that a sensitivity analysis has also been conducted in which the treatment effect of ivabradine was modelled only on heart failure hospitalisation with non-HF hospitalisation modelled to be equivalent to standard care. In this scenario no treatment effect for ivabradine was consequently modelled for other (non-heart failure) CV hospitalisation and non-CV hospitalisation. This analysis was equivalent to the sensitivity analysis undertaken on the ivabradine treatment effect on mortality and was used to demonstrate robustness of results to alternative model structures.

Treatment interaction: hospitalisation

The variables reviewed for treatment effect modification reflected those covariates with prior clinical evidence of potential modification of the treatment effect on hospitalisation (age, ischaemia, beta-blocker use, heart rate (8)). The Poisson regression model indicated that there was significant evidence that patient baseline heart rate modified the ivabradine treatment effect ($p=0.01$). However, there was no significant evidence that beta-blocker use modified the ivabradine treatment effect once differences in baseline heart rate had been taken into account ($p>0.05$); other interaction terms (age, ischaemia) were also non-significant. These results were consistent with results of analyses undertaken for the clinical section of this submission, see Section 5.5.

Table 42 Rate of all-cause hospitalisation: Poisson regression model

Description	RR	Coefficient	SE	p-value	95% LCI	95% UCI
Treatment	0.8700	-0.1393	0.0453	0.0020	-0.2281	-0.0504
Heart rate bpm	1.0155	0.0154	0.0030	0.0000	0.0094	0.0213
Eastern Europe vs Western	0.7157	-0.3345	0.0666	0.0000	-0.4650	-0.2040
Latin America vs Western	0.7041	-0.3508	0.0900	0.0000	-0.5272	-0.1745
Asia vs Western	0.5079	-0.6775	0.1179	0.0000	-0.9087	-0.4464
LVEF ≥26% <30% *vs* <26%	0.8120	-0.2083	0.0665	0.0020	-0.3387	-0.0779
LVEF ≥30% <33% *vs* <26%	0.7181	-0.3312	0.0622	0.0000	-0.4532	-0.2092
LVEF ≥33% *vs* <26%	0.6983	-0.3591	0.0627	0.0000	-0.4820	-0.2361
Prior atrial fibrillation	1.3532	0.3025	0.0756	0.0000	0.1543	0.4507
Prior stroke	1.2977	0.2606	0.0713	0.0000	0.1208	0.4004
Prior renal disease	1.3212	0.2786	0.0798	0.0000	0.1221	0.4350
Beta blocker use < half target dose (td)	0.9601	-0.0407	0.0704	0.5630	-0.1787	0.0972
Beta blocker use ≥ half td< td	0.8222	-0.1958	0.0786	0.0130	-0.3498	-0.0417
Beta blocker use ≥ td	0.7530	-0.2836	0.0817	0.0010	-0.4438	-0.1235
NYHA III (*vs* II)	1.1767	0.1627	0.0482	0.0010	0.0683	0.2571
NYHA IV (*vs* II)	1.4671	0.3833	0.1678	0.0220	0.0544	0.7121
Digitalis use	1.2697	0.2388	0.0557	0.0000	0.1297	0.3479
Loop diuretics dose/kg/day	1.1071	0.1018	0.0225	0.0000	0.0578	0.1458
Allopurinol	1.3224	0.2794	0.0853	0.0010	0.1123	0.4466
Diabetes	1.2283	0.2056	0.0473	0.0000	0.1129	0.2984
Tobacco use	1.2118	0.1921	0.0472	0.0000	0.0995	0.2847
Sodium*	0.9761	-0.0242	0.0062	0.0000	-0.0363	-0.0121
HF duration ≥0.6<2 yrs *vs* <0.6 yrs	1.0872	0.0836	0.0703	0.2340	-0.0542	0.2213
HF duration ≥2<4.8 yrs *vs* <0.6 yrs	1.0640	0.0620	0.0696	0.3730	-0.0745	0.1985
HF duration ≥4.8 yrs *vs* <0.6 yrs	1.3814	0.3231	0.0639	0.0000	0.1978	0.4484
Age (years)*	1.0106	0.0106	0.0023	0.0000	0.0060	0.0152
Systolic Blood Pressure*	0.9971	-0.0029	0.0015	0.0520	-0.0059	0.0000
Coronary Artery Disease	1.1418	0.1326	0.0569	0.0200	0.0212	0.2441
Treat*heart rate*	0.9894	-0.0106	0.0042	0.0120	-0.0189	-0.0024
Cons	0.0394	-3.2334	0.1102	0.0000	-3.4493	-3.0174

Footnotes: *LCI – lower confidence interval, UCI upper confidence interval, NYHA – New York Heart Association, LVEF – left ventricular ejection fraction, td – target dose*

**Variables centred on the mean*

Hospitalisation length of stay, within-trial period

The length of stay (LoS) associated with a hospitalisation has been estimated using data external to the SHIfT trial based on expert clinical advice. This advice indicated that country variation in length of stay would be expected.

In the base case model patient average length of stay was estimated to vary according to the hospitalisation admission diagnosis (heart failure, other CV and non-CV) and was based on a weighted average of elective and non-elective NHS reference cost data (2010-2011) (93). In sensitivity analyses the length of stay for an admission with a heart failure diagnosis was taken from the UK 2010 National Heart Failure Audit data and from Hospital Episode Statistic (HES) (4);(94).

Table 43 Hospitalisation length of stay by diagnosis and data source

Admission type	NHS reference costs	HES data	National HF audit
Heart failure	7.57	11.50	9.0 (median)
CV	3.97	7.54	-
Non-CV	5.13	5.25	-

Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

The following calculations were used to estimate the survival functions S(t) for the Gompertz, Weibull and exponential models considered for CV mortality:

Exponential: $S(t) = \exp\{-\lambda t\}$
Weibull: $S(t) = \exp\{(-\lambda t)p\}$
Gompertz: $S(t) = \exp\{(-\lambda t)p^{-1}(\exp(pt)-1)\}$

t = time; λ = location parameter; p = shape parameter

Transition probabilities tp(t) were estimated as follows:

$tp(t) = S(t)/S(t-1)$

The following calculation was used to estimate the probability of hospitalisation per person month:

$\exp(Y/t) = \alpha + \beta\chi$

Y = count (number of hospitalisations); t = time (person months)

Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

The Gompertz (and Weibull) parametric survival model(s) developed to predict CV mortality include a time varying covariate and, consequently, transition probabilities for CV mortality in the base case model (Gompertz distribution) and in the sensitivity analysis, which uses the Weibull distribution, may vary over time.

There was no evidence that the rate of hospitalisations varied over time in SHIfT, hence in the base case model hospitalisation rates have been modelled to occur at a constant rate over the entire modelled time horizon.

The proportion of patients in each NYHA class has been modelled to change over time for the within-trial period (time varying covariate included in the regression model). In the extrapolation this has been assumed to be fixed after 29 months due to the absence of evidence of potential patterns post-trial. In the extrapolated period for the standard care arm the NYHA distribution has been fixed at 7%, 58%, 32% and 2% for NYHA class I-IV respectively, in the ivabradine plus standard care arm this distribution has been fixed at 9%, 59%, 30%, 1% for NYHA I-IV, see section 6.3.1, Table 40 and Table 41. A sensitivity analysis has been undertaken to test the robustness of this result to other assumptions. In this sensitivity analysis an increasing proportion of patients are distributed into NYHA class III relative to NYHA class II in the extrapolated period and no difference in NYHA distribution is modelled between treatment arms.

Implementation of the risk equations and calculation of the ICER

The base case results have been reported for the licensed population (≥75 bpm) derived from a model based on the overall SHIfT study cohort. The ICER for ivabradine plus standard care *versus* standard care alone has been calculated using individual patient characteristics from the SHIfT cohort (patients with a baseline heart rate ≥75 bpm). Individual patient profiles (characteristics) have been applied in each of the SHIfT adjusted risk equations in the model (sequentially - one profile at a time) for both the ivabradine plus standard care and standard care alone arms. In the base case analysis the estimates of costs and QALYs generated by each iteration have been averaged to calculate incremental cost per life year and incremental QALY. This approach was taken in preference to using the proportion with each given characteristic (e.g. 0.24 for female) in the regression equation to provide a more accurate assessment of the ICER, see Section 6.9.3.

Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

Surrogate outcomes were not used as SHIfT provided estimates for the modelled outcomes: CV death and all-cause hospitalisation.

If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[3]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

A clinical expert in heart failure was asked to review SHIfT regression models (covariates selected for the risk equations and face validity of derived estimates) and to provide comment on the economic analysis plan during the initial phases of the project. These discussions were undertaken via telephone and email correspondence.

An advisory board was subsequently convened to review the draft model and provide comment and critique on model assumptions. A list of over 30 cardiology and health economic experts was researched to identify those individuals considered as having the most relevant experience. Individuals were selected to ensure a range of academic, HTA and hands-on clinical experience was represented. The panel consisted of six external experts, two clinical experts in heart failure and four health economists with experience of modelling in this indication. A second advisory board met to discuss the amended model; at both meetings the panel was presented with the model and an open forum discussion took place on the plausibility and legitimacy of assumptions employed. All participants were asked to comment on the modelling methods as well as any issues around the generalisation of SHIfT data to a UK population. All experts approached agreed to take part, and participants were asked to declare conflicts of interest at the start of the process.

[3] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

The advisory board suggested that a regional variable should be included in the hospitalisation risk equation to account for potential differences in treatment practice between countries. The two issues identified were hospitalisation rate and length of stay. Regarding hospitalisation rates, the variation in rate of hospitalisation was explored across different countries (see Section 6.10.3). Regarding length of stay, which varies between healthcare systems, we elected to use UK data sources rather than SHIfT. In addition, the specific type of standard care medications (e.g. type of ACE inhibitor) should be modified to reflect those medications more commonly used in the UK. Expert review of the overall economic model indicated that the Gompertz parametric model provided the most appropriate distribution for CV mortality over and was considered to offer the most plausible prediction for the extrapolated portion of the survival curve. The proportion of patients in each NYHA class was also suggested to be fixed using the last observation carried forward in the post-trial period due to the absence of evidence of potential patterns post-trial.

Summary of selected values

Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

Table 44: Summary of variables applied in the economic model

Parameter description	Base case value	95% LCI	95% UCI	PSA Distribution	Reference for section in NICE submission
Model structure	Two State Markov cohort model	-	-	-	Section 2.3.1-2.3.3
Modelled cycle length	1 month	-	-	-	Section 6.2.6; Table 33
Time horizon	Lifetime	-	-	-	Section 6.2.6; Table 33
Population	SHIfT population HR >75 bpm.	-	-	-	Section 2.3.1
Costs discount rate	3.50%	-	-	-	Section 6.2.6; Table 33
Effects discount rate	3.50%	-	-	-	Section 6.2.6; Table 33
Treatment duration months Ivabradine	360.00	-	-	-	Section 6.3.1
Parametric survival model CV mortality	Gompertz	See Footnotes		Lognormal	Section 6.3.1
Extrapolation CV mortality post trial	Gompertz	See Footnotes		Lognormal	Section 6.3.1
Hazard ratio CV mortality Ivabradine vs std care	0.90	0.80	1.03	Lognormal	Section 6.3.1
Regression model hospitalisation	Poisson	See Footnotes		Lognormal	Section 6.3.1
Rate ratio hospitalisation Ivabradine vs std care	0.83	0.78	0.93	Lognormal	Section 6.3.1
Regression model NYHA class	Ordered logistic regression	See Footnotes		Lognormal	Section 6.3.1
Regression model QoL	Mixed model	See Footnotes		Lognormal	Section 6.4.9; Table 49
NYHA I	0.82	See Footnotes		Normal	Section 6.4.9; Table 49
NYHA II	0.74	See Footnotes		Normal	Section 6.4.9; Table 49
NYHA III	0.64	See Footnotes		Normal	Section 6.4.9; Table 49
NYHA IV	0.46	See Footnotes		Normal	Section 6.4.9; Table 49
Utility decrement hospitalisation					
NYHA I	-0.07	See Footnotes		Normal	Section 6.4.9; Table 49
NYHA II	-0.03	See Footnotes		Normal	Section 6.4.9; Table 49
NYHA III	-0.08	See Footnotes		Normal	Section 6.4.9; Table 49
NYHA IV	-0.21	See Footnotes		Normal	Section 6.4.9; Table 49

Parameter description	Base case value	95% LCI	95% UCI	PSA Distribution	Reference for section in NICE submission
Utility increment Ivabradine	0.01	See Footnotes		Normal	Section 6.4.9; Table 49
Drug costs per month					
BSC	9.54	-	-	Deterministic	Section 6.2.7; 6.5.5
Ivabradine	42.10	-	-	Deterministic	Section 6.2.7; 6.5.5
Other therapy related costs		**Lower quartile**	**Upper quartile**		
ECG Ivabradine	31.28	12.01	44.30	Lognormal	Section 6.2.8; 6.5.5; Table 54
Cardiovascular specialist visit	118.81	89.48	138.97	Lognormal	Section 6.2.8; 6.5.5; Table 54
Hospitalisations cost per event					
HF diagnosis (general ward)	2307.98	-	-	Lognormal	Section 6.5.7 Table 56
HF diagnosis (cardiac ward)	3295.12	-	-	Lognormal	Section 6.5.7 Table 56
Other CV diagnosis (general ward)	1942.44	-	-	Lognormal	Section 6.5.7 Table 56
Other CV diagnosis (cardiac ward)	1729.60	-	-	Lognormal	Section 6.5.7 Table 56
Non-CV diagnosis (general ward)	2643.56	-	-	Lognormal	Section 6.5.7 Table 56
Probability of general ward admission HF or CV diagnosis	0.50	0.40	0.60	Lognormal	Section 6.5.7 Table 56
Probability of cardiac ward admission HF or CV diagnosis	0.50	-	-		Section 6.5.7 Table 56
Other resource use					
HF management costs	26.77	20.08	33.47	Lognormal	Section 6.5.8 Table 56

Footnotes: *LCI – lower confidence interval, UCI upper confidence interval, PSA – probabilistic sensitivity analysis*

Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan-Meier plots.

Extrapolation of baseline mortality to the post-trial period

CV mortality has been extrapolated using the parametric survival model based on a Gompertz distribution. However, it is acknowledged that only ~17% of the standard care arm of SHIfT had died at study close and that this may not be a sufficient proportion of patients from which to extrapolate mortality data for the remainder of the cohort. In view of this uncertainty, mortality data from an external data source has also been considered in sensitivity analyses (CARE-HF data, Cleland 2011 (95)).

CARE-HF was an RCT conducted in heart failure patients (NYHA class III or IV) with a prior hospitalisation event, on pharmacologic therapy with a left ventricular ejection fraction (LVEF) ≤ 35% and QRS interval ≥120 ms. Further trial details are summarised in Table 100, Appendix 16. CARE-HF currently offers the longest follow up data of a recent HF RCT population. Whilst CARE-HF was conducted in a more severe HF population, there are to our knowledge, no other recent studies that offer 10 year follow up (9). CARE-HF long term mortality data has currently only been published in conference abstract form. The estimates applied in the sensitivity analysis consequently consist of a crude all-cause mortality rate estimated from Kaplan Meier data. The extrapolation assumes that 50% of the cohort will have died by 2000 days (65 months) as suggested by reported Kaplan Meier data; this is represented as a constant hazard assumption in the model (9). The CARE-HF crude mortality estimate does not taken into account any change in mortality risk by age. The crude mortality risk has consequently been adjusted for changes in the rate of death by age using a multiplier estimated from UK interim life tables, see Table 45. The age multiplier has been calculated as the increase or decrease in mortality evidenced in UK interim life table for each 5-year age band relative to patients aged 65-69 (the mean starting age of patients in CARE-HF).

Table 45 Estimated probability of death per month using data from CARE-HF (95)

Age group	CARE-HF mortality rate male	CARE-HF mortality rate female	UK annual probability of death (gender adjusted)	Age multiplier based on UK data	Probability of death per month age, gender adjusted CARE-HF
Age 20-24	0.0035	0.0013	0.0030	0.0279	0.00029
Age 25-29	0.0041	0.0017	0.0035	0.0327	0.00034
Age 30-34	0.0053	0.0024	0.0046	0.0432	0.00045
Age 35-39	0.0068	0.0037	0.0061	0.0569	0.00060
Age 40-44	0.0093	0.0058	0.0085	0.0792	0.00083
Age 45-49	0.0140	0.0091	0.0128	0.1197	0.00125
Age 50-54	0.0218	0.0146	0.0201	0.1876	0.00197
Age 55-59	0.0329	0.0218	0.0303	0.2827	0.00296
Age 60-64	0.0510	0.0342	0.0471	0.4389	0.00460
Age 65-69	0.0772	0.0532	0.0716	0.6675	0.00698
Age 70-74	0.1139	0.0855	0.1073	1.0000	0.01044
Age 75-79	0.1679	0.1397	0.1614	1.5039	0.01566
Age 80-84	0.2223	0.2158	0.2208	2.0573	0.02136
Age 85-89	0.2265	0.2764	0.2381	2.2188	0.02301
Age 90-94	0.1705	0.2651	0.1924	1.7935	0.01864
Age 95 and over	0.0790	0.1576	0.0972	0.9060	0.00946

Extrapolation in NYHA class

There is little external evidence to predict the potential trend in NYHA mix over time. The SHIfT NYHA equations, which include a time covariate, predict some (small) increase in the absolute number of patients in NYHA I and II over time, a pattern observed during SHIfT. Whilst it is likely that many of the observed deaths would be in the higher NYHA classes (III, IV), hence increasing the relative proportion of the cohort alive in NYHA I and II, and some improvement in symptoms could be anticipated by optimal heart failure management, it would be clinically unexpected to find an overall increase in the absolute numbers of patients in NYHA I and II in the long term given the progressive nature of the disease.

The current model therefore assumes that the distribution of patients by NYHA class is equivalent to the last observation carried forward (LOCF) at 29 months. This scenario assumes that the proportion of patients in each NYHA class remains fixed post trial (although in absolute terms numbers in each category vary according to survival estimates, see Figure 14). This approach was considered more conservative than the extrapolation of SHIfT data using the ordered logistic regression which would have predicted an implausibly high proportion with minimal or mild symptoms in the long-term and which would have resulted in a more favourable ICER estimate for ivabradine. A final sensitivity analysis was employed to consider a scenario in which a greater proportion of patients were assumed to be distributed into NYHA class III each year, see Table 46.

Figure 14 Standard care: model predicted proportion of patients by NYHA class over time

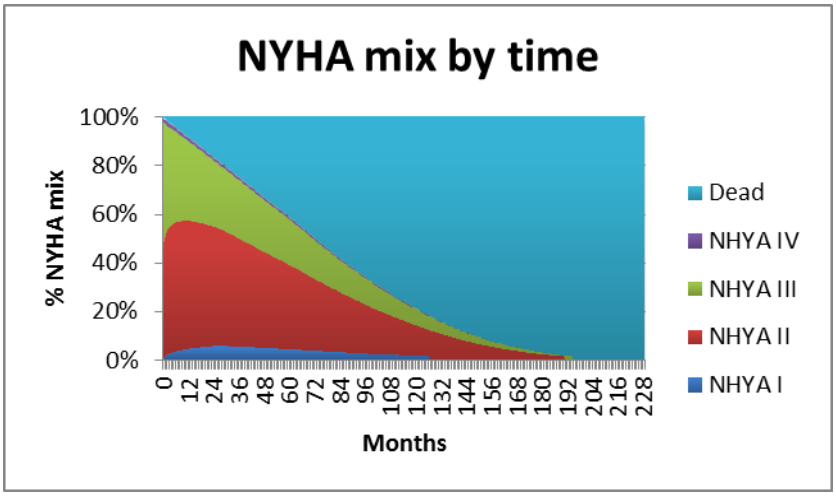


Figure 15 Ivabradine plus standard care: model predicted proportion of patients by NYHA class over time

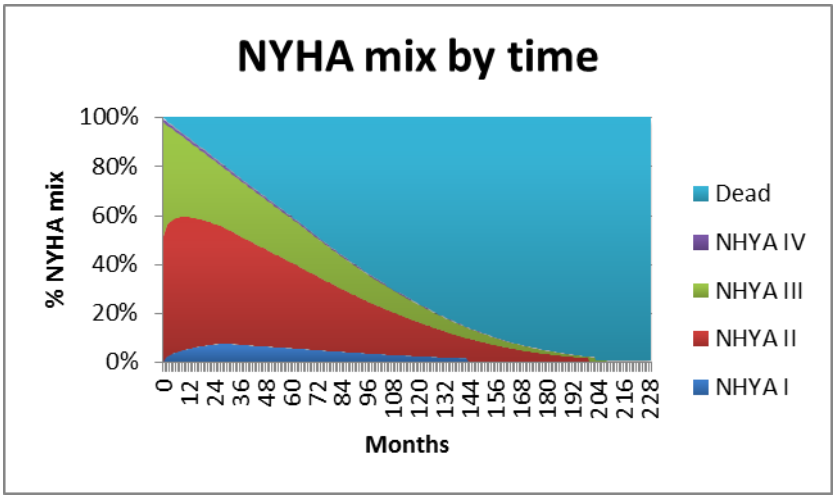


Table 46 Proportion of patients distributed in each NYHA class over time: sensitivity analysis (more patients in NYHA III)

Months	NYHA1	NYHA2	NYHA3	NYHA4	Total
24	0.073	0.556	0.363	0.008	1.000
36	0.069	0.532	0.391	0.008	1.000
48	0.066	0.509	0.418	0.008	1.000
60	0.063	0.486	0.443	0.008	1.000
72	0.060	0.465	0.468	0.008	1.000
84	0.057	0.445	0.491	0.008	1.000
96	0.054	0.426	0.513	0.008	1.000
108	0.051	0.407	0.534	0.008	1.000
120	0.048	0.389	0.555	0.008	1.000
132	0.046	0.372	0.574	0.008	1.000
144	0.044	0.356	0.593	0.008	1.000
156	0.042	0.340	0.611	0.008	1.000
168	0.039	0.325	0.628	0.008	1.000
180	0.038	0.311	0.644	0.008	1.000

Extrapolation of baseline hospitalisation rates and QoL

Hospitalisations are assumed to occur at a constant rate throughout the modelled period and have been modelled to be equivalent to the within-trial period. In the base case model no adjustment has been made for the ageing of the population. Increasing baseline age was found to be associated with a significant increase in all-cause hospital admissions. The SHIfT adjusted regression equation predicted that for every 10 years increase in baseline age the risk of hospitalisation increased by 7%. An increase in underlying rate of hospitalisation due to population ageing would result in a larger difference in the incremental costs between therapies (ivabradine would be expected generate a larger reduction in hospitalisations in hospitalisations given the same relative treatment effect). The inclusion of an increased rate of hospitalisations due to the ageing of the modelled population would consequently drive a more favourable (lower ICER) for ivabradine, this potential benefit has not been captured in the base case model.

QoL has been assumed to remain the same for each NYHA class in the post-trial period and in the base case model estimates are not modelled to change as patients age. This simplification may result in higher utility values being applied to patients in later cycles than would be naturally expected in an older population and may favour ivabradine since additional survival time will be associated with a greater modelled QALY benefit. In the SHIfT QoL regression model, every 10 additional years of age were associated with a small but significant utility loss (- 0.0074, 95% CI: -0.012 to -0.003; $p<0.001$). The age covariate in the mixed regression model was derived using the baseline cohort age and was not a time varying covariate. In order to demonstrate robustness of the model results, a sensitivity analysis was undertaken which adjusted for the increasing age of the modelled cohort by resetting baseline age each cycle to reflect the increasing age of the modelled cohort.

Extrapolation of the treatment effect of ivabradine

In the base case model the relative treatment effect of ivabradine on CV death, hospitalisation and QoL has been modelled to continue post trial. Two sensitivity analyses have been undertaken to test the robustness of results to changes in this assumption. Firstly a maximum duration of ivabradine therapy was considered (five years) and after this period the treatment effect of ivabradine (hazard ratio for CV mortality, rate ratio hospitalisations) was modelled instantaneously to return to 1 and the QoL benefit and costs associated with ivabradine therapy were ceased. In a second sensitivity analysis, a worst case scenario, subjects were modelled to continue with ivabradine in the long term but the effects of therapy (CV mortality, hospitalisation, QoL) were modelled to gradually reduce over a specified time period (5-10 year range considered). These methods are consistent with NICE methods guidance which recommends exploring the ongoing treatment effect in the post-trial period.

Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

Assumption	Rationale
Mortality, hospitalisation and QoL endpoints capture the most relevant outcomes for therapy in HF	The primary clinical consequences of HF are an increased risk of mortality and hospitalisation, and a reduction in QoL (see Section 2.1).
The SHIfT population is representative of a UK HF population	SHIfT was a large RCT designed to reflect a current heart failure population. As with other major RCTs in heart failure, patients in SHIfT were generally younger than UK HF patients (see Section 5.10.4). An older population reflective of the average age of UK HF patients has been considered in sensitivity analyses.
Standard care therapy use in SHIfT reflects UK treatment patterns	Evidence from UK GP databases and European survey data (33;63) indicates that treatment of HF patients in SHIfT appears consistent with UK treatment patterns. However, a population treated with target dose beta-blocker therapy has been considered in a sensitivity analysis. (see Section 5.10.4)
The Gompertz distribution is the most suitable distribution to model CV mortality	A review of six parametric distributions indicated that the Gompertz model provided the most appropriate fit of the data statistically, visually and in consideration of the plausibility of the tail of the curve. Two other parametric distributions have been considered in sensitivity analyses.

Ivabradine reduces CV mortality	Ivabradine demonstrated a significant reduction in CV mortality for patients with heart rate ≥75 bpm.
The hazard ratio for ivabradine in the post-trial period remains constant and equivalent to SHIfT within-trial estimates.	It is expected that ivabradine efficacy will be maintained in the long term (see Section 5.10.4), therefore the base case analysis models a continuation of the treatment effect in the post-trial period. This assumption has been tested in sensitivity analyses.
The rate of hospitalisation remains constant over time.	SHIfT data indicated no change in the rate of hospitalisation over time. A time varying covariate was tested in the regression equation developed to predict the rate of hospitalisation but was not significant.
Ivabradine reduces hospitalisation events	SHIfT demonstrated a statistically significant reduction in all-cause hospitalisation events.
The rate ratio for hospitalisation remains equivalent to trial estimates in the post-trial period.	It is expected that ivabradine efficacy will be maintained in the long term consequently the base case analysis models a continuation of the treatment effect in the post-trial period. This assumption has been tested in sensitivity analyses.
Ivabradine improves patient QoL	A mixed model designed to estimate quality of life from data with repeated measures over time indicated that ivabradine was associated with a significant improvement in patient QoL during the SHIfT trial period.
The improvement in QoL associated with ivabradine is maintained in the post-trial period.	It is expected that ivabradine will remain efficacious in the long term, consequently the improvement in QoL is modelled to continue post-trial.

Measurement and valuation of health effects

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.4.

The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.

All parameters used to estimate cost-effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

Patient experience

Please outline the aspects of the condition that most affect patients' quality of life.

Chronic heart failure is a complex clinical syndrome that is characterised by dyspnoea, fatigue and fluid retention which may lead to peripheral oedema and pulmonary congestion. Patient health related quality of life (HRQL) is likely to diminish as the severity of patients' symptoms increases. This pattern has been demonstrated in previous large-scale QoL studies (Gohler et al. 2009(85)

Please describe how a patient's HRQL is likely to change over the course of the condition.

The most commonly used classification of severity of HF symptoms is the NYHA classification of functional capacity. This system assigns patients to one of four functional classes depending on patient symptoms. It is anticipated that patient QoL is likely to deteriorate as symptoms progress and patients are classified into higher NYHA classes. It is well established that NYHA class captures differences in quality of life. Within the model EQ-5D data was used to derive quality of life values for each NYHA class. It was also used to determine a quality of life decrement associated with hospitalisation and any incremental benefit from treatment.

Table 47 New York Heart Association classification of heart failure symptoms

Class I	Patients with cardiac disease which does not limit physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or angina pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. Less than ordinary activity causes fatigue, palpitation, dyspnea, or angina pain.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

HRQL data derived from clinical trials

If HRQL data were collected in the clinical trials identified in section 5 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

The current model applies EQ-5D index scores calculated using UK population tariff values consistent with the NICE reference case. Patient HRQL was captured using the SHIfT patient reported outcome sub-study which collected HRQL estimates at intervals (baseline, 4, 12, 24 and 36 months) from patients in countries with a validated EuroQoL EQ-5D questionnaire (n=5313/6505). EQ-5D index scores were calculated from SHIfT data using tariff values taken from UK population survey data (96) for all patients regardless of country of origin. The estimates employed in the model are considered appropriate for a cost-effectiveness model.

SHIfT EQ-5D data have been analysed using a mixed regression model, which is specifically designed for datasets with repeated observations over time. The clinical variables considered to potentially predict patient QoL were consistent with those considered in the CV and hospitalisation risk equations, plus two additional time-varying variables - hospitalisation within a 60 day time interval (EQ-5D visit date +/- 30 days) and NYHA class. The EQ-5D QoL weights from a recent study in HF patients have been applied in a sensitivity analysis to test the robustness of results to external QoL.

Ivabradine treatment effect on QoL: overview

The treatment effect on CV mortality for ivabradine plus standard care has been modelled using a utility increment for ivabradine relative to the baseline utility estimate. It has been assumed that the treatment effect of ivabradine continues in the post-trial period and is equivalent to that demonstrated within the SHIfT study, see Section 6.3.7. In sensitivity analysis alternative scenarios were considered for the treatment effect of ivabradine in the post-trial period, see Section 6.6. In order to avoid breaking randomisation, the risk equations used to populate the economic model have been developed using the full patient cohort (patients with a baseline heart rate >70 bpm). The regression equation which adjusts for treatment and other baseline characteristics (but excludes interaction terms) has been reported in Table 52. There is strong evidence that treatment is significantly associated with an improvement in patient QoL (p=0.01).

Treatment effect modification QoL

The variables reviewed for treatment effect modification (treatment interaction terms) reflect those covariates with prior clinical evidence of potential modification of the treatment effect and which were a significant predictor of patient QoL (age, heart rate; Diaz 2005 (26)). The interaction effect between hospitalisation and NYHA class was also considered due to strong clinical rationale. The potential interaction of treatment with other baseline covariates, and between other baseline covariates, was not considered in order to prevent the generation of spurious results.

The mixed regression model indicated that the ivabradine treatment effect on quality of life was not significantly modified by baseline heart rate (p=0.1) although there appeared to be a potential trend in the data towards an interaction effect.

The interaction term for treatment and heart rate was retained since heart rate had been found to significantly modify the ivabradine treatment effect in other clinical outcomes. It is noted that due to a weaker interaction between ivabradine and heart rate for patient quality of life, the treatment interaction term appears non-significant in the final regression equation. The full risk equation with interaction terms is reported in Table 53.

Mapping

If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

N/A. No mapping was undertaken for the current model.

HRQL studies

Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 9.12, appendix 12.

A systematic search of the literature was carried out in January 2012. The following databases were searched:

- Medline and Medline in process
- Embase
- Cochrane library
- NHS Economic Evaluation Database (NHS EED)
- Econlit

Full details of the search strategies are included in section 9.12, Appendix 12.

The search strategies included controlled vocabulary terms applicable to the particular database and free-text terms. The controlled vocabulary used was MeSH terms in Medline, Medline in process, Cochrane library and NHS EED; and Emtree terms in Embase. The search in EconLit comprised free-text terms only since subject headings used in this database are not relevant to QoL searches. The search strategy in EconLit and in NHS EED included terms for heart failure only as these databases contain references to economic literature only. The search strategies in Medline, Medline in process, Embase, and Cochrane included terms for heart failure and a filter to identify HRQL studies. All searches were limited to the year 2000 onwards. The inclusion criteria were as follows:

- Target population: Adult patients with chronic heart failure
- Type of studies: Generic measures of utility (EQ 5D, SF-36, HUI)
- Utility level by NYHA class
- Utility measure obtained using TTO or Standard Gamble method

The exclusion criteria were as follows:

- Studies published prior to 2000
- Studies not in the English language
- References to studies from conference abstracts

In total 9 full papers were included, details of abstracts reviewed and studies excluded at each stage are presented in the PRISMA flow diagram in Figure 1.

Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.
- Appropriateness of the study for cost-effectiveness analysis.

All identified studies have been described in Section 9.12, Appendix 12.

Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

The EQ-5D results from SHIfT are very similar to estimates of QoL published in external literature. SHIfT data indicated that the utility scores for patients by NYHA class I-IV (no hospitalisation event) would range from 0.82-0.46 respectively. The largest study in HF patients which reported EQ-5D data (Gohler et al. 2009; n = 1395(85)) estimated that utility scores for NYHA classes I-IV would range between 0.85-0.53; data from this trial has been employed in the model in sensitivity analysis.

Adverse events

Please describe how adverse events have an impact on HRQL.

Ivabradine plus standard care was associated with significantly fewer serious adverse events in SHIfT compared to standard care alone (48% standard care *versus* 45% ivabradine p=0.025). The proportion of patients experiencing non-serious adverse events including symptomatic and asymptomatic bradycardia, atrial fibrillation and visual disturbances in the ivabradine treatment group was higher than placebo, although the number of patients that withdrew from SHIfT as a result of symptoms was only higher for bradycardia, see Table 48 (Swedberg 2010 (8)).

It is not anticipated that treatment-related side effects of ivabradine therapy would impact measurably on patient QoL. Treatment-related adverse events have not therefore been separately modelled in the current analysis and any utility loss associated with treatment related adverse events is assumed to be captured by the treatment covariate included in the mixed regression model.

Table 48: Patients with selected adverse events leading to drug withdrawal (Swedberg 2010 (8))

Adverse event	Ivabradine (n=3232)	Placebo (n=3260)	p-value
Symptomatic bradycardia	20 (1%)	5(<1%)	0.002
Asymptomatic bradycardia	28(1%)	5(<1%)	<0.0001
Atrial fibrillation	135(4%)	113(3%)	0.137
Phosphenes*	7(<1%)	1(<1%)	0.224
Blurred vision	17(1%)	7(<1%)	1.00

Data are number of patients (%). Patients included in this safety analysis are those who had taken at least one dose of study drug. p values are calculated on the basis of number of patients.

*Transient enhanced brightness in a restricted area of the visual field.

Quality-of-life data used in cost-effectiveness analysis

Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 6.4.3 to 6.4.8. Justify the choice of utility values, giving consideration to the reference case.

The utility values by NYHA class, hospitalisation and treatment group, derived from the SHIfT risk equations for the average SHIfT population, are detailed in the following tables. Table 53 describes the full risk equation.

Table 49: Summary of quality-of-life (utility) values for cost-effectiveness analysis

State	Utility value*	Confidence interval	Reference in submission	Justification
Alive				
NYHA I	0.823	Refer to table below	Table 53	Estimates based on regression equations developed from SHIfT. SHIfT was the largest study with QoL data in HF. SHIfT was considered to provide the best QoL data for use in the current cost-effectiveness model.
NYHA II	0.738			
NYHA III	0.643			
NYHA IV	0.457			
Hospitalisation decrement				
NYHA I	-0.07			
NYHA II	-0.03			
NYHA III	-0.08			
NYHA IV	-0.21			
Treatment (ivabradine)	[redacted]			

*Reported values estimated using SHIfT average characteristics in regression equation in Table 53.

Table 50: Mixed regression model controlling for treatment covariate only; patients with a baseline heart rate ≥70 bpm

EQUK	Coefficient	Standard Error	P-value	95% LCI	95% UCI
Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: *LCI – lower confidence interval, UCI upper confidence interval*

Table 51: Mixed regression model controlling for treatment covariate only; patients with a baseline heart rate ≥75 bpm

EQUK	Coef.	SE	p-value	95% LCI	95% UCI
Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 52: EQ-5D index score: Mixed regression model based on SHIfT patient level data including treatment without interactions

Coefficient	SE	p-value	95% LCI	95% UCI	Probabilistic estimate
Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age (years)*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation within 30 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NYHA II vs I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NYHA III vs I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NYHA IV vs I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ischaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HF duration ≥0.6<2 yrs vs <0.6 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HF duration ≥2<4.8 yrs vs <0.6 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HF duration ≥4.8 yrs vs <0.6 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Allopurinol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI kg/m2*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart rate bpm*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loop diuretics dose/kg/day	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Potassium	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
_cons	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: *LCI – lower confidence interval, UCI upper confidence interval*

**Variables centred on the mean*

Table 53: EQ5D index score: Mixed regression model based on SHIfT patient level data including treatment and treatment interaction terms

Description	Coefficient	SE	p-value	95% LCI	95% UCI
Treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age (years)*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisation within 30 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NYHA II vs I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NYHA III vs I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NYHA IV vs I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ischaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HF duration ≥0.6<2 yrs vs <0.6 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

HF duration ≥2<4.8 yrs vs <0.6 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HF duration ≥4.8 yrs vs <0.6 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Allopurinol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI kg/m2*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Heart rate bpm*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loop diuretics dose/kg/day	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Potassium	-0.0142	0.0060	0.0190	-0.0261	-0.0023
Hosp30*nyha1	0.1403	0.0832	0.0920	-0.0228	0.3035
Hosp30*nyha2	0.1792	0.0352	0.0000	0.1102	0.2482
Hosp30*nyha3	0.1281	0.0344	0.0000	0.0607	0.1955
Treatment*heart rate	0.0008	0.0005	0.1330	-0.0002	0.0017
Cons	0.9082	0.0108	0.0000	0.8870	0.9293

Footnotes: *LCI – lower confidence interval, UCI upper confidence interval*

**Variables centred on the mean*

If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[4]:

Please see section 6.3.5.

Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

The current model estimates patient utility scores using patient baseline characteristics, NYHA class (time varying) and hospitalisation event history (time varying). Patients on ivabradine are modelled to incur a small treatment-related gain in utility based on results from the mixed regression model on SHIfT EQ-5D data which indicated that ivabradine resulted in a small increase in utility for patients with a baseline heart rate ≥70 bpm and ≥75 bpm, see Table 50 to Table 53. Patient utility has been modelled to vary according to the baseline characteristics of the modelled population subgroup, heart failure severity (NYHA class), the underlying rate of hospitalisation and patient treatment group, see Table 53.

Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

Ivabradine patients experience higher rates of symptomatic and asymptomatic bradycardia, atrial fibrillation and visual disturbances than placebo. However, it is not anticipated that the side effects of ivabradine would impact on patient QoL. A treatment covariate was included in the QoL regression model to capture any impacts of ivabradine on QoL. It is noted that ivabradine was found to statistically

[4] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

significantly improve patient QoL, see Table 50, Table 51 and Table 52. This further supports the assumption that any treatment-related adverse events have a minimal impact on patient QoL and appear to be outweighed by the benefit of therapy.

If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

The utility values were derived from a regression equation developed from SHIfT data. The baseline estimates employed in the current model depend on the characteristics of the patient population, NYHA class, treatment group and whether patients incurred a hospitalisation.

Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

Patients' QoL has been modelled to vary over time during the within-trial period according to the distribution of patients in each NYHA class (see Section 6.4.2). In the base case model no further adaptation of estimates has been undertaken to account for the ageing of the cohort over time, although an adjustment has been considered in a sensitivity analysis.

Have the values in sections 6.4.3 to 6.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

A regression model has been developed to predict patient QoL according to baseline characteristics, NYHA class (time varying), treatment and hospitalisation events, see Section 6.4.9.

Resource identification, measurement and valuation

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.5.

All parameters used to estimate cost-effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

Ivabradine is not currently refunded through a PbR tariff and consequently there are no NHS reference costs or PbR tariffs relevant to ivabradine drug procurement or delivery. However, in order to provide a conservative estimate of potential resource use associated with ivabradine therapy, two NHS reference costs were included in the current model for ivabradine patients: a face to face outpatient visit with a cardiology specialist (code 320) for dose titration and an ECG (code DA01) (93). It should be noted however that dosage titration is most likely to take place in primary care, probably in a routine visit, and the ECG is likely to the undertaken as part of standard care as recommended in NICE CG108. Heart rate may in any case be satisfactorily measured without performing an ECG, provide the patient has five minutes rest prior to taking the reading (Palatini 2006 (69)).

The costs associated with a hospitalisation episode have been estimated using NHS reference costs for HF admissions (general ward and cardiac ward), CV admissions (general ward and cardiac ward) and non-CV admissions (general ward). The proportion of patients admitted to a general ward *versus* an acute coronary ward was estimated from National Heart Failure audit data (4). SHIfT data were not used to estimate admission type since these data indicated that a substantial proportion of patients were treated in high dependency, intensive care units. UK expert opinion suggested that this was not reflective of UK practice.

All NHS reference cost estimates have been derived from the National Schedule of Reference Costs 2010-11 for NHS Trusts and PCTs Combined (the most recent available costs at the time of model development) (93).

Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

There are no NHS reference costs or PbR tariffs relevant to ivabradine drug procurement or delivery.

Resource identification, measurement and valuation studies

Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 9.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- country of study
- date of study
- applicability to UK clinical practice
- cost valuations used in study
- costs for use in economic analysis
- technology costs.

The resource use data applied in the current model was taken primarily from SHIfT data (unit quantity), NHS reference costs (hospitalisation and ivabradine therapy titration cost estimates) and British National Formulary (unit drug prices). The cost of heart failure management was identified using a search of previous HTA documents and economic evaluations (undertaken for the cost-effectiveness analysis (97)). The details of this search are documented in Section 6.1 and no further cost-specific search was undertaken.

If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[5]:

Please see section 6.3.5.

[5] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Intervention and comparators' costs

Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.

Standard care drug costs have been estimated using the overall proportions of patients using each standard care medication taken by patients in SHIfT. An average dose has been assumed for each medication which is then multiplied by relevant drug prices (calculated as the cost per mg). The drugs included in the analysis reflect those drugs currently recommended in ESC guidelines (beta-blockers, ACE inhibitors, diuretics, aldosterone antagonists, angiotensin receptors blockers, cardiac glycosides); other CV drugs were included if more than 10% of patients used them in SHIfT. The unit costs for concomitant medications have been based on the lowest generic list price from the British National Formulary (BNF) using an estimated price per mg.

The cost of ivabradine has been estimated using the proportion of patients using 2.5mg (7%) and 5mg/7.5 mg (93%) in SHIfT, and the current BNF list price for ivabradine (£40.17 per 56 tab pack). The price of 2.5 mg was assumed to reflect a half dose of the 5 mg cost, and is consistent with clinical practice (i.e. the scored tablets may be halved). It is assumed that there are no administration costs for ivabradine or other standard care medications although, as a conservative assumption, additional costs have been included for ivabradine therapy titration (specialist visit) and an ECG, see Section 6.5.1.

Table 54: Unit costs associated with the technology in the economic model (£)

Items	Ivabradine plus Std Care	Ref. in submission	Standard care alone	Ref. in submission
Technology cost per pack	40.17	Section 6.5.5	-	Section 6.5.5
Mean cost of technology treatment (per month)	42.10	Section 6.5.5	-	Section 6.5.5
Mean cost Standard Care treatment	9.54	Section 6.5.5	9.54	Section 6.5.5
Administration cost	-	Section 6.5.5	-	Section 6.5.5
Specialist visit (one-off)	118.81	Section 6.5.5	-	Section 6.5.5
ECG (one-off)	31.28	Section 6.5.5	-	Section 6.5.5
Total cost per month (month 1)	**201.73**		**9.54**	
Total cost per month (subsequent months)	**51.64**		**9.54**	

Health-state costs

Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 6.2.4.

Table 55: List of health states and associated costs in the economic model (£)

Health states	Items	Value	Reference in submission
Alive	Therapy costs, ivabradine per month	42.10	Section 6.5.5
	Therapy costs, standard care per month	9.54	Section 6.5.5
	Hospitalisation HF diagnosis	2801.55	Section 6.5.7
	Hospitalisation CV diagnosis	1836.02	Section 6.5.7
	Hospitalisation All cause diagnosis	2643.56	Section 6.5.7
	Heart failure management per month	26.77	Section 6.5.8

Adverse-event costs

Please summarise the costs for each adverse event listed in section 5.9 (Adverse events). These should include the costs of therapies identified in section 2.7. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.

Serious adverse events have been captured using the hospitalisation endpoint, non-serious adverse events have not been included (see Section 6.4.8). The adverse events included in the model are reported in Table 56.

Table 56: List of adverse events and summary of costs included in the economic model (£)

Adverse events	Items	Value	Reference in submission
Hospitalisation	HF diagnosis (general ward)	2307.98	Section 6.5.7
	HF diagnosis (cardiac ward)	3295.12	Section 6.5.7
	Other CV diagnosis (general ward)	1942.44	Section 6.5.7
	Other CV diagnosis (cardiac ward)	1729.60	Section 6.5.7
	Non-CV diagnosis (general ward)	2643.56	Section 6.5.7

Miscellaneous costs

Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

Other modelled resources included background management of heart failure, (physician visits, outpatient procedures, diagnostic tests). This has been estimated from British Heart Foundation statistics, consistent with methods used for the previous NHS National Institute for Health Research (NIHR) assessment of aldosterone antagonists in heart failure patients (10). The total cost of heart failure to the NHS was estimated by the British Heart Foundation in 2005 as £192.5 million per annum (excluding drug costs and inpatient hospitalisations) or £272 per annum per patient. This cost has been inflated to 2011 costs to derive a monthly heart failure management cost and is used for all living patients regardless of treatment received (ivabradine plus standard care or standard care alone).

Sensitivity analysis

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions Fused in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost-effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

A range of structural sensitivity analyses have been conducted (base case model assumptions have been underlined):

Treatment effect of ivabradine

- Treatment effect ivabradine modelled on CV mortality and all cause hospitalisation *versus* HF mortality and HF hospitalisation only.
- Continued therapy *versus* cessation of therapy at 5 years (hazard ratio/rate ratio hospitalisation returns to 1 instantly at 5 years, costs cease)
- Continued treatment effect post trial *versus* reduction of treatment benefit post-trial period (hazard ratio linearly returns to 1 over 5-10 year range, drug costs cease once hazard ratio reaches 1).
- (Please note the potential heterogeneity of treatment effect of ivabradine according to beta-blocker dose is discussed in subgroup analyses; see Section 6.9).

Baseline risk: mortality

- Alternative parametric distributions CV mortality (Gompertz, exponential, Weibull)
- Alternative survival modelling within the trial period (parametric model vs Kaplan Meier data)
- Alternative data source for extrapolation of mortality post trial (SHIfT parametric model vs external data (CARE-HF))

Baseline rate: hospitalisation

- Alternative regression models hospitalisation (Poisson vs negative binomial)
- Alternative categorisation country/region variable (UK plus Western European vs UK plus Northern European)
- Alternative data source length of stay (NHS reference cost data, Hospital Episode Statistics, UK national heart failure data, SHIfT data).

HRQL

- Alternative data source for utility estimates (SHIfT vs external data from Gohler, 2009)
- Modelling an additional utility loss associated with an ageing population
- Alternative data: utility mixed regression model *vs* observed data

General

- Alternative model time horizon (within-trial, 5 years, 10 years, lifetime)
- Inclusion and exclusion of the additional specialist visit and ECG for ivabradine therapy titration

Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in Section 6.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

One way sensitivity analyses were conducted on a range of parameter values including:

- Hazard ratio CV mortality (95% confidence interval)
- Rate ratio hospitalisation (95% confidence interval)
- Utility decrement of treatment (95% confidence interval)
- Length of stay of hospitalisation (95% confidence interval)
- Cost per day of hospitalisation
- Inclusion/Exclusion of titration visit and ECG costs

Drug costs were considered deterministic and excluded from sensitivity analyses – drug prices reflect the current UK BNF list price.

Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 6.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

The model has been designed to quantify uncertainty probabilistically. Multivariable regression functions generated using SHIfT individual patient data have been entered in the model along with a Cholesky decomposition to account for correlated parameters. Monte Carlo simulation has been used to generate the resulting joint distributions of total costs and QALYs in the model (98). The model outputs have also been expressed in terms of 'decision uncertainty' using cost-effectiveness acceptability curves (CEACs) which show the probability of each therapy being optimal given a particular threshold value for cost-effectiveness (99). Cost-effectiveness frontiers (CEAFs) are also presented which show, for the treatment option with the highest expected (mean) cost-effectiveness, the probability of it being the most cost-effective (100), see 6.3.6.

Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Link between clinical- and cost-effectiveness results.
- Costs, QALYs and incremental cost per QALY.
- Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A statement as to whether the results are based on a PSA.
- Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.
- Scatter plots on cost-effectiveness quadrants.
- A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost-effective at thresholds of £20,000–£30,000 per QALY gained and the error probability.

Clinical outcomes from the model

For the outcomes highlighted in the decision problem (see section 4), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Table 57: Summary of model results compared with clinical data: number of events (licensed population; ≥75 bpm)

Outcome	Clinical trial result Std Care	Model result Std Care	% error in predictions	Clinical trial result Ivabradine	Model result Ivabradine	% error prediction
HF mortality	126.00	107.66	-14.56%	78.00	74.56	-4.40%
CV mortality	364.00	325.70	-10.52%	304.00	291.15	-4.23%
All-cause mortality	407.00	401.59	-1.33%	340.00	367.81	8.18%
Hospitalisations	2213.00	1814.00	-18.03%	1754.00	1629.75	-7.08%

The risk equations developed from the SHIfT data appear to under-predict clinical events (CV death and hospitalisation) relative to observed data. In a model that considers the entire SHIfT cohort (patients with a heart rate ≥70 bpm) the ivabradine risk equations generated approximately 5-10% fewer clinical events according to the endpoint and treatment specified than that of the observed data for this population. It is expected that there would be some discrepancy between observed events and those predicted from a regression model since predictions are constrained by the

clinical covariates considered in the equation. It is possible that some predictors may not have been captured by the available clinical data.

If the risk equations developed from the full cohort are used to predict outcomes for patients with a heart ≥75 bpm, the discrepancy between observed and predicted events is greater, see Table 57. The risk equations under-predict clinical events in this licensed population and under-predict the relative difference in events between ivabradine plus standard care and standard care alone. However, it is important to consider the direction of effect of these under-predictions and the potential impact this may have on the ICER estimates. The incremental benefit of ivabradine has been underestimated by these equations relative to the observed data and consequently this will generate conservative (higher) estimates of the ICER and bias against ivabradine.

Nevertheless, in light of these issues two additional sensitivity analyses were undertaken. The purpose of these analyses was to demonstrate the robustness of the base case ICER to alternative modeling strategies. In the first sensitivity analysis the heart rate covariate included in the CV mortality risk equation was transformed using a cubic function. This analysis was designed to account for the reduced association between heart rate and CV mortality in patients with a heart rate below 75 bpm. In the second sensitivity analysis a separate cost-effectiveness model was developed using risk equations developed using only data from patients with baseline heart rate ≥75 bpm (n=4154). This model was developed to see whether the model predictions could be improved for the ≥75 bpm population by using data only from this population. The ICER from both models was lower than the ICER generated from the base case model. The results of both of these additional models have been reported in subgroup analysis results (Section 6.9.4 and 6.9.3).

Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

The proportion of the cohort in the 'Alive' state over time has been extracted from the Markov trace for both the ivabradine plus standard care and standard care alone, see **Table** 58.

Table 58 The proportion of cohort in the 'Alive' health state over time

Time t (years)	Time t (months)	Proportion of patients Alive Std Care	Proportion of patients Alive Ivabradine plus Std Care
0	0	100%	100%
1	12	92%	93%
2	24	84%	85%
3	36	75%	77%
4	48	67%	70%
5	60	59%	62%
6	72	50%	54%
7	84	42%	46%
8	96	35%	38%
9	108	28%	31%
10	120	22%	25%
11	132	16%	19%
12	144	12%	14%
13	156	8%	10%
14	168	6%	7%
15	180	4%	5%

Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

Total patient quality adjusted life months (QALMs) accrued in each cycle were calculated by multiplying QoL (utility) values derived for each NYHA class by the proportion of patients alive in each NYHA class in each cycle. Total QALMs in each cycle were calculated by subtracting the reduction in QALMs associated with hospitalisation events from total cohort QALMs (summed across all NYHA classes). The QALMs accrued in each cycle for the first 15 years of the model are detailed in Table 59.

Table 59: Standard Care: QALMs accrued by cycle NYHA class, hospitalisation and Total QALMs

Time (years)	QALMs NYHA I	QALMs NYHA II	QALMs NYHA III	QALMs NYHA IV	Decrement (total QALMs) hospitalisation within 30 days end of cycle	Total QALMs
0	17.78	747.27	660.18	18.05	-5.43	1437.86
1	75.13	817.91	450.40	14.79	-4.59	1353.65
2	103.10	757.27	372.51	13.03	-4.11	1241.81
3	103.69	682.98	326.60	11.64	-3.69	1121.20
4	92.30	607.98	290.73	10.36	-3.29	998.09
5	81.07	534.00	255.36	9.10	-2.89	876.64
6	69.33	456.68	218.38	7.78	-2.47	749.70
7	57.95	381.71	182.53	6.50	-2.06	626.62
8	47.50	312.92	149.64	5.33	-1.69	513.70
9	38.10	250.97	120.01	4.28	-1.36	412.01
10	29.81	196.37	93.91	3.35	-1.06	322.38
11	22.45	147.86	70.70	2.52	-0.80	242.72
12	16.29	107.30	51.31	1.83	-0.58	176.14
13	11.41	75.14	35.93	1.28	-0.41	123.35
14	7.67	50.54	24.17	0.86	-0.27	82.97
15	4.93	32.49	15.53	0.55	-0.18	53.33

Table 60: Ivabradine plus standard Care: QALMs accrued by cycle NYHA class, hospitalisation and Total QALMs

Time (years)	QALMs NYHA I	QALMs NYHA II	QALMs NYHA III	QALMs NYHA IV	Decrement (total QALMs) hospitalisation within 30 days end of cycle	Total QALMs
0	18.08	761.24	674.34	18.60	-4.52	1467.74
1	90.27	859.20	442.24	10.69	-3.74	1398.66
2	124.38	795.56	367.95	9.50	-3.40	1293.99
3	126.08	722.45	325.46	8.56	-3.08	1179.47
4	113.44	650.04	292.84	7.71	-2.77	1061.25
5	100.85	577.87	260.33	6.85	-2.47	943.43
6	87.43	500.98	225.69	5.94	-2.14	817.90
7	74.21	425.24	191.57	5.04	-1.81	694.25
8	61.91	354.73	159.81	4.20	-1.51	579.13
9	50.64	290.16	130.71	3.44	-1.24	473.71
10	40.51	232.13	104.57	2.75	-0.99	378.98
11	31.28	179.22	80.74	2.12	-0.76	292.59
12	23.35	133.80	60.28	1.59	-0.57	218.44
13	16.88	96.74	43.58	1.15	-0.41	157.95
14	11.78	67.47	30.40	0.80	-0.29	110.15
15	7.88	45.17	20.35	0.54	-0.19	73.75

Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

The clinical outcomes (total Lys and total QALYs) associated with the 'Alive' health state have been disaggregated by NYHA distribution and for the standard care and ivabradine plus standard care groups in the table below. The QALY decrement associated with hospitalisation episodes has also been disaggregated separately.

Table 61: Model outputs by clinical outcomes

	Outcome	LY	QALY	Cost (£)
Standard care	*NYHA I*	*0.38*	*0.32*	*166.16*
	NYHA II	*3.23*	*2.41*	*1409.26*
	NYHA III	*1.90*	*1.23*	*829.37*
	NYHA IV	*0.09*	*0.04*	*40.01*
	Hospitalisation	*-*	*-0.01*	*7000.94*
	Total	***5.61***	***3.99***	***9445.74***
Ivabradine plus standard care	**Outcome**	**LY**	**QALY**	**Cost (£)**
	NYHA I	*0.47*	*0.39*	*443.38*
	NYHA II	*3.44*	*2.60*	*3365.75*
	NYHA III	*1.89*	*1.25*	*1909.14*
	NYHA IV	*0.07*	*0.03*	*67.36*
	Hospitalisation	*-*	*-0.01*	*6036.32*
	Total	***5.86***	***4.27***	***11821.96***

Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Table 62: Summary of QALY gain for Ivabradine plus Standard Care by health state

Health state	QALY Std Care	QALY Ivrabradine plus Std Care	Absolute increment	% Absolute increment
NYHA I	*0.32*	*0.39*	*0.08*	*28%*
NYHA II	*2.41*	*2.60*	*0.19*	*69%*
*NYHA III**	*1.23*	*1.25*	*0.02*	*6%*
*NYHA IV**	*0.04*	*0.03*	*-0.01*	*-4%*
Hospitalisation	*-0.01*	*-0.01*	*0.00*	*1%*
Total	***3.99***	***4.27***	***0.28***	***100%***

** fewer patients in NYHA III and IV in ivabradine plus std care arm*
QALY, quality-adjusted life year

Table 63: Summary of costs by health state

Health state	Costs Std Care	Costs Ivabradine plus Std Care	Absolute increment	% Absolute increment
NYHA I	*166.16*	*443.38*	*277.22*	*12%*
NYHA II	*1409.26*	*3365.75*	*1956.49*	*82%*
*NYHA III**	*829.37*	*1909.14*	*1079.78*	*45%*
*NYHA IV**	*40.01*	*67.36*	*27.35*	*1%*
Hospitalisation	*7000.94*	*6036.32*	*-964.62*	*-41%*
Total	***9445.74***	***11821.96***	***2376.22***	***100%***
**Fewer patients in NYHA III and IV in ivabradine plus std care*				

Table 64: Summary of predicted resource use by category of cost

Item	Cost Std Care	Cost Ivabradine plus Std Care	Absolute increment	% absolute increment
Technology cost (therapy titration and drug costs)	*642.21*	*3901.50*	*3259.30*	*137%*
Follow up costs	*1802.59*	*1884.14*	*81.54*	*3%*
Hospitalisations	*7000.94*	*6036.32*	*-964.62*	*-41%*
Total costs	***9445.74***	***11821.96***	***2376.22***	***100%***

Base-case analysis

Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

Table 65 Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) *versus* baseline (LYs)	ICER (£) incremental (QALYs)
Std Care	*9445.74*	*5.61*	*3.99*	-	-	-	-	-
Ivrabradine plus Std Care	*11821.96*	*5.86*	*4.27*	*2376*	*0.25*	*0.28*	*9363*	*8498*

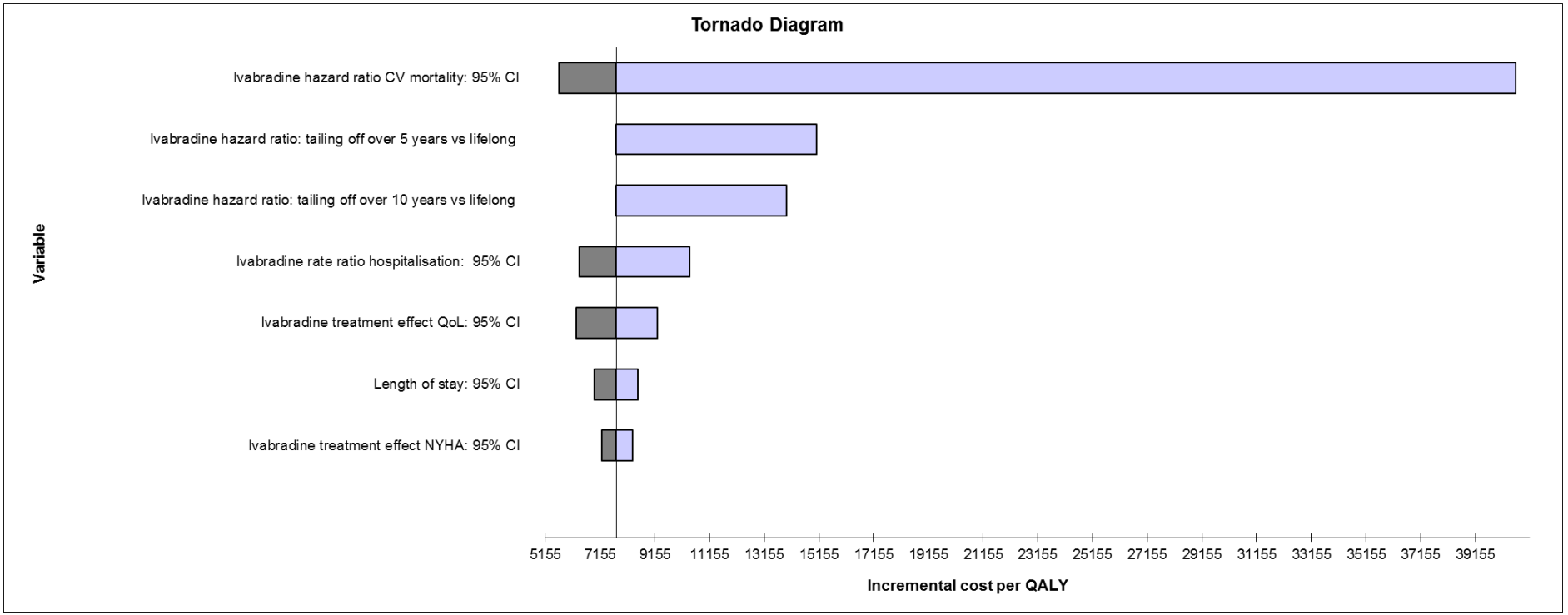
Sensitivity analyses

Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams

The results of the sensitivity analyses conducted on parameter estimates are reported in the Tornado diagram featured in Figure 16. A description of these results may be found in Section 6.7.10.

The base case ICER (£8498) was estimated by applying individual patient profiles from SHIfT into the risk equations sequentially, one at time, see Section 6.9.3 for further details on analysis methods. Whilst the base case ICER estimate was estimated by applying individual patient profiles to give the most accurate ICER estimate, this analysis is computationally expensive (takes 120+minutes to run) and consequently, to avoid protracted analysis time, the PSA, CEAC and Tornado diagrams presented have been estimated using average covariate values in the regression equations. Whilst there is some loss in accuracy in the ICER estimates from these analyses, overall, this approach was considered a reasonable and pragmatic method to assess the potential parameter and structural uncertainty present in the model.

Figure 16 Tornado diagram



Footnote: Tornado diagram presented has been estimated by applying average covariate values into the risk equations (note: base case ICER estimate derived using this method £7742 – approximately £700 less than the base case ICER estimate (£8498) which was derived by applying individual patient profiles into the risk equations one at a time).

Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

The PSA, CEAC and Tornado diagrams presented were estimated using average covariate values in the regression equations to avoid protracted analysis time, see Section 6.7.7 and Section 6.9.3 for further details on analysis methods.

The probabilistic sensitivity analysis indicates that ivabradine plus standard care would have over a 95% chance of being the optimal therapy when compared to standard care alone, considering the current maximally accepted ICER that NICE tend to consider (£20,000 per QALY). This can be seen in Figure 17and Figure 18.

Figure 17 Probabilistic Sensitivity Analysis

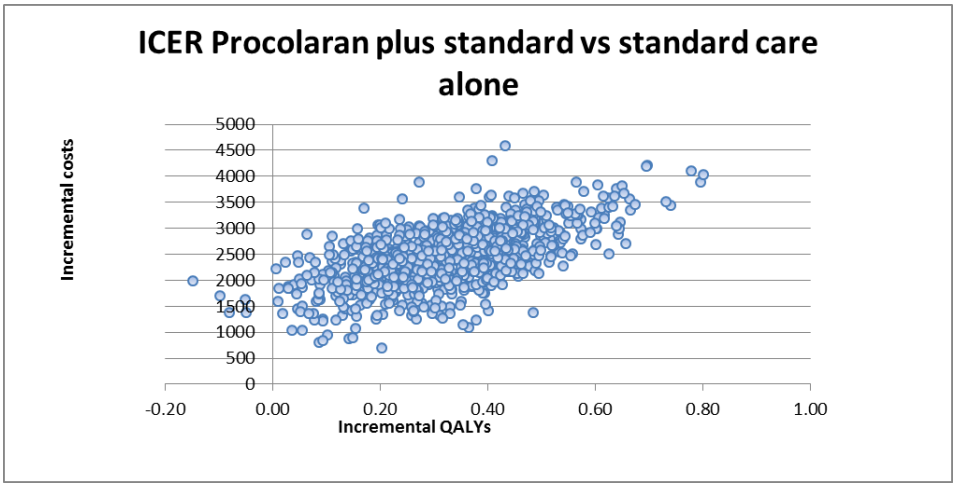
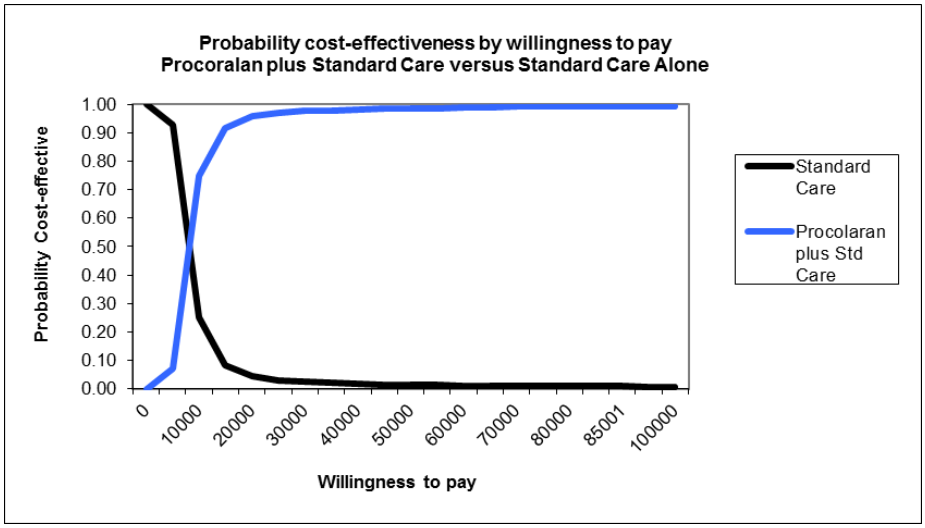


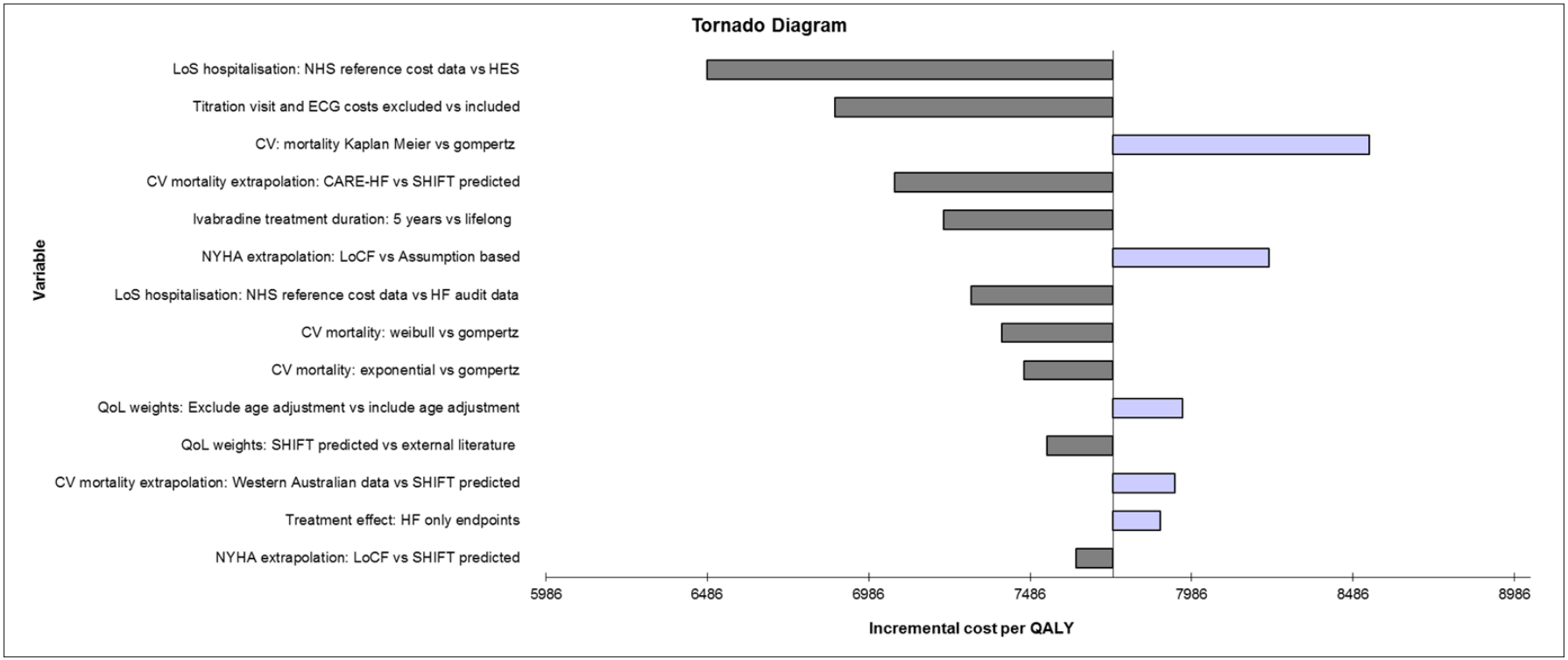
Figure 18 Cost-Effectiveness Acceptability Curve (CEAC)



Please present the results of scenario analysis. Include details of structural sensitivity analysis.

The structural scenario analyses indicate that our assumptions have generally been conservative with respect to the ivabradine ICER. The use of alternative external data sources for hospitalisation costs and QoL weights (utility values) both yielded more favourable ICER estimates for ivabradine. The use of alternative parametric distributions (exponential and Weibull) also both resulted in a more favourable ICER estimate.

Figure 19 Structural scenario analyses



Footnote: Tornado diagram presented has been estimated by applying average covariate values into the risk equations (note: base case ICER estimate derived using this method £7742 – approximately £700 less than the base case ICER estimate (£8498) which was derived by applying individual patient profiles into the risk equations one at a time).

What were the main findings of each of the sensitivity analyses?

The results of deterministic sensitivity analyses indicated that the ICER was likely to remain below the £20,000 per QALY threshold in all considered scenarios which suggested robustness of results to clinically plausible changes in assumptions. Further details of these results have been detailed below.

Mortality

The model showed some sensitivity to changes in the hazard ratio for CV mortality within 95% confidence intervals, and in structural scenario analyses which varied assumptions regarding the ongoing treatment effect in the post-trial period. In scenarios where ivabradine therapy is stopped and the hazard ratio returns to 1, ivabradine continues to demonstrate favourable ICER values if the costs of therapy are ceased once the benefit of therapy stopped. In a worst case scenario where the benefit of ivabradine therapy reduces linearly to zero over a specified period (e.g. 5 years), but the costs of ivabradine continue to be incurred, the ICER increases to approximately £15,000 per QALY but crucially remains well below a threshold of £20,000 per QALY.

The ICER was insensitive to changes in the data source for the extrapolation of CV mortality (SHIfT, CARE-HF) or changes in the parametric distribution selected.

Hospitalisation

The model showed some sensitivity to changes in the rate ratio for hospitalisation within 95% confidence intervals (ICER range approximately £6400-£10400) and the modelled hospitalisation length of stay (ICER range approximately £6900-£8500). In a scenario which considered a length of stay based on National Heart Failure Audit data (median 9 days) rather than NHS reference cost data (5.13 days) the ICER decreased to approximately £7300 per QALY saved. The model was insensitive to changes in the underlying rate of hospitalisations.

QoL

The model showed some sensitivity to changes in the treatment effect on QoL within 95% confidence intervals (ICER range approximately £6300-£9300). However, the model was insensitive to changes in utility estimates to other data sources (SHIfT predicted *versus* Gohler et al.2009) or inclusion of an age-adjustment (higher utility loss as the modelled cohort aged).

General

The ICER increased to approximately £15,200 if a within-trial time horizon was selected. The ICER reduced to approximately £6900 if costs of a titration visit and ECG were excluded.

What are the key drivers of the cost-effectiveness results?

The primary driver in the ICER in the base case lifetime model was the relative treatment effect of ivabradine on hospitalisation and associated costs of care and CV mortality. Ivabradine was associated with a substantial reduction in hospitalisations which offset a large proportion of the costs of therapy. Ivabradine was also associated with survival gains and a small improvement in QoL. The model indicated that together these benefits generated a favourable ICER estimate.

Validation

Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

Quality control checks were included at several points during the modelling process and were designed to be consistent with published health technology assessment good practice guidelines (101).The following validation tasks were performed:

- The economic analysis plan was informed by a full systematic review of previous economic models of pharmaceutical interventions in HF.
- The draft model was presented to senior clinical advisors and health economic experts to review key assumptions and the core model structure in two separate advisory board meetings.
- The STATA code derived for each regression model used in the economic analysis was independently checked by a senior analyst not involved in the original risk equation development.
- All STATA analyses were reviewed by an independent biostatistician to verify that the most appropriate models had been developed for each clinical endpoint.
- The predicted outcomes from the model (mortality, hospitalisation, NYHA distribution and QoL) were compared to observed estimates to test whether the model results accurately reflected SHIfT observed data.
- A range of structural sensitivity analyses were undertaken to test whether the model results were unduly affected by the model structure.
- A range of parameter sensitivity analyses were undertaken to test the robustness of results to plausible changes in values.
- The results of the model were analysed to ensure that the direction and magnitude of effect reflected expectations in view of the inputs used.
- A senior analyst *not* involved in the original modelling reviewed each Excel worksheet for potential referencing, input and calculation errors.
- A senior analyst *not* involved in the original modelling independently rebuilt the Markov trace.

These steps were designed to ensure that all aspects of potential error in the model – a lack of internal validity, a lack of external validity and any omissions or biases from an individual analyst – were addressed. The intention was to force the model building to remain an iterative process, where errors were progressively eradicated.

Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost-effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost-effectiveness due to known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 5.3.7.

The ICER values have been estimated for a series of subgroup populations; these subgroup populations were identified with reference to the predefined subgroups within the clinical trial protocol and previous SHIfT study publications, see Section 6.9.2. It is noted that some analyses have examined patient subgroups using a greater number of categories than the analyses originally reported in the SHIfT clinical study.

In addition to the subgroup analyses referred to above (which relate to the licensed population with heart rate ≥75 bpm, based on a model derived from the total SHIfT population) additional analyses were undertaken for a modelled population designed to be representative of a UK heart failure patient group. The characteristics chosen for this population reflected SHIfT modal characteristics (patients with a heart rate ≥75 bpm) for all binary and categorical variables (except region, which was changed to the UK and age which was changed to reflect the UK median age of a HF patient).

This population, therefore, differed from other subgroup populations which considered the average SHIfT population (heart rate ≥75 bpm) displaying a particular characteristic of interest.

Please clearly define the characteristics of patients in the subgroup.

In subgroup analyses individual patient characteristics from the licensed patient cohort (patients with a baseline heart rate ≥75 bpm) have been used to estimate overall costs and QALYs for ivabradine plus standard care *versus* standard care alone. Individual patient profiles (characteristics) have been applied to the SHIfT adjusted risk equations in the model (sequentially - one profile at a time), to estimate total costs, life years and QALYs. In subgroup analyses cost per QALY has been estimated using cost and outcome data from patient profiles containing the sub-group defining the characteristic of interest. Thus the model is designed to reflect heterogeneity in SHIfT patients' risk factors.

The subgroup analyses consider patients with the following characteristics (note: only in SHIfT patients with a heart rate above 75 bpm to reflect the European licence for ivabradine):

- Patients ≥75 years/ <75 years
- NYHA class (II, III and IV)
- Beta blocker use (no beta-blocker use, < half target dose, ≥ half target dose <target dose, and ≥ target dose)
- HF duration (quartiles: >0.6 yrs, ≥0.6 <2 yrs, ≥2 <4.8 yrs, ≥ 4.8 years)
- LVEF (quartiles: <26%, ≥26%<30%, ≥30%<33%, ≥33%)
- Prior medical history (coronary artery disease, diabetes)
- Ischaemic aetiology (yes/no)

The population designed to be reflective of a typical UK HF population specified baseline characteristics in the SHIfT risk equations:

- Western European male
- Age: UK median age of heart failure patients (78 years) (National Heart Failure Audit 2008 - 2009 (102)).
- Beta blockade: at least half target dose beta-blockade.

Other binary and categorical variables reflected SHIfT modal values whilst continuous variables reflected mean values based on data from the SHIfT cohort with heart rate ≥75 bpm. It is noted that the assumptions regarding beta-blockade were considered conservative and all patients were treated with at least half target dose beta-blockade (but less than target dose); evidence from a current GP database indicates that this is better than current UK practice (63). In the second low risk

population, the population was identical to that considered above but patients were treated with at least target dose beta-blockade.

Please describe how the statistical analysis was undertaken.

The risk equations employed in the base case economic analysis have been developed using data from the entire SHIfT population (patients with a heart rate ≥70bpm). However, these equations under-predict the underlying risk of clinical outcomes (mortality, hospitalisation) and the treatment effect of ivabradine on CV mortality. Two sensitivity analyses were developed, designed to improve estimates for the sub-population with heart rate ≥75bpm (as per the European licence). In the first sensitivity analysis the heart rate covariate was transformed using a cubic function in the risk equation for CV mortality (also see Section 6.7.1). The resulting risk equation provided a better statistical fit of the data and generated a hazard for ivabradine on CV mortality which more closely reflected observed estimates in patients with a heart rate ≥75bpm. However, this model was non-intuitive due to the use of the cubic function and was not used as the base case estimate. In a second separate model , the risk equations for each clinical endpoint were re-developed using data only from the SHIfT cohort with a heart rate ≥75 bpm (n=4154). This model was developed to provide an alternative means of predicting mortality, hospitalisation, NYHA distribution and QoL specifically for the SHIfT population with a heart rate ≥75 bpm.

In both alternative models, the ICER generated for ivabradine plus standard care *versus* standard care alone was more favourable than the ICER reported in the base case model. In the model which used a cubic transformation to capture baseline heart rate in the CV mortality risk equations, the base case ICER reduced to approximately £7,250 per QALY saved. A summary of the results of the second model are detailed in Table 69; the full report which documents model inputs and results is available on request.

The regression equations employed in the current model require each patient characteristic to be specifically defined. For example, gender must be specified as either male or female, although in SHIfT 24% of the population was female. Whilst it is possible to specify the average proportion of patients with each given characteristic in the regression equation (e.g. 0.24 for female), applying values in this fashion may lead to some inaccuracy in the estimated ICER due to the inherent non-linearity present in a cost-effectiveness model. The current analysis overcomes this problem by applying individual patient profiles from the SHIfT study cohort into the risk equations one at a time. The total costs and QALYs for each given profile are simulated as if the patient had been treated with ivabradine plus standard care or standard care therapy alone. The incremental cost per QALY for ivabradine plus standard care *versus* standard care alone has been calculated for the base case analysis by averaging total costs and QALYs across all patient profiles with heart rate ≥75 bpm. In subgroup analyses, ICER estimates have been calculated by averaging

total costs and QALYs across patient profiles with the subgroup characteristic of interest (again only in those patients with resting heart rate ≥75 bpm).

It is noted that the PSA has been developed to use average proportions of patients with each given characteristic to provide an estimate of the potential joint parameter uncertainty whilst avoiding protracted analysis time.

What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 6.7.6 (Base-case analysis).

Results of the specified subgroup analyses showed that ivabradine in addition to standard care consistently remained cost effective when compared with standard care alone (Table 66). The subgroups defined by beta-blocker dose are of particular interest, and show that ivabradine remains cost-effective across all dose ranges investigated, even in patients at target dose beta-blockade (£10,374 per QALY).

Patients with more severe heart failure (NYHA class III and IV) were likely to be more cost-effective to treat than patients in a milder NYHA class.

Table 66: Subgroup results (£)

Subgroup	Standard Care		Ivabradine plus std care		Incremental costs and outcomes				
	Total Costs	Total QALYs	Total Costs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	Incremental Cost/LY	Incremental Cost/QALY
All patients (HR>=75 bpm.)	9446	3.987	11822	4.267	2376	0.254	0.280	9363	8498
Age<75 years	9585	4.139	12061	4.432	2476	0.266	0.293	9308	8464
Age>=75 years	8117	2.537	9538	2.693	1421	0.137	0.156	10375	9101
NYHA II	9752	4.554	12496	4.836	2744	0.243	0.283	11305	9712
NYHA III	9280	3.554	11369	3.834	2090	0.265	0.280	7878	7467
NYHA IV	6610	1.792	7693	2.000	1083	0.223	0.208	4853	5197
HF duration <0.6 years	10078	5.024	12997	5.353	2919	0.280	0.329	10439	8886
HF duration >=0.6<2 years	9373	4.104	11839	4.394	2466	0.263	0.290	9379	8489
HF duration >=2<4.8 years	8540	3.657	10858	3.918	2318	0.243	0.260	9556	8901
HF duration >=4.8 years	9805	3.197	11625	3.437	1820	0.231	0.240	7894	7573
No beta blocker	9689	3.081	11342	3.389	1652	0.309	0.308	5341	5361
Beta blocker < half target dose	9198	3.603	11296	3.874	2098	0.253	0.271	8304	7726
Beta blocker =>half target dose < target dose	9746	4.449	12449	4.728	2703	0.242	0.279	11152	9689
Beta blocker =>target dose	9413	4.640	12309	4.920	2896	0.238	0.279	12145	10374
LVEF < 26%	9930	3.312	11715	3.597	1785	0.276	0.285	6478	6258
LVEF >=26%<30%	8890	3.664	11075	3.936	2185	0.253	0.272	8644	8030
LVEF >=30<33%	9114	4.188	11696	4.472	2582	0.256	0.284	10102	9090
LVEF >= 33%	9629	4.640	12494	4.915	2865	0.232	0.275	12343	10427
Non-diabetic	8802	4.044	11289	4.324	2487	0.253	0.280	9848	8883
Diabetic	10850	3.862	12986	4.141	2135	0.257	0.279	8320	7654
No prior CAD	9111	4.203	11588	4.521	2477	0.291	0.318	8522	7785
Prior CAD	9583	3.898	11918	4.162	2335	0.239	0.264	9783	8851

Table 67: Subgroup results for a typical UK HF population ≥75 bpm treated with ≥ half target dose beta-blockade (less than target dose) (£)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) *versus* baseline (LYs)	ICER (£) incremental (QALYs)
Std Care	*8199.93*	*4.36*	*3.05*	*-*	*-*	*-*	*-*	*-*
Ivrabradine plus Std Care	*9891.82*	*4.52*	*3.25*	*1692*	*0.16*	*0.19*	*10643*	*8735*

Table 68: Subgroup results for a typical UK HF population ≥75 bpm treated with ≥ target dose beta-blockade (£)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) *versus* baseline (LYs)	ICER (£) incremental (QALYs)
Std Care	*7745.26*	*4.41*	*3.09*	*-*	*-*	*-*	*-*	*-*
Ivrabradine plus Std Care	*9525.69*	*4.57*	*3.28*	*1780*	*0.16*	*0.19*	*11260*	*9185*

Table 69 Base case and subgroup results: ivabradine model developed using risk equations from the SHIfT ≥75 bpm population

Subgroup	Standard Care		Ivabradine		Ivabradine vs Standard care		
	Total Costs	Total QALYs	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	Incremental Cost/QALY
All patients (HR ≥75 bpm)	9588	3.92	12121	4.32	2532	0.40	6307
Age<75 years	9721	4.06	12357	4.48	2637	0.42	6286
Age≥75 years	8325	2.54	9860	2.77	1535	0.23	6666
NYHA II	9670	4.44	12566	4.86	2896	0.42	6945
NYHA III	9635	3.52	11881	3.91	2246	0.39	5731
NYHA IV	6627	1.83	7953	2.12	1326	0.29	4625
HF duration <0.6 years	10163	4.89	13177	5.35	3014	0.46	6585
HF duration ≥0.6<2 years	9491	4.00	12099	4.41	2608	0.41	6291
HF duration ≥2<4.8 years	8929	3.61	11400	3.99	2471	0.38	6492
HF duration ≥4.8 years	9785	3.21	11838	3.57	2052	0.35	5786
No beta blocker	9861	3.12	11718	3.52	1857	0.40	4700
Beta blocker < half target dose	9205	3.56	11513	3.95	2308	0.39	5919
Beta blocker ≥half target dose < target dose	9454	4.21	12239	4.62	2785	0.41	6855
Beta blocker ≥target dose	10266	4.65	13278	5.07	3012	0.42	7169
LVEF < 26%	10038	3.26	12032	3.66	1994	0.40	5025
LVEF ≥26%<30%	9334	3.76	11765	4.16	2431	0.40	6093
LVEF ≥30<33%	9489	4.12	12184	4.53	2696	0.41	6595
LVEF ≥ 33%	9408	4.45	12363	4.85	2955	0.40	7369
Non-diabetic	9028	3.96	11650	4.37	2622	0.40	6485
Diabetic	10812	3.82	13148	4.22	2335	0.40	5909
No prior CAD	9501	4.09	12094	4.54	2592	0.45	5814
Prior CAD	9624	3.85	12132	4.23	2508	0.38	6542

Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 4.

All obvious subgroups were considered.

Interpretation of economic evidence

Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

The results of SHIfT are consistent with published literature which suggests that an elevated resting heart rate is a risk factor for excess mortality and morbidity in both the general population, and in particular in patients with heart failure (Fox et al. 2008; McAlister et al. 2009; Metra et al. 2005; Pocock et al. 2006 (27);(60); (5);(30)). As discussed earlier (Section 5.10.2) , there is a very strong association between heart rate reduction with beta-blockers and decreasing all-cause mortality (McAlister 2007 (5)). Other heart failure studies such as the CHARM trial of candesartan (Pocock 2006 (30)) and the COMET trial of carvedilol both add weight to this relationship (Metra 2005 (60)).

The external evidence, therefore, is consistent with the SHIfT trial data and indicates that a reduction in heart rate is associated with improvement patient outcomes. The combined action on mortality, hospitalisation and quality of life is expected to translate into a strong economic argument.

Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 4?

The economic evaluation suggests that ivabradine is likely to be cost-effective in the identified subgroups relevant to the ivabradine licensed indication (NYHA II-IV, LVEF <35%, heart rate ≥75 bpm) including those patients treated with target dose beta-blockade.

What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The current study has applied data primarily from SHIfT, a large double blind RCT which demonstrated that the addition of ivabradine to standard care therapies in a HF population with left ventricular systolic dysfunction achieves favourable clinical outcomes, reduces hospitalisations and improves QoL.

In Section 5.10.4 we discussed the SHIfT study in terms of generalisability and found the trial to be very relevant to a UK heart failure population. Key issues relating to differences between the trial population and UK practice in terms of age, standard care treatment practice and hospitalisation event history warrant further discussion in the context of the economic model.

Patients in SHIfT were younger than an average UK HF population (SHIfT mean age was 61 years, UK HF population mean age reported in the UK National Heart Failure audit was 78 years) and 66% (4621/6505) of SHIfT patients were of Eastern European origin and, consequently, may have been treated differently to UK patients. All patients in SHIfT were required to have experienced a hospitalisation event within the 12 months prior to randomisation for study inclusion. The potential impact of these differences is discussed in the following paragraphs.

Cohort Age

The results of SHIfT indicate that, in patients ≥75 years, the ICER would be approximately £9100 per QALY, slightly higher than the SHIfT average ICER. This result is driven by competing effects of increasing baseline risk and reducing the lower baseline heart rate associated with older patients.

However, although SHIfT patients are considerably younger than an average HF patient in the UK, patients with systolic heart failure are younger than those with preserved ejection fraction (Section 5.10.4). Recent analysis of Hull audit data shows the median age of 'SHIfT-like' patients to be *ca.* 69 years).

Treatment practice

The management of chronic heart failure patients may vary between countries. In the current model the differences in treatment practice between a UK population and the predominantly Eastern European SHIfT population may affect standard care therapy use, especially beta-blockade (see Section 6.2.7), and also serious adverse event management which would impact modelled resource use and clinical outcomes. However, the current evidence indicates that there was slightly higher use of standard care heart failure therapies in SHIfT (including beta-blockade) compared with current UK treatment patterns. Furthermore, even in patients optimally treated with beta-blockade, ivabradine would be expected to remain cost-effective (see Table 69).

In the current model a large proportion of the modelled benefit for ivabradine stems from a reduction in hospitalisations. However, it is acknowledged that serious adverse event management may also differ by country. A covariate representing the region in which the patient was randomised was found to be a significant predictor of the hospitalisation rate (regional categories: Western European plus Australia and Canada (Western), Eastern European, Latin American, Asian). The regression equations predicted the lowest rates of hospitalisation for Eastern European populations (0.046 hospitalisations per person month) and the highest rates of

hospitalisation for Western European, Australian and Canadian populations (0.063 hospitalisations per person month). A subsequent review of these data by a UK clinical expert suggested that countries such as France and Germany, also grouped in Western European, may have higher rates of hospitalisation and longer length of stay than the UK. Expert opinion suggested that the UK was likely to have similar treatment patterns to other Northern European countries (Sweden, Netherlands, Finland, Denmark and Norway). However, further analysis demonstrated that, contrary to expectations, the UK and Northern European countries (n=266) had the highest rates of hospitalisation in SHIfT (0.076 per person month). The available evidence suggests that, if the UK demonstrates similar treatment patterns to Northern European countries, average SHIfT hospitalisation rates based primarily on an Eastern European population for the base case are conservative with respect to the impact on the cost effectiveness of ivabradine.

Trial eligibility criteria

SHIfT trial eligibility criteria specified patients must have incurred a hospitalisation event in past 12 months, which may have driven a higher clinical event rate for the SHIfT cohort relative to general UK patients of a comparable age. The hospitalisation rate in the placebo arm of SHIfT was approximately 0.52 hospitalisations per person year. However, this rate appears slightly lower than hospitalisation rates previously reported in other HF studies. A previous trial programme (CHARM) reported hospitalisation rates for two related trials in HF patients (NYHA II-IV, LVEF <40%). One trial was in patients who had a prior hospitalisation event in the past 6 months (CHARM added; n=2548, mean age 64 years), the other included patients who had no prior hospitalisation event (CHARM alternative; n=2028, mean age 67 years). Despite the difference in inclusion criteria between these trials, the reported placebo event rates were extremely close (0.75 and 0.71 hospitalisations per person year respectively) (15). The CHARM data indicates hospitalisation rates in SHIfT to be low in comparison, and that there may be little increase in the rate of hospitalisation in a HF population resulting from study inclusion criteria requiring a prior hospitalisation event.

It is also noted that any increase in hospitalisation event rates due to SHIfT study inclusion criteria is likely to be offset by the reduction in hospitalisation events expected in an Eastern European population relative to a Western European (UK) population, and to the low mean age of the SHIfT cohort. This difference in baseline risk is also borne out by the observation (Section 5.10.4) that all-cause and CV mortality rates are lower in the SHIfT placebo arm than in a study of ‘SHIfT-like’ patients in Hull (35).On balance, the current available evidence suggests that SHIfT hospitalisation rates are likely to be conservative relative to a UK HF population.

Summary

In summary, SHIfT is believed to generalise well to a UK HF population. Whilst there are differences between UK HF patients and SHIfT patients, these differences are overall expected to lead to the ICER for ivabradine being less favourable than might

expected in the wider clinical setting. The low SHIfT cohort age is likely to result in a slightly lower clinical event rate in SHIfT compared to a UK population, and variation in treatment practice between the UK and the mainly Eastern European population will potentially result in a more conservative estimate of hospitalisation event rates. The evidence also indicates that the use of standard care heart failure therapies in SHIfT, in particular beta-blockade, is slightly better than current UK treatment patterns. This study has consequently applied SHIfT demographic and clinical population characteristics in the base case cost effectiveness analysis.

However, a sensitivity analysis has been undertaken to verify the effect of changes in patient characteristics to more closely fit the UK. In this analysis a theoretical patient population has been considered, reflecting SHIfT mean values for continuous variables and modal values for binary and categorical values, with the exception of heart rate, region, age and beta-blocker use. Baseline heart rate has been assumed to reflect the mean value for patients with heart rate above 75 bpm (84 bpm), region has been changed to Western European, age has been modified to 78 years, consistent with the average (median) age of HF patients in the UK National Heart Failure Audit (4). In addition, assumptions regarding beta-blockade, already considered plausible for a UK population, have been made more conservative whereby all patients were assumed to receive at least half target dose beta-blocker therapy. The purpose of this sensitivity analysis was to demonstrate robustness of results to changes in assumptions which more closely reflect UK HF population characteristics and conservative assumptions regarding beta-blocker use. The analysis demonstrated that, in the modelled UK population optimally treated with beta-blockade, ivabradine would be expected to remain highly cost-effective (see Table 69).

What further analyses could be undertaken to enhance the robustness/completeness of the results?

Further collection of long term data in heart failure patients would help reduce uncertainty in the treatment effect of ivabradine on CV mortality, hospitalisation and QoL in the post-trial period.

Section C – Implementation

7 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

Servier undertook a targeted review of UK epidemiological data for chronic heart failure (report dated Nov 2011 (103)). A search on 14-15th October 2011 of UK National data sources identified a relevant report from the British Heart Foundation (Petersen 2002). A search of the life-sciences bibliographic databases conducted on 26th October 2011 identified five further studies; two of these, Cowie 1999 and Davies 2001, were considered the most robust estimate of disease incidence and prevalence in the UK. These sources were also referenced in NICE CG108 so were utilised in the calculation of eligible patients.

The prevalence of definite heart failure in the UK in patients aged ≥45 years is 2.3% (Davies 2001). 2% of HF patients are <45 years (National Heart failure Audit 2011 (4)). Cowie 1999 estimates that there are 63,000 new cases of heart failure per annum. The annual mortality rate from HF is estimated to be 9% in the ECHOES study (Hobbs 2007 (104)). Therefore, the net number of patients in England and Wales with definite heart failure in year 1 is 550,837, rising to 754,163 in year 5 (Table 70).

Table 70: Estimate of the number of patients with heart failure in England and Wales

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated number of patients with HF (prevalence + incidence)	605,315	661,174	717,033	772,892	828,751
Annual mortality rate for patients with HF	9.0%	9.0%	9.0%	9.0%	9.0%
Net number of patients with HF	**550,837**	**601,668**	**652,500**	**703,332**	**754,163**

To identify the maximum number of patients eligible for ivabradine therapy it is necessary to estimate the number of heart failure patients in England and Wales that meet the following criteria:

1. Heart failure with systolic dysfunction - Davies 2001 estimates that the prevalence of definite heart failure and LVSD is 41.3%.

Table 71: Estimate of the number of patients with HF and LVSD in England and Wales

	Year 1	Year 2	Year 3	Year 4	Year 5
Net number of patients with HF	550,837	601,668	652,500	703,332	754,163
Patients with HF and LVSD	**227,496**	**248,489**	**269,482**	**290,476**	**311,469**

2. NYHA class II-IV
3. Sinus rhythm
4. Resting heart rate ≥75 bpm

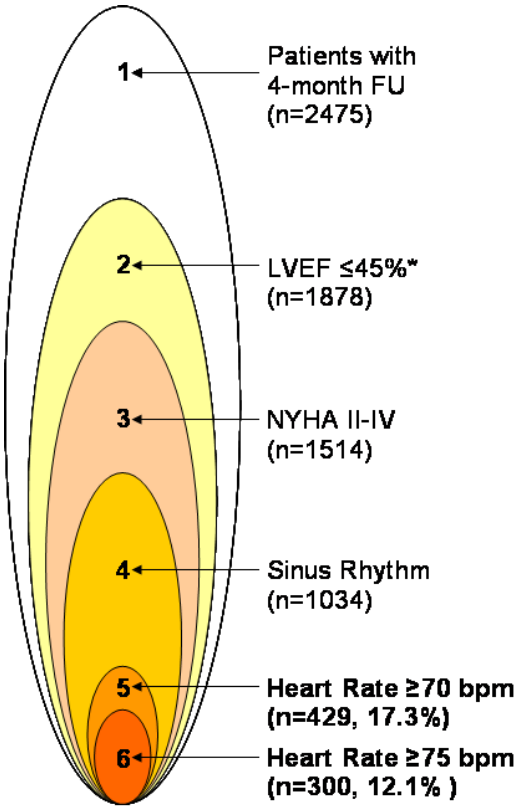
Cleland 2012 estimated the number of patients eligible for ivabradine therapy through an audit of a heart failure out-patient service. Referrals to this service come from primary and secondary care. The only criterion for referral is that patients are regarded as being at high risk of developing heart failure. Patients are evaluated and treated appropriately, with GPs then instructed on therapy optimisation such as titration of beta-blockade, before returning to the clinic for a 4 month review. By this stage patients may be viewed as having received therapy optimisation, and may therefore be considered appropriate for ivabradine therapy if they meet the additional licence criteria (points 2-4 above).

Figure 20 indicates the proportion of patients with heart failure and LVSD who may be eligible for ivabradine therapy is 16% (300/1878), considering a LVEF threshold of ≤45%. This corresponds to *ca.* 36,000 eligible patients in England and Wales based on the licence criteria (Table 72). It should be noted that this estimate includes patients treated with a beta-blocker as well as those contra-indicated or intolerant to beta-blockade.

Table 72: Estimate of patients in England and Wales that may be eligible for ivabradine therapy

	Year 1	Year 2	Year 3	Year 4	Year 5
Patients with HF and LVSD	227,496	248,489	269,482	290,476	311,469
Proportion of patients with HF, LVSD and other licence criteria	16%	16%	16%	16%	16%
Potential number of eligible patients treated each year in licence	**36,345**	**39,699**	**43,053**	**46,407**	**49,761**

Figure 20: Patients in the Hull audit considered eligible for ivabradine therapy at 4 months



What assumption(s) were made about current treatment options and uptake of technologies?

For patients to be considered for ivabradine they must first receive optimal beta-blocker therapy (unless contra-indicated or intolerant) and other therapies recommended in NICE CG108. Ivabradine is indicated for use on top of standard therapy and will not therefore displace any existing treatments.

Patients eligible for treatment with ivabradine will already be diagnosed with HF and LVSD and will therefore be known to the NHS in England and Wales. As ivabradine is a new treatment for heart failure uptake will be influenced by clinician knowledge of the therapy and familiarity with its usage in heart failure. Servier has a small commercial team that is unable to cover all NHS trusts (this represents a cohort of 70-75% of all Cardiologists) and has no presence in primary care. Therefore Servier estimate that the maximum uptake of ivabradine in eligible patients will be 10% in year 1 rising to 50% in year 5.

What assumption(s) were made about market share (when relevant)?

N/A – there are no alternatives to ivabradine for the specified patient population.

In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

There are no other significant costs associated with treatment with Ivabradine. As a conservative assumption in the cost-effectiveness analysis two NHS reference costs were included in the base case for ivabradine patients; an ECG (code DA01) for determination of resting heart rate prior to initiation of treatment and a face to face outpatient visit with a cardiology specialist (code 320) for dose titration. It should be noted that dosage titration is most likely to take place in primary care, probably in a routine visit, and the ECG is likely to the undertaken as part of standard care as recommended in NICE CG108. These costs are therefore unlikely to be realised and have been omitted from the budget impact analysis. In any case they are relatively low and it is doubtful whether they will be of interest to commissioners. (see Section 7.7)

What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

Unit costs for drugs and hospitalisations applied in the budget impact analysis are generally the same as those used in the cost-effectiveness analysis and are detailed in Sections 6.5.5 and 6.5.6. For the purpose of budget impact calculation, one exception is that no reduction in the acquisition cost of ivabradine has been made to allow for 7% of patients in the SHIfT study who received a 2.5 mg dose of ivabradine. The mean cost of hospitalisation (£2,479) was estimated using NHS reference costs and weightings for HF, CV and non-CV admissions (see Section 6.5.1). Resource use savings are estimated to be £0.5m in year 1, rising to £3.5m in year 5 (Table 73).

Were there any estimates of resource savings? If so, what were they?

In the licensed population of the SHIfT trial, addition of ivabradine to optimised heart failure therapy reduced hospitalisation for any cause by 18% (HR 0.82, 95% CI 0.75-0.90, p<0.0001). Therefore resource use savings due to a reduction of hospitalisations are expected. The annualised risk of hospitalisation for any cause was 27.5% *vs* 33.7% in the ivabradine and placebo groups respectively, representing a difference of 6.2%. This difference has been applied to the annual estimate of patients eligible for ivabradine and the mean cost of hospitalisation (£2,479) to determine resource use savings.

What is the estimated annual budget impact for the NHS in England and Wales?

The estimated annual budget impact for the NHS is shown in Table 73. The cost of ivabradine has been applied without half cycle correction, and the calculation allows for the discontinuation rate associated with ivabradine therapy (the annual withdrawal rate in SHIfT for ivabradine treated patients was 8.9%PY for emergent adverse events in the population with heart rate ≥75 bpm). Servier expect therapy initiation to be carried out in either secondary or primary care as part of a routine visit (i.e. the patient will not be referred specifically for the initiation of ivabradine); as such no costs for this attendance would be incurred. As discussed in 7.4, additional costs included as a conservative assumption in the cost-effectiveness analysis have been excluded from these calculations. The net budget impact of ivabradine in England and Wales is £1.2m in year 1 rising to £8.4m in year 5.

Table 73: Budget Impact of ivabradine in England and Wales

Budget Impact (£)	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients treated in each year	3,311	7,233	11,766	16,911	22,666
Medicine acquisition cost per patient per annum	£524	£524	£524	£524	£524
Total cost of ivabradine	£1,734,990	£3,790,191	£6,165,604	£8,861,228	£11,877,064
Less					
Resource use savings	-£508,898	-£1,111,720	-£1,808,464	-£2,599,131	-£3,483,720
NET TOTAL BUDGET IMPACT	£1,226,091	£2,678,471	£4,357,140	£6,262,098	£8,393,344

Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Opportunities for resource savings have all been identified. However, for the population of relevance to the licensed indication and NICE decision problem, it should be noted that only 35 patients need to be treated with ivabradine to prevent a death. The addition of ivabradine to optimised recommended therapy for heart failure will therefore reduce mortality and help fulfill one of the aims identified in NICE CG108.

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9 Appendices

Appendix 1

SUMMARY OF PRODUCT CHARACTERISTICS (Feb 2012)

1. NAME OF THE MEDICINAL PRODUCT

▼Procoralan 5 mg film-coated tablets
▼Procoralan 7.5 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Procoralan 5 mg
One film-coated tablet contains 5 mg ivabradine (equivalent to 5.390 mg ivabradine as hydrochloride).
Excipient: 63.91 mg lactose monohydrate

Procoralan 7.5 mg
One film-coated tablet contains 7.5 mg ivabradine (equivalent to 8.085 mg ivabradine as hydrochloride).
Excipient: 61.215 mg lactose monohydrate

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Procoralan 5 mg: salmon-coloured, oblong, film-coated tablet scored on both sides, engraved with "5" on one face and **Error! Objects cannot be created from editing field codes.** on the other face.
The tablet can be divided into equal halves.

Procoralan 7.5 mg: salmon-coloured, triangular, film-coated tablet engraved with "7.5" on one face and **Error! Objects cannot be created from editing field codes.**on the other face.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of coronary artery disease
Symptomatic treatment of chronic stable angina pectoris in coronary artery disease adults with normal sinus rhythm. Ivabradine is indicated:

- in adults unable to tolerate or with a contra-indication to the use of beta-blockers

- or in combination with beta-blockers in patients inadequately controlled with an optimal beta-blocker dose and whose heart rate is > 60 bpm.

Treatment of chronic heart failure
Ivabradine is indicated in chronic heart failure NYHA II to IV class with systolic dysfunction, in patients in sinus rhythm and whose heart rate is ≥ 75 bpm, in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated. (see section 5.1)

4.2 Posology and method of administration

Posology

For the different doses, film-coated tablets containing 5 mg and 7.5 mg ivabradine are available.

Treatment of coronary artery disease
The usual recommended starting dose of ivabradine is 5 mg twice daily. After three to four weeks of treatment, the dose may be increased to 7.5 mg twice daily depending on the therapeutic response. If, during treatment, heart rate decreases persistently below 50 beats per minute (bpm) at rest or the patient experiences symptoms related to bradycardia such as dizziness, fatigue or hypotension, the dose must be titrated downward including the possible dose of 2.5 mg twice daily (one half 5 mg tablet twice daily). Treatment must be discontinued if heart rate below 50 bpm or symptoms of bradycardia persist (see section 4.4).

Treatment of chronic heart failure
The treatment has to be initiated only in patient with stable heart failure. It is recommended that the treating physician should be experienced in the management of chronic heart failure.
The usual recommended starting dose of ivabradine is 5 mg twice daily. After two weeks of treatment, the dose can be increased to 7.5 mg twice daily if resting heart rate is persistently above 60 bpm or decreased to 2.5 mg twice daily (one half 5 mg tablet twice daily) if resting heart rate is persistently below 50 bpm or in case of symptoms related to bradycardia such as dizziness, fatigue or hypotension. If heart rate is between 50 and 60 bpm, the dose of 5 mg twice daily should be maintained.
If during treatment, heart rate decreases persistently below 50 beats per minute (bpm) at rest or the patient experiences symptoms related to bradycardia, the dose must be titrated downward to the next lower dose in patients receiving 7.5 mg twice daily or 5 mg twice daily. If heart rate increases persistently above 60 beats per minute at rest, the dose can be up titrated to the next upper dose in patients receiving 2.5 mg twice daily or 5 mg twice daily.
Treatment must be discontinued if heart rate remains below 50 bpm or symptoms of bradycardia persist (see section 4.4).

Special population

Elderly
In patients aged 75 years or more, a lower starting dose should be considered for these patients (2.5 mg twice daily i.e. one half 5 mg tablet twice daily) before up-titration if necessary.

Renal impairment
No dose adjustment is required in patients with renal insufficiency and creatinine clearance above 15 ml/min (see section 5.2).
No data are available in patients with creatinine clearance below 15 ml/min. Ivabradine should therefore be used with precaution in this population.

Hepatic impairment
No dose adjustment is required in patients with mild hepatic impairment. Caution should be exercised when using ivabradine in patients with moderate hepatic impairment. Ivabradine is contra-indicated for use in patients with severe hepatic insufficiency, since it has not been studied in this population and a large increase in systemic exposure is anticipated (see sections 4.3 and 5.2).

Paediatric population
The safety and efficacy of ivabradine in children aged below 18 years have not yet been established.
No data are available.

Method of administration

Tablets must be taken orally twice daily, i.e. once in the morning and once in the evening during meals (see section 5.2).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients (see section 6.1)
- Resting heart rate below 60 beats per minute prior to treatment
- Cardiogenic shock
- Acute myocardial infarction
- Severe hypotension (< 90/50 mmHg)
- Severe hepatic insufficiency
- Sick sinus syndrome
- Sino-atrial block
- Unstable or acute heart failure
- Pacemaker dependent (heart rate imposed exclusively by the pacemaker)
- Unstable angina
- AV-block of 3rd degree
- Combination with strong cytochrome P450 3A4 inhibitors such as azole antifungals (ketoconazole, itraconazole), macrolide antibiotics (clarithromycin, erythromycin *per os*, josamycin, telithromycin), HIV protease inhibitors (nelfinavir, ritonavir) and nefazodone (see sections 4.5 and 5.2)

- Pregnancy, lactation (see section 4.6)

4.4 Special warnings and precautions for use

Special warnings

Cardiac arrhythmias
Ivabradine is not effective in the treatment or prevention of cardiac arrhythmias and likely loses its efficacy when a tachyarrhythmia occurs (eg. ventricular or supraventricular tachycardia). Ivabradine is therefore not recommended in patients with atrial fibrillation or other cardiac arrhythmias that interfere with sinus node function.
It is recommended to regularly clinically monitor ivabradine treated patients for the occurrence of atrial fibrillation (sustained or paroxysmal), which should also include ECG monitoring if clinically indicated (e.g. in case of exacerbated angina, palpitations, irregular pulse). The risk of developing atrial fibrillation may be higher in chronic heart failure patients treated with ivabradine. Atrial fibrillation has been more common in patients using concomitantly amiodarone or potent class I anti-arrhythmics.
Chronic heart failure patients with intraventricular conduction defects (bundle branch block left, bundle branch block right) and ventricular dyssynchrony should be monitored closely.

Use in patients with AV-block of 2nd degree
Ivabradine is not recommended in patients with AV-block of 2nd degree.

Use in patients with a low heart rate
Ivabradine must not be initiated in patients with a pre-treatment resting heart rate below 60 beats per minute (see section 4.3).
If, during treatment, resting heart rate decreases persistently below 50 bpm or the patient experiences symptoms related to bradycardia such as dizziness, fatigue or hypotension, the dose must be titrated downward or treatment discontinued if heart rate below 50 bpm or symptoms of bradycardia persist (see section 4.2).

Combination with calcium channel blockers
Concomitant use of ivabradine with heart rate reducing calcium channel blockers such as verapamil or diltiazem is not recommended (see section 4.5). No safety issue has been raised on the combination of ivabradine with nitrates and dihydropyridine calcium channel blockers such as amlodipine. Additional efficacy of ivabradine in combination with dihydropyridine calcium channel blockers has not been established (see section 5.1).

Chronic heart failure
Heart failure must be stable before considering ivabradine treatment. Ivabradine should be used with caution in heart failure patients with NYHA functional classification IV due to limited amount of data in this population.

Stroke
The use of ivabradine is not recommended immediately after a stroke since no data is available in these situations.

Visual function
Ivabradine influences on retinal function (see section 5.1). To date, there is no evidence of a toxic effect of ivabradine on the retina, but the effects of long-term ivabradine treatment beyond one year on retinal function are currently not known. Cessation of treatment should be considered if any unexpected deterioration in visual function occurs. Caution should be exercised in patients with retinitis pigmentosa.

Precautions for use

Patients with hypotension
Limited data are available in patients with mild to moderate hypotension, and ivabradine should therefore be used with caution in these patients. Ivabradine is contra-indicated in patients with severe hypotension (blood pressure < 90/50 mmHg) (see section 4.3).

Atrial fibrillation - Cardiac arrhythmias
There is no evidence of risk of (excessive) bradycardia on return to sinus rhythm when pharmacological cardioversion is initiated in patients treated with ivabradine. However, in the absence of extensive data, non urgent DC-cardioversion should be considered 24 hours after the last dose of ivabradine.

Use in patients with congenital QT syndrome or treated with QT prolonging medicinal products
The use of ivabradine in patients with congenital QT syndrome or treated with QT prolonging medicinal products should be avoided (see section 4.5). If the combination appears necessary, close cardiac monitoring is needed.

Hypertensive patients requiring blood pressure treatment modifications.
In the SHIFT trial more patients experienced episodes of increased blood pressure while treated with ivabradine (7.1%) compared to patients treated with placebo (6.1%). These episodes occurred most frequently shortly after blood pressure treatment was modified, were transient, and did not affect the treatment effect of ivabradine. When treatment modifications are made in chronic heart failure patients treated with ivabradine blood pressure should be monitored at an appropriate interval (see section 4.8).

Excipients
Since tablets contain lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Concomitant use not recommended
QT prolonging medicinal products

- Cardiovascular QT prolonging medicinal products (e.g. quinidine, disopyramide, bepridil, sotalol, ibutilide, amiodarone).
- Non cardiovascular QT prolonging medicinal products (e.g. pimozide, ziprasidone, sertindole, mefloquine, halofantrine, pentamidine, cisapride, intravenous erythromycin).

The concomitant use of cardiovascular and non cardiovascular QT prolonging medicinal products with ivabradine should be avoided since QT prolongation may be exacerbated by heart rate reduction. If the combination appears necessary, close cardiac monitoring is needed (see section 4.4).

Pharmacokinetic interactions

Cytochrome P450 3A4 (CYP3A4)
Ivabradine is metabolised by CYP3A4 only and it is a very weak inhibitor of this cytochrome. Ivabradine was shown not to influence the metabolism and plasma concentrations of other CYP3A4 substrates (mild, moderate and strong inhibitors). CYP3A4 inhibitors and inducers are liable to interact with ivabradine and influence its metabolism and pharmacokinetics to a clinically significant extent. Drug-drug interaction studies have established that CYP3A4 inhibitors increase ivabradine plasma concentrations, while inducers decrease them. Increased plasma concentrations of ivabradine may be associated with the risk of excessive bradycardia (see section 4.4).

Contra-indication of concomitant use
The concomitant use of potent CYP3A4 inhibitors such as azole antifungals (ketoconazole, itraconazole), macrolide antibiotics (clarithromycin, erythromycin *per os*, josamycin, telithromycin), HIV protease inhibitors (nelfinavir, ritonavir) and nefazodone is contra-indicated (see section 4.3). The potent CYP3A4 inhibitors ketoconazole (200 mg once daily) and josamycin (1 g twice daily) increased ivabradine mean plasma exposure by 7 to 8 fold.

Concomitant use not recommended
Moderate CYP3A4 inhibitors: specific interaction studies in healthy volunteers and patients have shown that the combination of ivabradine with the heart rate reducing agents diltiazem or verapamil resulted in an increase in ivabradine exposure (2 to 3 fold increase in AUC) and an additional heart rate reduction of 5 bpm. The concomitant use of ivabradine with these medicinal products is not recommended (see section 4.4).

Concomitant use with precautions
- Moderate CYP3A4 inhibitors: the concomitant use of ivabradine with other moderate CYP3A4 inhibitors (e.g. fluconazole) may be considered at the starting dose of 2.5 mg twice daily and if resting heart rate is above 60 bpm, with monitoring of heart rate.
- Grapefruit juice: ivabradine exposure was increased by 2-fold following the co-administration with grapefruit juice. Therefore the intake of grapefruit juice should be restricted during the treatment with ivabradine.
- CYP3A4 inducers: CYP3A4 inducers (e.g. rifampicin, barbiturates, phenytoin, *Hypericum perforatum* [St John's Wort]) may decrease ivabradine exposure and activity. The concomitant use of CYP3A4 inducing medicinal products may

require an adjustment of the dose of ivabradine. The combination of ivabradine 10 mg twice daily with St John's Wort was shown to reduce ivabradine AUC by half. The intake of St John's Wort should be restricted during the treatment with ivabradine.

Other concomitant use
Specific drug-drug interaction studies have shown no clinically significant effect of the following medicinal products on pharmacokinetics and pharmacodynamics of ivabradine: proton pump inhibitors (omeprazole, lansoprazole), sildenafil, HMG CoA reductase inhibitors (simvastatin), dihydropyridine calcium channel blockers (amlodipine, lacidipine), digoxin and warfarin. In addition there was no clinically significant effect of ivabradine on the pharmacokinetics of simvastatin, amlodipine, lacidipine, on the pharmacokinetics and pharmacodynamics of digoxin, warfarin and on the pharmacodynamics of aspirin.
In pivotal phase III clinical trials the following medicinal products were routinely combined with ivabradine with no evidence of safety concerns: angiotensin converting enzyme inhibitors, angiotensin II antagonists, beta-blockers, diuretics, anti-aldosterone agents, short and long acting nitrates, HMG CoA reductase inhibitors, fibrates, proton pump inhibitors, oral antidiabetics, aspirin and other anti-platelet medicinal products.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of ivabradine in pregnant women. Studies in animals have shown reproductive toxicity. These studies have shown embryotoxic and teratogenic effects (see section 5.3). The potential risk for humans is unknown. Therefore, ivabradine is contra-indicated during pregnancy (see section 4.3).

Breastfeeding
Animal studies indicate that ivabradine is excreted in milk. Therefore, ivabradine is contra-indicated during breast-feeding (see section 4.3).

Fertility
Studies in rats have shown no effect on fertility in males and females (see section 5.3).

4.7 Effects on ability to drive and use machines

A specific study to assess the possible influence of ivabradine on driving performance has been performed in healthy volunteers where no alteration of the driving performance was evidenced. However, in post-marketing experience, cases of impaired driving ability due to visual symptoms have been reported. Ivabradine may cause transient luminous phenomena consisting mainly of phosphenes (see section 4.8). The possible occurrence of such luminous phenomena should be taken into account when driving or using machines in situations where sudden variations in light intensity may occur, especially when driving at night.

Ivabradine has no influence on the ability to use machines.

4.8 Undesirable effects

Ivabradine has been studied in clinical trials involving nearly 14,000 participants. The most common adverse reactions with ivabradine, luminous phenomena (phosphenes) and bradycardia, are dose dependent and related to the pharmacological effect of the medicinal product.

The following adverse reactions have been reported during clinical trials and are ranked using the following frequency: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

System Organ Class	**Frequency**	**Preferred Term**
Blood and lymphatic system disorders	Uncommon	Eosinophilia
Metabolism and nutrition disorders	Uncommon	Hyperuricaemia
Nervous system disorders	Common	Headache, generally during the first month of treatment
		Dizziness, possibly related to bradycardia
	Uncommon*	Syncope, possibly related to bradycardia
Eye disorders	Very common	Luminous phenomena (phosphenes)
	Common	Blurred vision
Ear and labyrinth disorders	Uncommon	Vertigo
Cardiac disorders	Common	Bradycardia
		AV 1st degree block (ECG prolonged PQ interval)
		Ventricular extrasystoles
	Uncommon	Palpitations, supraventricular extrasystoles
	Very rare	Atrial fibrillation
		AV 2nd degree block, AV 3rd degree block
		Sick sinus syndrome
Vascular disorders	Common	Uncontrolled blood pressure
	Uncommon*	Hypotension, possibly related to bradycardia
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnoea
Gastrointestinal disorders	Uncommon	Nausea
		Constipation
		Diarrhoea
Skin and subcutaneous tissue disorders	Uncommon*	Angioedema
		Rash
	Rare*	Erythema
		Pruritus
		Urticaria

System Organ Class	Frequency	Preferred Term
Musculoskeletal and connective tissue disorders	Uncommon	Muscle cramps
General disorders and administration site conditions	Uncommon*	Asthenia, possibly related to bradycardia
		Fatigue, possibly related to bradycardia
	Rare*	Malaise, possibly related to bradycardia
Investigations	Uncommon	Elevated creatinine in blood

* Frequency calculated from clinical trials for adverse events detected from spontaneous report

Luminous phenomena (phosphenes) were reported by 14.5% of patients, described as a transient enhanced brightness in a limited area of the visual field. They are usually triggered by sudden variations in light intensity. The onset of phosphenes is generally within the first two months of treatment after which they may occur repeatedly. Phosphenes were generally reported to be of mild to moderate intensity. All phosphenes resolved during or after treatment, of which a majority (77.5%) resolved during treatment. Fewer than 1% of patients changed their daily routine or discontinued the treatment in relation with phosphenes.

Bradycardia was reported by 3.3% of patients particularly within the first 2 to 3 months of treatment initiation. 0.5% of patients experienced a severe bradycardia below or equal to 40 bpm.

4.9 Overdose

Overdose may lead to severe and prolonged bradycardia (see section 4.8).
Severe bradycardia should be treated symptomatically in a specialised environment. In the event of bradycardia with poor haemodynamic tolerance, symptomatic treatment including intravenous beta-stimulating medicinal products such as isoprenaline may be considered. Temporary cardiac electrical pacing may be instituted if required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cardiac therapy, other cardiac preparations, ATC code: C01EB17.

Mechanism of action

Ivabradine is a pure heart rate lowering agent, acting by selective and specific inhibition of the cardiac pacemaker I_f current that controls the spontaneous diastolic depolarisation in the sinus node and regulates heart rate. The cardiac effects are specific to the sinus node with no effect on intra-atrial, atrioventricular or intraventricular conduction times, nor on myocardial contractility or ventricular repolarisation.

Ivabradine can interact also with the retinal current I_h which closely resembles cardiac I_f. It participates in the temporal resolution of the visual system, by curtailing the retinal response to bright light stimuli. Under triggering circumstances (e.g. rapid changes in luminosity), partial inhibition of I_h by ivabradine underlies the luminous phenomena that may be occasionally experienced by patients. Luminous phenomena (phosphenes) are described as a transient enhanced brightness in a limited area of the visual field (see section 4.8).

Pharmacodynamic effects

The main pharmacodynamic property of ivabradine in humans is a specific dose dependent reduction in heart rate. Analysis of heart rate reduction with doses up to 20 mg twice daily indicates a trend towards a plateau effect which is consistent with a reduced risk of severe bradycardia below 40 bpm (see section 4.8).
At usual recommended doses, heart rate reduction is approximately 10 bpm at rest and during exercise. This leads to a reduction in cardiac workload and myocardial oxygen consumption. Ivabradine does not influence intracardiac conduction, contractility (no negative inotropic effect) or ventricular repolarisation:

- in clinical electrophysiology studies, ivabradine had no effect on atrioventricular or intraventricular conduction times or corrected QT intervals;
- in patients with left ventricular dysfunction (left ventricular ejection fraction (LVEF) between 30 and 45%), ivabradine did not have any deleterious influence on LVEF.

Clinical efficacy and safety

The antianginal and anti-ischaemic efficacy of ivabradine was studied in five double-blind randomised trials (three *versus* placebo, and one each *versus* atenolol and amlodipine). These trials included a total of 4,111 patients with chronic stable angina pectoris, of whom 2,617 received ivabradine.

Ivabradine 5 mg twice daily was shown to be effective on exercise test parameters within 3 to 4 weeks of treatment. Efficacy was confirmed with 7.5 mg twice daily. In particular, the additional benefit over 5 mg twice daily was established in a reference-controlled study *versus* atenolol: total exercise duration at trough was increased by about 1 minute after one month of treatment with 5 mg twice daily and further improved by almost 25 seconds after an additional 3-month period with forced titration to 7.5 mg twice daily. In this study, the antianginal and anti-ischaemic benefits of ivabradine were confirmed in patients aged 65 years or more. The efficacy of 5 and 7.5 mg twice daily was consistent across studies on exercise test parameters (total exercise duration, time to limiting angina, time to angina onset and time to 1mm ST segment depression) and was associated with a decrease of about 70% in the rate of angina attacks. The twice-daily dosing regimen of ivabradine gave uniform efficacy over 24 hours.
In a 889-patients randomised placebo-controlled study, ivabradine given on top of atenolol 50 mg o.d. showed additional efficacy on all ETT parameters at the trough of drug activity (12 hours after oral intake).

In a 725-patients randomised placebo-controlled study, ivabradine did not show additional efficacy on top of amlodipine at the trough of drug activity (12 hours after oral intake) while an additional efficacy was shown at peak (3-4 hours after oral intake).

Ivabradine efficacy was fully maintained throughout the 3- or 4-month treatment periods in the efficacy trials. There was no evidence of pharmacological tolerance (loss of efficacy) developing during treatment nor of rebound phenomena after abrupt treatment discontinuation. The antianginal and anti-ischaemic effects of ivabradine were associated with dose-dependent reductions in heart rate and with a significant decrease in rate pressure product (heart rate x systolic blood pressure) at rest and during exercise. The effects on blood pressure and peripheral vascular resistance were minor and not clinically significant.

A sustained reduction of heart rate was demonstrated in patients treated with ivabradine for at least one year (n = 713). No influence on glucose or lipid metabolism was observed.

The antianginal and anti-ischaemic efficacy of ivabradine was preserved in diabetic patients (n = 457) with a similar safety profile as compared to the overall population.

A large outcome study, BEAUTIFUL, was performed in 10917 patients with coronary artery disease and left ventricular dysfunction (LVEF<40%) on top of optimal background therapy with 86.9% of patients receiving beta-blockers. The main efficacy criterion was the composite of cardiovascular death, hospitalization for acute MI or hospitalization for new onset or worsening heart failure. The study showed no difference in the rate of the primary composite outcome in the ivabradine group by comparison to the placebo group (relative risk ivabradine:placebo 1.00, p=0.945).
In a post-hoc subgroup of patients with symptomatic angina at randomisation (n=1507), no safety signal was identified regarding cardiovascular death, hospitalization for acute MI or heart failure (ivabradine 12.0% versus placebo 15.5%, p=0.05).

The SHIFT study was a large multicentre, international, randomised double-blind placebo controlled outcome trial conducted in 6505 adult patients with stable chronic CHF (for ≥ 4 weeks), NYHA class II to IV, with a reduced left ventricular ejection fraction (LVEF ≤ 35%) and a resting heart rate ≥ 70 bpm.
Patients received standard care including beta-blockers (89 %), ACE inhibitors and/or angiotensin II antagonists (91 %), diuretics (83 %), and anti-aldosterone agents (60 %). In the ivabradine group, 67% of patients were treated with 7.5 mg twice a day. The median follow-up duration was 22.9 months. Treatment with ivabradine was associated with an average reduction in heart rate of 15 bpm from a baseline value of 80 bpm. The difference in heart rate between ivabradine and placebo arms was 10.8 bpm at 28 days, 9.1 bpm at 12 months and 8.3 bpm at 24 months.

The study demonstrated a clinically and statistically significant relative risk reduction of 18% in the rate of the primary composite endpoint of cardiovascular mortality and hospitalisation for worsening heart failure (hazard ratio: 0.82, 95%CI [0.75;0.90] – p<0.0001) apparent within 3 months of initiation of treatment. The absolute risk reduction was 4.2%. The results on the primary endpoint are mainly driven by the

heart failure endpoints, hospitalisation for worsening heart failure (absolute risk reduced by 4.7 %) and deaths from heart failure (absolute risk reduced by 1.1 %).

Treatment effect on the primary composite endpoint, its components and secondary endpoints

	Ivabradine (N=3241) n (%)	Placebo (N=3264) n (%)	Hazard ratio [95% CI]	p-value
Primary composite endpoint	793 (24.47)	937 (28.71)	0.82 [0.75; 0.90]	<0.0001
Components of the composite: - CV death - Hospitalisation for worsening HF	449 (13.85) 514 (15.86)	491 (15.04) 672 (20.59)	0.91 [0.80; 1.03] 0.74 [0.66; 0.83]	0.128 <0.0001
Other secondary endpoints: - All cause death - Death from HF - Hospitalisation for any cause - Hospitalisation for CV reason	503 (15.52) 113 (3.49) 1231 (37.98) 977 (30.15)	552 (16.91) 151 (4.63) 1356 (41.54) 1122 (34.38)	0.90 [0.80; 1.02] 0.74 [0.58;0.94] 0.89 [0.82;0.96] 0.85 [0.78; 0.92]	0.092 0.014 0.003 0.0002

The reduction in the primary endpoint was observed consistently irrespective of gender, NYHA class, ischaemic or non-ischaemic heart failure aetiology and of background history of diabetes or hypertension.

In the subgroup of patients with HR ≥ 75 bpm (n=4150), a greater reduction was observed in the primary composite endpoint of 24 % (hazard ratio: 0.76, 95%CI [0.68;0.85] – p<0.0001) and for other secondary endpoints, including all cause death (hazard ratio: 0.83, 95%CI [0.72;0.96] – p=0.0109) and CV death (hazard ratio: 0.83, 95%CI [0.71;0.97] – p=0.0166). In this subgroup of patients, the safety profile of ivabradine is in line with the one of the overall population.

A significant effect was observed on the primary composite endpoint in the overall group of patients receiving beta blocker therapy (hazard ratio: 0.82, 95%CI [0.76;0.94]). In the subgroup of patients with HR ≥ 75 bpm and on the recommended target dose of beta-blocker, no statistically significant benefit was observed on the primary composite endpoint (hazard ratio: 0.97, 95%CI [0.74;1.28]) and other secondary endpoints, including hospitalisation for worsening heart failure (hazard ratio: 0.79, 95% CI [0.56;1.10]) or death from heart failure (hazard ratio: 0.69, 95% CI [0.31;1.56]).

There was a significant improvement in NYHA class at last recorded value, 887 (28%) of patients on ivabradine improved versus 776 (24%) of patients on placebo (p=0.001).

5.2 Pharmacokinetic properties

Under physiological conditions, ivabradine is rapidly released from tablets and is highly water-soluble (>10 mg/ml). Ivabradine is the S-enantiomer with no bioconversion demonstrated *in vivo*. The N-desmethylated derivative of ivabradine has been identified as the main active metabolite in humans.

Absorption and bioavailability
Ivabradine is rapidly and almost completely absorbed after oral administration with a peak plasma level reached in about 1 hour under fasting condition. The absolute bioavailability of the film-coated tablets is around 40%, due to first-pass effect in the gut and liver.
Food delayed absorption by approximately 1 hour, and increased plasma exposure by 20 to 30 %. The intake of the tablet during meals is recommended in order to decrease intra-individual variability in exposure (see section 4.2).

Distribution
Ivabradine is approximately 70% plasma protein bound and the volume of distribution at steady state is close to 100 l in patients. The maximum plasma concentration following chronic administration at the recommended dose of 5 mg twice daily is 22 ng/ml (CV=29%). The average plasma concentration is 10 ng/ml (CV=38%) at steady state.

Biotransformation
Ivabradine is extensively metabolised by the liver and the gut by oxidation through cytochrome P450 3A4 (CYP3A4) only. The major active metabolite is the N-desmethylated derivative (S 18982) with an exposure about 40% of that of the parent compound. The metabolism of this active metabolite also involves CYP3A4.
Ivabradine has low affinity for CYP3A4, shows no clinically relevant CYP3A4 induction or inhibition and is therefore unlikely to modify CYP3A4 substrate metabolism or plasma concentrations. Inversely, potent inhibitors and inducers may substantially affect ivabradine plasma concentrations (see section 4.5).

Elimination
Ivabradine is eliminated with a main half-life of 2 hours (70-75% of the AUC) in plasma and an effective half-life of 11 hours. The total clearance is about 400 ml/min and the renal clearance is about 70 ml/min. Excretion of metabolites occurs to a similar extent via faeces and urine. About 4% of an oral dose is excreted unchanged in urine.

Linearity/non linearity
The kinetics of ivabradine is linear over an oral dose range of 0.5 – 24 mg.

Special populations
- Elderly: no pharmacokinetic differences (AUC and Cmax) have been observed between elderly (≥ 65 years) or very elderly patients (≥ 75 years) and the overall population (see section 4.2).
- Renal insufficiency: the impact of renal impairment (creatinine clearance from 15 to 60 ml/min) on ivabradine pharmacokinetic is minimal, in relation with the

low contribution of renal clearance (about 20 %) to total elimination for both ivabradine and its main metabolite S 18982 (see section 4.2).
- Hepatic impairment: in patients with mild hepatic impairment (Child Pugh score up to 7) unbound AUC of ivabradine and the main active metabolite were about 20% higher than in subjects with normal hepatic function. Data are insufficient to draw conclusions in patients with moderate hepatic impairment. No data are available in patients with severe hepatic impairment (see sections 4.2 and 4.3).

Pharmacokinetic/pharmacodynamic (PK/PD) relationship
PK/PD relationship analysis has shown that heart rate decreases almost linearly with increasing ivabradine and S 18982 plasma concentrations for doses of up to 15-20 mg twice daily. At higher doses, the decrease in heart rate is no longer proportional to ivabradine plasma concentrations and tends to reach a plateau. High exposures to ivabradine that may occur when ivabradine is given in combination with strong CYP3A4 inhibitors may result in an excessive decrease in heart rate although this risk is reduced with moderate CYP3A4 inhibitors (see sections 4.3, 4.4 and 4.5).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential. Reproductive toxicity studies showed no effect of ivabradine on fertility in male and female rats. When pregnant animals were treated during organogenesis at exposures close to therapeutic doses, there was a higher incidence of foetuses with cardiac defects in the rat and a small number of foetuses with ectrodactylia in the rabbit.
In dogs given ivabradine (doses of 2, 7 or 24 mg/kg/day) for one year, reversible changes in retinal function were observed but were not associated with any damage to ocular structures. These data are consistent with the pharmacological effect of ivabradine related to its interaction with hyperpolarisation-activated I_h currents in the retina, which share extensive homology with the cardiac pacemaker I_f current.
Other long-term repeat dose and carcinogenicity studies revealed no clinically relevant changes.

Environmental Risk Assessment (ERA)
The environmental risk assessment of ivabradine has been conducted in accordance to European guidelines on ERA.
Outcomes of these evaluations support the lack of environmental risk of ivabradine and ivabradine does not pose a threat to the environment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Lactose monohydrate
Magnesium stearate (E 470 B)
Maize starch
Maltodextrin

Silica, colloidal anhydrous (E 551)
Film-coating
Hypromellose (E 464)
Titanium dioxide (E 171)
Macrogol 6000
Glycerol (E 422)
Magnesium stearate (E 470 B)
Yellow iron oxide (E 172)
Red iron oxide (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/PVC blister packed in cardboard boxes.

Pack sizes
Calendar packs containing 14, 28, 56, 84, 98, 100 or 112 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex
France

8. MARKETING AUTHORISATION NUMBER(S)

Procoralan 5 mg	EU/1/05/316/003	(pack of 56 tablets)
Procoralan 7.5 mg	EU/1/05/316/010	(pack of 56 tablets)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25/10/2005
Date of latest renewal: 31/08/2010

10. DATE OF REVISION OF THE TEXT

02/2012
Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

Appendix 2: Search strategy for section 5.1 (Identification of studies)

The following information should be provided.

Systematic review

For the original systematic review the following databases were searched:

- Embase.com (Embase plus Medline excluding Medline (R) – In Process)
- The Cochrane Library:
  - Cochrane Database of Systematic Reviews (CDSR)
  - Database of Abstracts of Reviews of Effects (DARE)
  - Cochrane Central Register of Controlled Trials (CENTRAL)
  - Cochrane Methodology Register (CMR)
  - Health Technology Assessment Database (HTA)
  - NHS Economic Evaluation Database (NHSEED)
  - Cochrane Groups.

For the updated systematic review the following databases were searched via OVID:

- OVID Embase
- OVID MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)
- The Cochrane Library:
  - Cochrane Database of Systematic Reviews (CDSR)
  - Database of Abstracts of Reviews of Effects (DARE)
  - Cochrane Central Register of Controlled Trials (CENTRAL)
  - Cochrane Methodology Register (CMR)
  - Health Technology Assessment Database (HTA)

The date on which the search was conducted.

For the original systematic review the search was conducted on 3rd May 2011. For the updated systematic review the electronic searches in OVID were conducted on 24th January 2012 and the searching of ClinicalTrials.gov was performed 4th January 2012.

The date span of the search

For the original systematic review the search was not restricted by date (other than EMBASE.com being from 1966). The Cochrane Library was 2011 Issue 4 (for CDSR) and Issue 2 (for CENTRAL and the other databases).

For the updated systematic review, the search strings in EMBASE (from 1980) were limited to those published since 2011. Publications from 1st January 2011 to 2nd May 2011 already identified in the original systematic review were then excluded during application of the selection criteria.

For the updated systematic review, the search strings in MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R), were designed to limit publications to those entered into Medline by the National Library of Medicine, or updated into Ovid's Medline, since 3rd May 2011 (irrespective of publication date). This enabled studies indexed since 3rd May 2011 to be identified (which could have been previously missed because MEDLINE(R) In-Process was not searched in the original systematic review), even if a study's publication date was prior to 3rd May 2011. Studies with a publication date after the original systematic review and studies currently in the process of being indexed would also be identified.

The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Search strategies used in the original systematic review

EMBASE.com search, 1966 to 3 May 2011

No.	Query	Results
#61	#31 OR #46 OR #50 OR #56 OR #60	112
#60	#19 AND #59	0
#59	#57 OR #58	32758
#58	(pooled NEXT/4 analys?s):ab,ti	32758
#57	'pooled analysis':de	11
#56	#19 AND #55	2
#55	#51 OR #52 OR #53 OR #54	106648
#54	cochrane:jt	10452
#53	quantitative*:ab OR systematic*:ab OR methodologic*:ab AND (review*:ab OR overview*:ab)	71830
#52	quantitative*:ti OR systematic*:ti OR methodologic*:ti AND (review*:ti OR overview*:ti)	21593
#51	'systematic review'/de	40740

No.	Query	Results
#50	#19 AND #49	4
#49	#47 OR #48	72062
#48	'meta analysis':ab,ti OR 'meta analyses':ab,ti OR 'meta analytical':ab,ti OR metanaly*:ab,ti	42381
#47	'meta analysis'/de	54207
#46	#19 AND #45	31
#45	#32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44	529399
#44	(matched NEXT/1 (communities OR schools OR population* OR pair OR pairs)):ab,ti	6263
#43	'comparison group':ab,ti OR 'comparison groups':ab,ti OR quasiexperimental:ab,ti OR 'quasi experimental':ab,ti OR pseudoexperimental:ab,ti OR 'pseudo experimental':ab,ti	14595
#42	'open label':ab,ti OR 'cross over':ab,ti OR crossover:ab,ti OR 'parallel design':ab,ti	77783
#41	((single OR double OR treble OR triple) NEXT/1 (blind* OR mask* OR dummy)):ab,ti	133972
#40	((assigned OR allocated OR allocation) NEAR/1 random*):ab,ti	78163
#39	(random* NEXT/1 (trial* OR study OR studies)):ab,ti	82565
#38	'quasi experimental study'/de	783
#37	'crossover procedure'/de	29632
#36	'parallel design'/de	2007
#35	'double blind procedure'/de	100660
#34	'single blind procedure'/de	13473
#33	'randomization'/de	52748
#32	'randomized controlled trial'/de	284546
#31	#19 AND #30	110
#30	#20 OR #21 OR #22 OR #23 OR #24 OR #29	4160927
#29	#27 AND #28	123972
#28	random*:ab,ti OR controlled:ab,ti OR 'control group':ab,ti OR 'control groups':ab,ti	1138913

No.	Query	Results
#27	#25 OR #26	1039503
#26	'prospective study'/de	163442
#25	'comparative study'/exp	898675
#24	((clinical OR controlled) NEXT/1 (trial* OR study OR studies)):ab,ti	418940
#23	'controlled study'/de	3486494
#22	'clinical trial'/exp	855718
#21	'coralan'/dd_ct	0
#20	'ivabradine'/dd_ct	223
#19	#8 AND #14 AND #18	129
#18	#15 OR #16 OR #17	261586
#17	placebo*:ab,ti	159959
#16	'placebo effect'/de	1141
#15	'placebo'/de	189718
#14	#9 OR #10 OR #11 OR #12 OR #13	824
#13	'148849 67 6':rn OR '148870 80 8':rn OR '155974 00 8':rn	690
#12	procoralan:de,tn,ab,ti OR corlentor:de,tn,ab,ti OR coraxan:de,tn,ab,ti	109
#11	ivabradine:tn,ab,ti OR coralan:tn,ab,ti OR 's 16257':tn,ab,ti OR s16257:tn,ab,ti OR 's 16257 2':tn,ab,ti OR 's16257 2':tn,ab,ti OR 's 16260 2':tn,ab,ti OR 's16260 2':tn,ab,ti	522
#10	'coralan'/de	15
#9	'ivabradine'/de	795
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	327747
#7	((cardiac OR heart OR myocardial) NEAR/4 (work OR load OR volume)):ab,ti	18078
#6	((forward OR output) NEXT/1 failure):ab,ti	161
#5	'cardiac stand still':ab,ti OR 'decompensatio cordis':ab,ti OR 'insufficientia cardis':ab,ti OR 'low output syndrome':ab,ti	639
#4	((heart OR cardia OR cardia?) NEAR/4 (decompensation OR incompetence OR output)):ab,ti	48367

No.	Query	Results
#3	((heart OR cardia OR cardia? OR myocardial) NEAR/4 (failure OR insufficiency)):ab,ti	150075
#2	'heart work'/exp	45835
#1	'heart failure'/exp	214384

This strategy was modified and repeated in The Cochrane Library databases. Slight changes were required to the syntax of the search, which is dependent upon the search platform used and to accommodate indexing differences in the databases. These searches were not limited by date and there were no database restrictions.

The Cochrane Library 2011 Issue 4 (CDSR) and Issue 2 (CENTRAL and the other databases), searched 3 May 2011

ID	Search	Hits
#1	MeSH descriptor Heart Failure explode all trees	4670
#2	((heart OR cardia OR cardia? OR myocardial) NEAR/4 (failure OR insufficiency)):ab,ti,kw	9100
#3	((heart OR cardia OR cardia?) NEAR/4 (decompensation OR incompetence OR output)):ab,ti,kw	3710
#4	("cardiac stand still" OR "decompensatio cordis" OR "insufficientia cardis" OR "low output syndrome"):ab,ti,kw	37
#5	((forward OR output) NEAR/1 failure):ab,ti,kw	1
#6	((cardiac OR heart OR myocardial) NEAR/4 (work OR load OR volume)):ab,ti,kw	2061
#7	(#1 OR #2 OR #3 OR #4 OR #5 OR #6)	13265
#8	MeSH descriptor Benzazepines, this term only	542
#9	(ivabradine OR Coralan OR "s 16257" OR s16257 OR "s 16257 2" OR "s16257 2" OR "s 16260 2" OR "s16260 2"):ti,ab,kw	44
#10	(Procoralan OR Corlentor OR Coraxan):ti,ab,kw	5
#11	(#8 OR #9 OR #10)	554
#12	MeSH descriptor Placebos, this term only	20183
#13	MeSH descriptor Placebo Effect, this term only	788
#14	placebo*:ti,ab,kw	125549
#15	(#12 OR #13 OR #14)	125549
#16	(#7 AND #11 AND #15)	39

Search strategies used in the updated systematic review

Embase 1980 to 2012 Week 03 Searched 24 January 2012

	Searches	Results
1	exp heart failure/	225946
2	exp heart work/	42746
3	((heart or cardia or cardia? or myocardial) adj4 (failure or insufficiency)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	202553
4	(cardiac stand still or decompensatio cordis or insufficientia cardis or low output syndrome).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	611
5	((forward or output) adj1 failure).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	153
6	((heart or cardia or cardia?) adj4 (decompensation or incompetence or output)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	60333
7	((cardiac or heart or myocardial) adj4 (work or load or volume)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	40723
8	or/1-7	329035
9	exp ivabradine/	963
10	exp coralan/	15
11	(ivabradine or coralan or s 16257 or s16257 or s 16257 2 or s16257 2 or s 16260 2 or s16260 2).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	995
12	(procoralan or corlentor or coraxan).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	120
13	(148849-67-6 or 148870-80-8 or 155974-00-8).rn.	803
14	9 or 10 or 11 or 12 or 13	996

15	exp placebo/	191316
16	exp placebo effect/	1589
17	placebo*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	264240
18	or/15-17	264240
19	8 and 14 and 18	163
20	exp clinical trial/	878758
21	exp controlled study/	3783662
22	((clinical or controlled) adj1 (trial* or study or studies)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	5134484
23	exp comparative study/	888936
24	prospective study.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	230701
25	23 or 24	1092059
26	(random* or controlled or control group or control groups).ti,ab.	1186545
27	25 and 26	138878
28	20 or 21 or 22 or 27	5202709
29	19 and 28	126
30	randomized controlled trial.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	315075
31	randomization.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	66924
32	single blind procedure.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	14718
33	double blind procedure.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	102759
34	parallel design.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	2990

35	crossover procedure.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	31717
36	quasi experimental study.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	1701
37	(random* adj1 (trial* or study or studies)).ti,ab.	90095
38	((assigned or allocated or allocation) adj1 random*).ti,ab.	82951
39	((single or double or treble or triple) adj1 (blind* or mask* or dummy)).ti,ab.	134022
40	(open label or cross over or crossover or parallel design).ti,ab.	81141
41	(comparison group or comparison groups or quasiexperimental or quasi experimental or pseudoexperimental or pseudo experimental).ti,ab.	15562
42	(matched adj1 (communities or schools or population* or pair or pairs)).ti,ab.	7803
43	or/30-42	570829
44	19 and 43	44
45	meta analysis.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	76547
46	(meta analysis or meta analyses or meta analytical or metanaly*).ti,ab.	48574
47	45 or 46	81046
48	19 and 47	5
49	systematic review.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	61746
50	((quantitative* or systematic* or methodologic) and (review* or overview*)).ti.	24742
51	((quantitative* or systematic* or methodologic) and (review* or overview*)).ab.	67980
52	cochrane.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	27234
53	or/49-52	114087
54	19 and 53	2

55	pooled analysis.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	3358
56	(pooled adj4 analys?s).ti,ab.	6933
57	55 or 56	6943
58	19 and 57	0
59	29 or 44 or 48 or 54 or 58	128
60	limit 59 to yr="2011 -Current"	25

OVID Medline (R) In-Process and other non-indexed citations and OVID Medline(R) 1946 to present, searched 24 January 2012

	Searches	Results
1	exp heart failure/	74682
2	exp Heart/ or heart work.mp.	371199
3	((heart or cardia or cardia? or myocardial) adj4 (failure or insufficiency)).ab,ti.	104843
4	((heart or cardia or cardia?) adj4 (decompensation or incompetence or output)).ab,ti.	37379
5	(cardiac stand still or decompensatio cordis or insufficientia cardis or low output syndrome).ab,ti.	487
6	((forward or output) adj1 failure).ab,ti.	122
7	((cardiac or heart or myocardial) adj4 (work or load or volume)).ab,ti.	15215
8	or/1-7	504029
9	ivabradine.mp.	389
10	coralan.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	2
11	(ivabradine or coralan or s 16257 or s16257 or s 16257 2 or s16257 2 or s 16260 2 or S16260 2).af,ab,ti.	389
12	(procoralan or corlentor or coraxan).af,ab,ti.	18
13	(148849-67-6 or 148870-80-8 or 155974-00-8).rn.	307
14	or/9-13	390
15	placebo.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	136542

16	exp Placebo Effect/	2725
17	"placebo*".ab,ti.	136640
18	or/15-17	137252
19	8 and 14 and 18	29
20	exp clinical trial/	659087
21	controlled study.af.	27332
22	((clinical or controlled) adj1 (trial* or study or studies)).ab,ti.	358232
23	exp comparative study/	1551432
24	prospective study.af.	82917
25	23 or 24	1619217
26	(random* or controlled or control group or control groups).ab,ti.	1009198
27	25 and 26	188220
28	20 or 21 or 22 or 27	985773
29	19 and 28	22
30	exp randomized controlled trial/	317671
31	randomization.mp. or exp Random Allocation/	84297
32	single blind procedure.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	15
33	single blind procedure.mp. or exp Single-Blind Method/	15560
34	exp Double-Blind Method/ or double blind procedure.mp.	112220
35	parallel design.mp.	781
36	Cross-Over Studies/ or crossover procedure.mp.	28591
37	quasi experimental study.mp.	906
38	(random* adj1 (trial* or study or studies)).ab,ti.	73890
39	((assigned or allocated or allocation) adj1 random*).ab,ti.	72639
40	((single or double or treble or triple) adj1 (blind* or mask* or dummy)).ab,ti.	113340
41	(open label or cross over or crossover or parallel design).ab,ti.	69449
42	(comparison group or comparison groups or quasiexperimental or quasi experimental or pseudoexperimental or pseudo experimental).ab,ti.	13852
43	(matched adj1 (communities or schools or population* or pair or	6789

	pairs)).ab,ti.	
44	or/30-43	515747
45	19 and 44	17
46	exp Meta-Analysis/	30994
47	(meta analysis or meta analyses or meta analytical or metanaly*).ab,ti.	38435
48	46 or 47	49470
49	19 and 48	0
50	systematic review.af.	27657
51	((quantitative or systematic or methodologic) and (review* or overview*)).ti.	20719
52	((quantitative or systematic or methodologic) and (review* or overview*)).ab.	49433
53	cochrane.mp.	20098
54	50 or 51 or 52 or 53	68932
55	19 and 54	0
56	pooled analysis.af.	2409
57	(pooled adj1 analys?s).ab,ti.	2881
58	56 or 57	2881
59	19 and 58	0
60	29 or 45 or 49 or 55 or 59	23
61	limit 60 to up=20110503-20120124	23
62	limit 60 to ed=20110503-20120124	4
63	61 or 62	23

Cochrane Library (via Ovid); Searched on 24 January 2012

(Cochrane Central Register of Controlled Trials to January 2012, Cochrane Database of Systematic Reviews 2005 to December 2011, Cochrane Methodology Register 1st Quarter 2012, Database of Abstracts and Reviews of Effects 4th Quarter 2011, Health Technology Assessment 1st Quarter 2012)

	Searches	Results
1	exp heart failure/	4230
2	exp Heart/ or heart work.mp.	4944
3	((heart or cardia or cardia? or myocardial) adj4 (failure or insufficiency)).ab,ti.	8474
4	((heart or cardia or cardia?) adj4 (decompensation or incompetence or output)).ab,ti.	2766
5	(cardiac stand still or decompensatio cordis or insufficientia cardis or low output syndrome).ab,ti.	38
6	((forward or output) adj1 failure).ab,ti.	1
7	((cardiac or heart or myocardial) adj4 (work or load or volume)).ab,ti.	1665
8	or/1-7	16117
9	ivabradine.mp.	47
10	coralan.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	0
11	(ivabradine or coralan or s 16257 or s16257 or s 16257 2 or s16257 2 or s 16260 2 or S16260 2).af,ab,ti.	51
12	(procoralan or corlentor or coraxan).af,ab,ti.	5
13	(148849-67-6 or 148870-80-8 or 155974-00-8).mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	0
14	or/9-13	53
15	placebo.mp. [mp=ti, ot, ab, sh, hw, kw, tx, ct]	126483
16	exp Placebo Effect/	815
17	"placebo*".ab,ti.	118636
18	or/15-17	126765
19	8 and 14 and 18	14

Details of any additional searches, such as searches of company databases (include a description of each database).

Additional searches were performed as detailed in Table 74

Table 74: Additional searches

Database	Systematic review	Number of studies identified	Database description
Australian New Zealand Clinical Trials Registry (ANZCTR)	Original systematic review	2	The ANZCTR accepts registrations of interventional clinical trials from all countries. It is funded by the National Health and Medical Research Council (NHMRC) and managed at the NHMRC Clinical Trials Centre at the University of Sydney, a not-for-profit agency. The ANZCTR is a primary registry, and is part of the World Health Organization's Registry Network, meeting the WHO Registry Criteria and entering clinical trials into its database before the first participant is recruited.
Manufacturer's ivabradine clinical trial database	Original systematic review	2	Servier TGA dossier for ivabradine
Manufacturer's ivabradine clinical trial database	Update systematic review	1	Servier TGA dossier for ivabradine
National Institutes of Health ClinicalTrials.gov	Original systematic review	12	ClinicalTrials.gov is both a registry and a results database of clinical trials conducted in the United States of America and around the world.
National Institutes of Health ClinicalTrials.gov	Update systematic review	3	

The inclusion and exclusion criteria.

This can be found in Table 2, Section 5.2.1.

The data abstraction strategy.

Identified studies were independently assessed by a reviewer in order to ascertain whether they met the pre-defined inclusion and exclusion criteria, and any uncertainties were resolved by discussion with a second reviewer.

Justification for exclusion of studies

The reasons for the exclusion of trials are detailed in Table 75, and references for these studies are presented in Table 76.

Table 75: Reasons for exclusion

Trial	Reason for exclusion
BEAUTIfUL	• Incorrect population • In addition the dosing regime was not in accordance with the licence (Procoralan® SPC)
Rajagopal	• Incorrect population
Sarullo	• Surrogate outcomes measured rather than the "hard endpoints" of morbidity and mortality

Table 76: Excluded trials

Trial	Reports/publications
Ivabradine trials vs placebo	
BEAUTIFUL	Fox K. Effects of ivabradine on cardiovascular events in patients with stable coronary artery disease and left-ventricular systolic dysfunction. A three-year randomised doubleblind placebo-controlled international multicentre study. 9 March 2009. Clinical Study Report: CL3-16257-056. Laboratories Servier. **Published as:** Fox, K., R. Ferrari, et al. (2006). Rationale and design of a randomized, double-blind, placebo-controlled trial of ivabradine in patients with stable coronary artery disease and left-ventricular systolic dysfunction: the morBidity-mortality EvAlUaTion of the If inhibitor ivabradine in patients with coronary disease and left-ventricular dysfunction (BEAUTIFUL) Study. American Heart Journal **152**(5): 860-866. (105) Fox, K., R. Ferrari, et al. (2008). The BEAUTIFUL study: Randomized trial of ivabradine in patients with stable coronary artery disease and left-ventricular systolic dysfunction - Baseline

Trial	Reports/publications
	characteristics of the study population. Cardiology **110**(4): 271-282. Fox, K., I. Ford, et al. (2008). "Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial." The Lancet **372**(9641): 807-816. Fox, K., I. Ford, et al. (2008). "Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomised controlled trial." The Lancet **372**(9641): 817-821. Fox, K., I. Ford, et al. (2009). "Relationship between ivabradine treatment and cardiovascular outcomes in patients with stable coronary artery disease and left-ventricular systolic dysfunction with limiting angina: A subgroup analysis of the randomized, controlled BEAUTIFUL trial." European Heart Journal **30**(19): 2337-2345. Ceconi, C., S. B. Freedman, et al. (2011). Effect of heart rate reduction by ivabradine on left-ventricular remodeling in the echocardiographic substudy of BEAUTIFUL. International Journal of Cardiology **146**(3): 408-414. Tendera, M., M. Talajic, et al. (2011). Safety of ivabradine in patients with coronary artery disease and left-ventricular systolic dysfunction (from the BEAUTIFUL Holter substudy). American Journal of Cardiology **107**(6): 805-811.
Raiagopal 2010	Rajagopal, J., S. Arun, et al. (2010). Use of ivabradine in the management of acute anterior wall myocardial infarction complicated by left-ventricular failure. Journal of the American College of Cardiology **55**(10): A101.
Sarullo 2010	Sarullo, F. M., G. Fazio, et al. (2010). "Impact of "off-Label" Use of ivabradine on exercise capacity, gas exchange, functional class, quality of life, and neurohormonal modulation in patients with ischemic chronic heart failure." Journal of Cardiovascular Pharmacology and Therapeutics **15**(4): 349-355.

Appendix 3: Quality assessment of RCT(s) (section 5.4)

N/A. Quality assessment is included in section 5.4

Appendix 4: Search strategy for section 5.7 (Indirect and mixed treatment comparisons)

N/A

Appendix 5: Quality assessment of comparator RCT(s) in section 5.7 (Indirect and mixed treatment comparisons)

N/A

Appendix 6: Search strategy for section 5.8 (Non-RCT evidence)

N/A. Non-RCT evidence was identified in systematic review covered in section 5.1, 5.2 and 9.2 appendix 2

Appendix 7: Quality assessment of non-RCT(s) in section 5.8 (Non-RCT evidence)

N/A

Appendix 8: Search strategy for section 5.9 (Adverse events)

N/A. SHIfT was the only trial identified as applicable to the decision problem. Adverse event data on this trial is detailed in section 5.9. Further Adverse event data is covered in section 9.15.3 appendix 15

Appendix 9: Quality assessment of adverse event data in section 5.9 (Adverse events)

N/A

Appendix 10: Search strategy for cost-effectiveness studies (section 6.1)

The following information should be provided.

The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter

The following databases were searched:

- Centre for reviews and dissemination (CRD) databases
    - NHS EED
    - DARE
    - HTA
- Cochrane Systematic review
- Cochrane CENTRAL
- Embase.com*
    - Embase: records from 1974 to present (including in-process records and articles in press)
    - MEDLINE records from 1950 to present

* Elsevier's Embase Biomedical Answers Web site combines Embase and MEDLINE content into a single, Web-accessible platform (http://www.embase.com), with duplicate citations removed. The single Embase.com platform means that the Embase and MEDLINE databases can be searched simultaneously.

The date on which the search was conducted.

Embase, Medline and Cochrane database - March 2011

CRD database - September 2010

The date span of the search.

The initial date span was 2000 onwards, however, inclusion criteria was subsequently limited to 2006 onwards to include only the most relevant and up to date economic evaluations.

The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Search Strategies

Table 77: Centre for Reviews and Dissemination 1st Sept 2010

Targeted search: CRD database - September 2010

	Search	Matching records
1	MeSH Heart Failure EXPLODE 1	619
2	heart AND failure	1222
3	chf	106
4	#1 or #2 or #3	1361

Of these 1,361 records, 705 were retrieved from NHS-EED:

DARE- N=518

HTA= N= 138

NHS-EDD= N= 705

Comprehensive search: Embase, Medline and Cochrane database - March 2011

Table 78: Embase.com search, 2000 to 22 March 2011 (*)

No.	Query	Results
#25	#23 NOT #24	668
#24	review:de,it OR editorial:de,it OR letter:de,it OR note:de,it	3428312
#23	#22 AND [english]/lim	1573
#22	#19 OR #20 OR #21	1715
#21	#18 AND [in process]/lim	1
#20	#18 AND [article in press]/lim	3
#19	#18 AND [2000-2011]/py	1715
#18	#13 AND #17	1983
#17	#14 OR #15 OR #16	278244
#16	'economic evaluation':ab,ti OR 'economic evaluations':ab,ti	6008
#15	'pharmacoeconomics'/exp	132982
#14	'economic evaluation'/exp	164577
#13	#6 AND #12	53817
#12	#7 OR #8 OR #9 OR #10 OR #11	1413465

#11	utility:ab,ti OR utilities:ab,ti OR mortal*:ab,ti OR survival:ab,ti	985481
#10	'quality of life':ab,ti OR qol:ab,ti OR 'health quality':ab,ti OR 'health related quality':ab,ti OR hrqol:ab,ti OR hrql:ab,ti	131422
#9	'survival'/exp	377018
#8	'mortality'/exp	463754
#7	'quality of life'/exp	170288
#6	#1 OR #2 OR #3 OR #4 OR #5	214321
#5	((forward OR output) NEXT/1 failure):ab,ti	160
#4	'cardiac stand still':ab,ti OR 'decompensatio cordis':ab,ti OR 'insufficientia cardis':ab,ti OR 'low output syndrome':ab,ti	639
#3	((heart OR cardia OR cardia?) NEAR/4 (decompensation OR incompetence OR output)):ab,ti	48075
#2	((heart OR cardia OR cardia? OR myocardial) NEAR/4 (failure OR insufficiency)):ab,ti	147899
#1	'heart failure'/de	88677

* The search was conducted using Elesvier's Embase Biomedical Answers Web site on 23 March 2011.

Table 79– The Cochrane Library search, 2011 Issue 3 (CDSR) and Issue 1 (CENTRAL and the other databases) (*)

	Search	Hits
#1	MeSH descriptor Heart Failure, this term only	4540
#2	((heart OR cardia OR cardia? OR myocardial) NEAR/4 (failure OR insufficiency)):ab,ti,kw	8935
#3	((heart OR cardia OR cardia?) NEAR/4 (decompensation OR incompetence OR output)):ab,ti,kw	3686
#4	("cardiac stand still" OR "decompensatio cordis" OR "insufficientia cardis" OR "low output syndrome"):ab,ti,kw	37
#5	((forward OR output) NEAR/1 failure):ab,ti,kw	1
#6	(#1 OR #2 OR #3 OR #4 OR #5)	11910
#7	MeSH descriptor Quality of Life, this term only	11646
#8	MeSH descriptor Quality-Adjusted Life Years, this term only	2854
#9	MeSH descriptor Heart Failure, this term only with qualifier: MO	820
#10	MeSH descriptor Mortality explode all trees	9092
#11	MeSH descriptor Survival, this term only	95

#12	MeSH descriptor Survival Analysis explode all trees	11936
#13	MeSH descriptor Survival Rate, this term only	6907
#14	("quality of life" OR qol OR "health quality" or "health related quality" or hrqol OR hrql):ti,ab,kw	20622
#15	(utility OR utilities OR mortal* OR survival):ti,ab,kw	52768
#16	(#7 OR #8 OR (#9 AND OR#10) OR #11 OR #12 OR #13 OR #14 OR #15)	72099
#17	(#6 AND #16)	3558
#18	(#17), from 2000 to 2011	2321
#19	(#18) in NHS Economic Evaluation Database	128
#20	(#18) in Health Technology Assessment Database	0
#21	MeSH descriptor Heart Failure, this term only with qualifier: EC	302
#22	("economic evaluation" OR "economic evaluations"):ti,ab,kw	2483
#23	(#21 OR #22)	2764
#24	(#18 AND #23)	118
#25	(#19 OR #20 OR #24)	180

* The search was conducted using Wiley Online on 23 March 2011.

Update comprehensive review – January 2012

Table 80 Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

	Searches	Results
1	exp heart failure/	74777
2	((heart or cardia or cardia? or myocardial) adj4 (failure or insufficiency)).ab,ti.	104971
3	((heart or cardia*) adj4 (decomposition or incompetence or output)).ab,ti.	36241
4	(cardiac stand still or decompensatio cordis or insufficientia cardis or low output syndrome).ab,ti.	487
5	((forward or output) adj1 failure).ab,ti.	122
6	or/1-5	159831

7	exp quality of life/	95123
8	exp mortality/	241244
9	exp survival/	3420
10	(quality of life or qol or health quality or health related quality or hrqol or hrql).ab,ti.	114978
11	(utility or utilities or mortal* or survival).ab,ti.	886414
12	or/7-11	1118943
13	6 and 12	33974
14	exp pharmacoeconomics/	2280
15	(economic evaluation or economic evaluations).ti,ab.	5176
16	(cost-effectiveness or sensitivity analys*).tw.	35432
17	exp "Costs and Cost Analysis"/ or exp Cost-Benefit Analysis/ or exp Economics/ or exp Models, Economic/ or economic evaluation.mp. or exp Models, Econometric/ or exp Economics, Medical/	448828
18	or/14-17	464247
19	13 and 18	1081
20	limit 19 to yr="2000 -Current"	845
21	limit 20 to english	783
22	limit 21 to (editorial or letter or "review")	183
23	21 not 22	600
24	limit 23 to ed=20110321-20120131	69
25	limit 23 to up=20110321-20120131	600
26	24 or 25	600

Table 81 EBM Reviews - NHS Economic Evaluation Database 1st Quarter 2012

	Searches	Results
1	exp heart failure/	74777
2	((heart or cardia or cardia? or myocardial) adj4 (failure or insufficiency)).ab,ti.	104971
3	((heart or cardia*) adj4 (decomposition or incompetence or output)).ab,ti.	36241
4	(cardiac stand still or decompensatio cordis or insufficientia cardis or low output syndrome).ab,ti.	487
5	((forward or output) adj1 failure).ab,ti.	122
6	or/1-5	159831
7	exp quality of life/	95123
8	exp mortality/	241244
9	exp survival/	3420
10	(quality of life or qol or health quality or health related quality or hrqol or hrql).ab,ti.	114978
11	(utility or utilities or mortal* or survival).ab,ti.	886414
12	or/7-11	1118943
13	6 and 12	33974
14	exp pharmacoeconomics/	2280
15	(economic evaluation or economic evaluations).ti,ab.	5176
16	(cost-effectiveness or sensitivity analys*).tw.	35432
17	exp "Costs and Cost Analysis"/ or exp Cost-Benefit Analysis/ or exp Economics/ or exp Models, Economic/ or economic evaluation.mp. or exp Models, Econometric/ or exp Economics, Medical/	448828
18	or/14-17	464247
19	13 and 18	1081
20	limit 19 to yr="2000 -Current"	845
21	limit 20 to english	783

22	limit 21 to (editorial or letter or "review")	183
23	21 not 22	600
24	limit 23 to ed=20110321-20120131	69
25	limit 23 to up=20110321-20120131	600
26	24 or 25	600

Table 82 Embase 1980 to 2012 Week 04

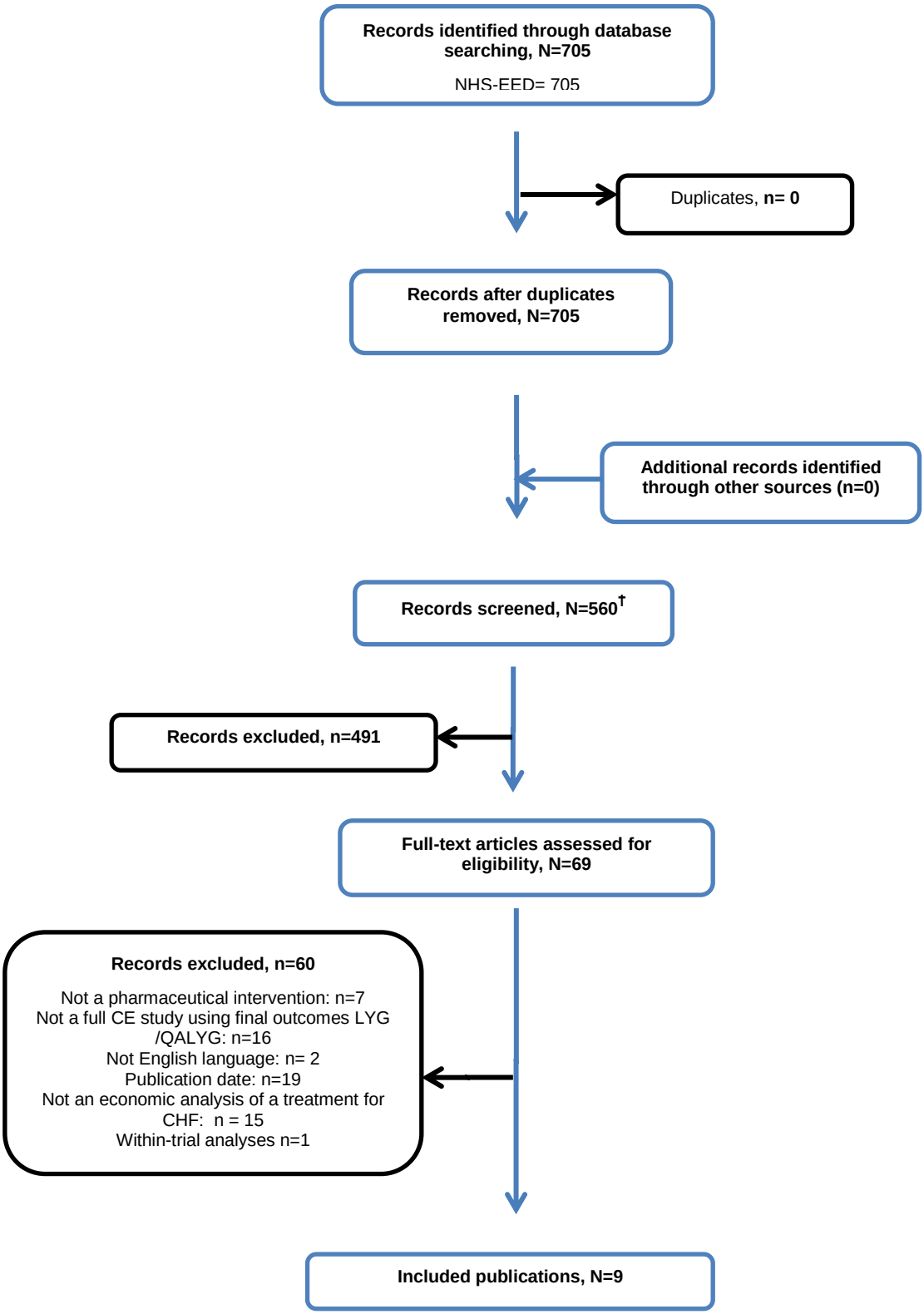
	Searches	**Results**
1	exp heart failure/	226204
2	((heart or cardia or cardia? or myocardial) adj4 (failure or insufficiency)).ab,ti.	135243
3	((heart or cardia*) adj4 (decomposition or incompetence or output)).ab,ti.	39735
4	(cardiac stand still or decompensatio cordis or insufficientia cardis or low output syndrome).ab,ti.	580
5	((forward or output) adj1 failure).ab,ti.	153
6	or/1-5	290252
7	exp quality of life/	193077
8	exp mortality/	498606
9	exp survival/	422394
10	(quality of life or qol or health quality or health related quality or hrqol or hrql).ab,ti.	154658
11	(utility or utilities or mortal* or survival).ab,ti.	1051250
12	or/7-11	1513519
13	6 and 12	74936
14	exp economic evaluation/	176566
15	exp pharmacoeconomics/	143042
16	exp economic evaluation/	176566

17	(economic evaluation or economic evaluations).ti,ab.	6799
18	or/14-17	298534
19	13 and 18	2922
20	limit 19 to yr="2011 -Current"	275
21	limit 20 to (editorial or letter or note or "review")	115
22	20 not 21	160
23	limit 22 to english	155

Table 83 Econlit 1961 to December 2011

	Searches	**Results**
1	heart failure.mp. [mp=heading words, abstract, title, country as subject]	51
2	((heart or cardiac or cardia* or myocardial) adj4 (failure or insufficiency)).mp.	60
3	((heart or cardia*) adj4 (decomposition or incompetence or output)).mp. [mp=heading words, abstract, title, country as subject]	1
4	(cardiac stand still or decompensatio cordis or insufficientia cardis or low output syndrome).mp. [mp=heading words, abstract, title, country as subject]	0
5	((forward or output) adj failure).mp. [mp=heading words, abstract, title, country as subject]	1
6	or/1-5	62
7	limit 6 to yr="2000 -Current"	42

Figure 21 PRISMA Flow Diagram – targeted literature review



†145 records were categorised as cost studies by the reviewer. The definition of cost study was: "This study has been evaluated by a health economist for CRD. This study is not an economic evaluation and has not received an abstract. It is considered to be a cost study and the bibliographic details are included here for information." According to this definition none of these references would meet the inclusion criteria for the review and were therefore not screened.

Figure 22 PRISMA Flow – comprehensive literature review

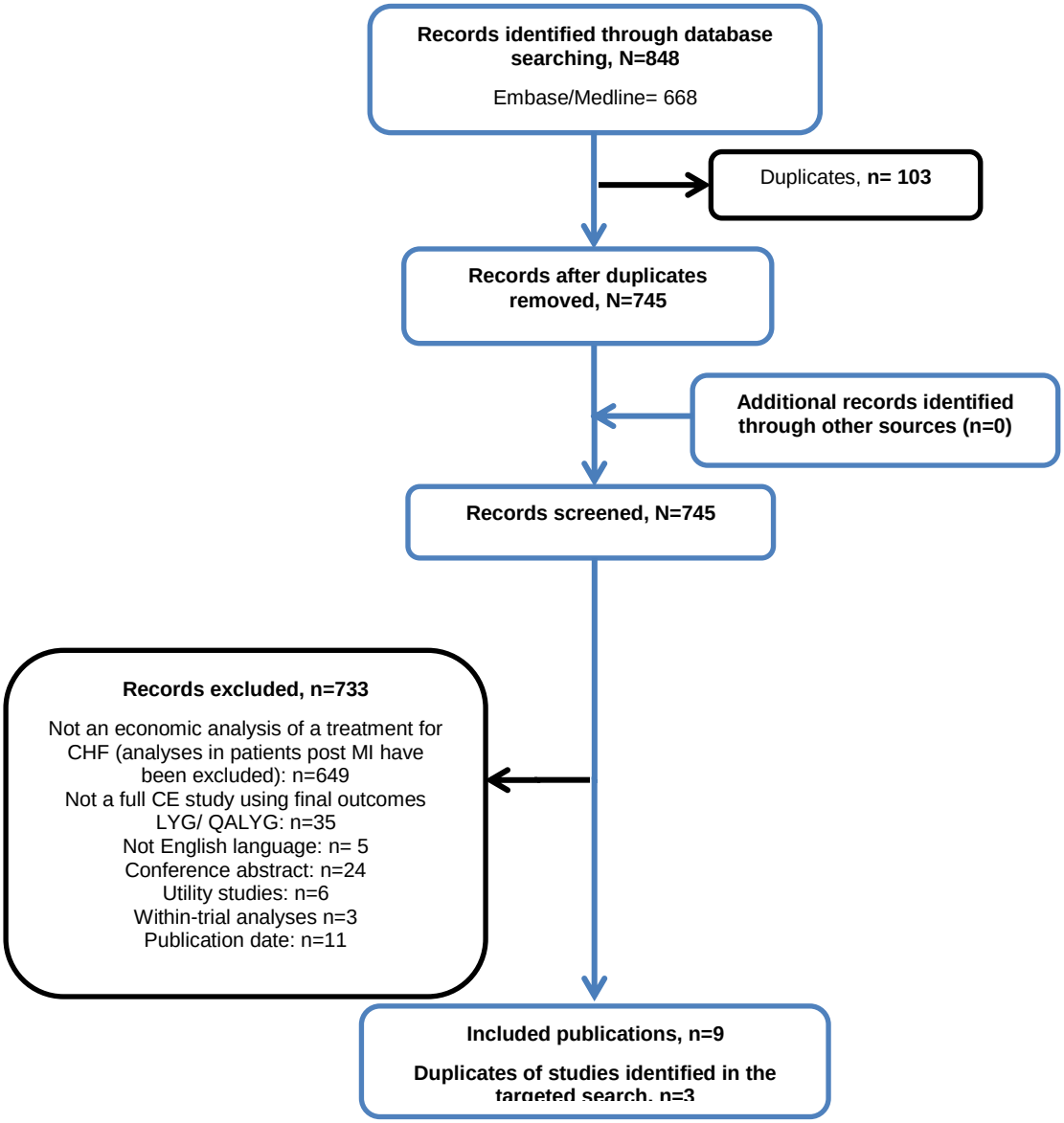


Figure 23 PRISMA Flow – update to comprehensive literature review

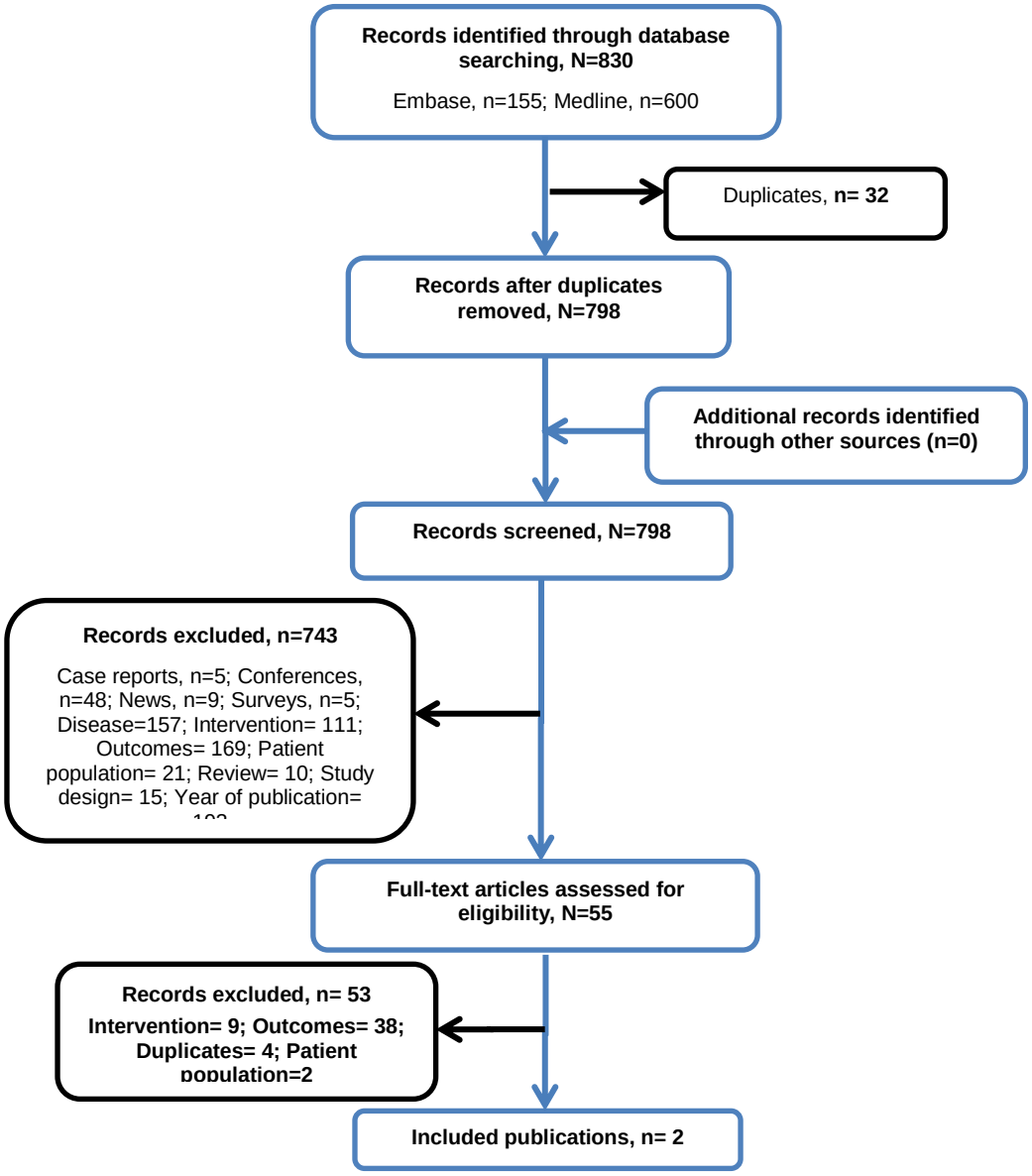


Table 84: Cost-effectiveness studies in heart failure

	Year	Country(ies) where study was performed	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
1. Aidelsburger, P., et al.	2008	COMPANION study -	Adaptation of published decision analytic model with CRT+OPT arm being replaced by CRT-D+OPT. Markov model used subsequently to model events which may occur in half year cycles.	Not stated	CRT-D+OPT = 1.261* OPT = 0.958* **accumulated discounted QALYs, base case, 2-year time horizon.*	CRT-D+OPT = €31,292* OPT = 4,618* **accumulated discounted costs, base case, 2-year time horizon.*	CRT-D+OPT vs. OPT = €88,143* (base case, 2-year time horizon). **varies with device longevity.*
2. Blomstrom, P., et al.	2008	12 European countries (CARE-HF trial)	Within-trial (mean follow-up 29.4 months) used to model costs and health effects during follow-up. Extended analysis used to model post-trial survival. Survival time within follow-up period estimated using Kaplan-Meier curves, extrapolated through fitting parametric survival function to trial data (different exponential models for treatment and control group).	Median age 65	CRT = 6.02 (mean) Medical therapy = 5.11 (mean)	Finland CRT = €15,635 (mean) Medical therapy = €12,385 (mean) Denmark CRT = €20,165 (mean) Medical therapy = €15,834 (mean) Sweden CRT = €22,553 (mean) Medical therapy = €16,645 (mean)	CRT vs. medical therapy: Finland = €3,571 Denmark = €4,759 Sweden = €6,493

3. Boersma, C., et al.	2006	The Netherland	Incremental cost analysis	Mean age 62.7	Not stated	Total inpatient and outpatient cost Valsartan = €8,810 Placebo = €8,442	Valsartan provided cost saving of €368 per person with heart failure in the Netherland.
4. Caro, J.J., et al.	2007	12 European countries (CARE-HF trial)	Discrete event simulation used to predict course of identical pair of patient with NYHA class III-V HF over 5 years – one receiving CRT+OPT, the other OPT alone.	Median age 65	CRT+OPT = 2.82 OPT = 2.39	CRT+OPT = £11,423 OPT = £4,900	CRT+OPT vs. OPT = £15,247
5. Colombo, GL., et al.	2008	Italy	Within trial analysis conducted based on three CHARM trials	Not stated	QALY not reported. Life year gain CHARM – alternative: 0.078 CHARM – Added: 0.061 Reduced LVEF: 0.068	Total or incremental cost not reported	Cost per LYG CHARM – alternative: €713 LYG CHARM – Added: dominant Reduced LVEF: Dominant

6. Heerey, A., et al.	2006	US (Cleveland Clinic Foundation)	Markov model with second-order Monte-Carlo simulation. *$US 2004.	52	1-year follow-up: Biventricular pacemaker group = 0.7449 Control group = 0.7261 5-year follow-up: Biventricular pacemaker group = 2.918 Control group = 2.769	1-year follow-up: Biventricular pacemaker group = £63,586* Control group = $65,573* 5-year follow-up: Biventricular pacemaker group = $169,558* Control group = $288,574*	1-year follow-up: On average the control group was both less effective and more expensive than biventricular pacemaker therapy. 5-year follow-up: On average the control group was both less effective and more expensive than biventricular pacemaker therapy.
7. Linde, C., et al.	2010	Denmark, France, Sweden and UK	Proportion in state model with Monte Carlo simulation. Health states defined by NYHA class (I-III) and death.	CRT-ON = 61.7 ± 10 years (baseline age) CRT-OFF = 60.4 ± 11.2 years (baseline)	CRT-ON = 5.98 (base case) CRT-OFF = 5.18 (base case)	CRT-ON = €28,081 (base case) CRT-OFF = 16,626 (base case)	CRT-ON vs. CRT-OFF = €14,278

8. Mark, D.B., et al.	2006	US, Canada & New Zealand (SCD-HeFT study)	Cumulative within-trial 5-year medical costs estimated using non-parametric partitioned estimator. Post-trial long term costs estimated using 2 covariate-specific regression models. Life expectancy estimated using extrapolated trial data. Two separate Cox proportional hazards models used with the hazard rate modelled as a function of patient's age.	Median age 60.1	1 year follow-up (utilities): ICD arm = 0.85 Placebo = 0.85	Amiodarone = $49,338* Placebo = $42,971* ICD = $61,938* **cumulative 5-year estimates.*	ICER per life-year saved (base case): ICD vs. medical therapy = $38,389 ICUR (1 year follow-up): $41,530 per QALY
9. McKenna, C., et al.	2010	RALES trial conducted in 15 countries, EPHESUS conducted in 37 countries. AREA IN-CHF study also used.	Two-part Markov model used - Part I is a short term model which captures costs and outcomes in first 3 months post-MI. Part II is a long term model which captures long term costs and outcomes after 3 months.	Median age 64 (AREA IN-CHF trials)	Eplerenone = 4.8486 Spironolactone = 4.5551 Standard care = 4.5972	Eplerenone = £5,249 Spironolactone = £4,191 Standard care = £4,129	Eplerenone vs. Standard care = £4,457 Spironolactone vs. Standard care = Dominated

10. McMurray et al	2006	France, Germany, UK	Within trial analysis conducted based on three CHARM trials	Not stated	QALY not reported. Life year gain CHARM – alternative: 0.078 CHARM – Added: 0.061 Reduced LVEF: 0.068	Total or incremental cost not reported	**France** Cost per LYG CHARM – alternative: dominant CHARM – Added: dominant Reduced LVEF: Dominant **Germany** Cost per LYG CHARM – alternative: €3,881 CHARM – Added: €1,427 Reduced LVEF: €2,997 **UK** Cost per LYG CHARM – alternative: €2,547 CHARM – Added: dominant Reduced LVEF: €1,348
11. Perez, A., et al	2011	USA	A Markov model was developed to compare pharmalogic rate control versus rhythm control to determine which strategy was the most cost and clinical effective for patients with both heart failure and atrial fibrillation.	Starting age of the model was 65 years	Rate control†: 2.395 (95% uncertainty interval 2.366-2.424) Rhythm control‡: 2.197 (95% uncertainty interval 2.155-2.237)	Rate control: $7,231 (95% UI $5,517-$9,016) Rhythm control: $16,291 (95% UI $11, 033-$21, 434)	ICER (calculated by separately reported QALYs and Costs) Rate control vs Rhythm control= -45, 606

12. Pourvourville, G., et al.	2008	EPHESUS study conducted in 37 countries.	Within-trial study designed, piecewise regression model produced survival gains and death rates adjusted for patients' characteristics. Comparable patients extracted from Saskatchewan database. Long term survival predicted using piecewise regression and Cox proportional hazards models.	Not stated	∆ life-years gained: Saskatchewan model: Eplerenone = 0.066 (no discount) Framingham model: Eplerenone = 0.108 (no discount)	∆ cost: Saskatchewan model: Eplerenone = €970 (no discount) Framingham model: Eplerenone = €970 (no discount)	ICER per life-year saved: Saskatchewan model: €15,382 Framingham model: €8,954
13. Pradelli, L., et al.	2009	Val-HeFT study included patients from 16 countries.	Markov model with patient-level simulation. 4 health states were used corresponding with NYHA classes.	Mean age 62.7	Valsartan = 1.674 Placebo = 1.659	Valsartan = €6,289* Placebo = €6,843* **2007 €'s*	Valsartan was dominant vs. Placebo across the total patient population.
14. Ribiero, R.A., et al.	2010	US, Canada and New Zealand (SCD-HeFT study) & US and 5 European centres (MADIT-II)	Decision tree model with Markov transitional states. This tracked hypothetical cohort of patients with HF over time who received ICD + conventional therapy, or conventional therapy alone.	Median age 59	ICD = 6.15 (mean) Conventional therapy (comparator) = 5.23 (mean)	ICD = $70,841 (PPP terms) Conventional therapy = $24,619 (PPP terms)	ICD vs. Conventional = £50,345 (PPP terms)

15. Rosen, V.M., et al.	2010	US	Lifetime cohort Markov model used to assess cost-effectiveness of A80 vs. A10 by predicting likelihood of major and minor cardiovascular events. Model composed of several health states according to major CVD event status, minor events and survival.	64	Life-years gained (base case): A80 = 8.85 A10 (comparator) = 8.64	Total discounted costs estimated to be $2,000 higher per patient for those receiving A80 (base case).	Base case: A80 vs. A10 = $13,600 ($9,600 per life-year saved).
16. Stecker, E.C., et al.	2006	US	Markov model developed through adapting published decision tree model.	60	Mean increase in survival (base case): 1.3 years	Incremental cost (base case): $7,800	ICER per life-year saved (base case) = $6,100
17. Szucs, T., et al	2006	Clinical trial carried in Europe, Latin America, USA and Canada. The data was assumed to transferred to Switzerland	Cost-effectiveness analysis; No model description reported. The majority of data in this study were taken from the EPHESUS study. Survival estimates obtained from other sources.	Patients with acute MI complicated by left ventricular dysfunction and HF Mean age: Eplerenone group= 64.2(sd, 11.3); Place group= 64.7(sd, 11.7)	No individual QALYs reported. However, incremental gains in QALYs were: Framingham study=0.0722; Saskatchewan study=0.0446 Worcester study=0.1029	Costs (over 1.3 years or 16 months) in Swiss Francs: Eplerenone= 16,969.78 Placebo= 5,941.29	Incremental costs per QALY gained: Framingham study= CHF15,219; Saskatchewan study= CHF23,965; Worcester study=CHF11,337

18. Taylor, M., et al.	2009	*Not stated*	Markov model consisting of 5 health states, data taken from VALIANT and other trials developed to predict future health pathways, resource use and costs.	Not stated	Valsartan = 5.021 Placebo = 4.519	Valsartan = £8,878 Placebo = £6,198	Valsartan vs. Placebo = £5,338
19.Yao, G., et al.	2007	Patients from 82 European countries, UK cost data.	Markov model with Monte Carlo simulation captured short and long term costs and outcomes of CRT-P, CRT-ICD and MT. CARE-HF trial source of NYHA class distributions & transitions, health utilities, rates, cause of hospitalisation and death.	Base case starting age 65	Mean life-time QALYs (base case): MT (comparator) = 4.08. CRT-P + MT = 6.06. CRT-ICD + MT = 6.75.	Base case: MT = €39,060. CRT-P + MT = €53,996. CRT-ICD + MT = €87,350.	Base case: CRT-P + MT (vs. MT) = €7,538. CRT-ICD + MT (vs. CRT-P + MT) = €47,909. CRT-ICD + MT (vs. MT) = €18.017.
20. Yao, G., et al.	2008	SENIORS trial carried out in 11 European countries.	Individual simulation model based on Markov framework, health states defined by NYHA classes.	Mean age 76	Nebivolol: 5.843 Standard care: 5.194	Nebivolol: €9,288* Standard care: €6,740* **2006 €'s*	Nebivolol vs. Standard care = €3,926*

Details of any additional searches (for example, searches of company databases [include a description of each database]).

N/A

Appendix 11: Quality assessment of cost-effectiveness studies (section 6.1)

Table 85 quality assessment for each cost-effectiveness study identified (studies 1-3)

Question	Aidelsburger, 2008	Blomstrom. 2008	Boersma, 2006
1. Was a well-defined question posed in an answerable form?	Yes – to assess the ICER of CRT-D with OMT versus OMT on its own in patients with HF.	Yes – to investigate the cost-effectiveness of CRT in Denmark, Finland and Sweden; an analysis based on the CARE-HF trial.	Yes – the study (based on Val-HeFT) assesses the cost-effectiveness of valsartan with standard care in patient with heart failure who are on a stable regimen of heart failure medication in the Netherland setting.
2. Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where and how often)?	Yes – the use of OMT discussed in detail, along with comparison to previous methods. The model in use in this study is a modification of a previous model by Banz *et al* [2005]	Yes – Existing pharmacotherapeutic interventions were discussed in some detail as being the realistic alternative to CRT therapy.	No – no discussion of alternatives to valsartan. It may be part of the original economic analysis of Val-HeFT study
3. Was there evidence that the programme's effectiveness had been established?	Yes – previous clinical trials have supported the use of CRT-D, effectiveness data for this model is taken directly from the COMPANION trial.	Yes – previous clinical trials, including CARE-HF have illustrated the potential benefits of CRT therapy relative to MT.	Yes – some discussion regarding the clinical effectiveness and efficacy of valsartan through Val-HeFT trial. Some discussion of existing cost-effectiveness analysis of valsartan in the US setting and the need to observe the economic impact in The Netherland.

Question	Aidelsburger, 2008	Blomstrom. 2008	Boersma, 2006
4. Were all the important and relevant outcomes and costs for each alternative identified?	Yes – statement of fact detailing the intent of the authors to analyse the data from a German Health care system perspective, reporting costs in € with 2005 as the cost year.	Yes – the rationale was to evaluate the data using the Nordic health care settings of Denmark, Sweden and Finland. Data from CARE-HF was combined with locally sourced data to produce the overall results. Breakdown of costs etc. are provided for each country in the analysis.	Yes – Dutch perspective was used. A breakdown of the costs used in the economic analysis is provided.
5. Were outcomes and costs measured accurately in appropriate units (e.g. hours of nursing time, number of physician visits, years-of-life gained) prior to evaluation?	Yes – costs and other input information sourced within Germany (GOA and EBM for example). Interestingly costs per QALY also reported, despite the QALY not being recognised in Germany as an acceptable measure.	Yes – all units were appropriately selected, costs were in € and all the temporal data was assigned sensible units. Cost per QALY and ICERs also reported.	Yes – appropriate units used throughout, incremental cost was reported. Costs stated in €.
6. Were the outcomes and costs valued credibly?	Can't tell – discussion surrounding costs not as detailed as elsewhere, still, useful values are reported.	Yes – costs associated with selecting CRT as opposed to MT were reported but again the overall benefit bestowed by the presence of the CRT device favours this in the long run despite the higher initial cost.	Can't say – good discussion throughout of associated costs yet no explicit discussion of the opportunity cost of valsartan.
7. Were outcomes and costs adjusted for different times at which they occurred (discounting)?	Yes – Both costs and benefits were discounted at 3% annually in line with German guidelines on the subject.	Yes – both health effects and costs were discounted at 3% annually.	Yes – discounting was applied at a rate of 3% and this was varied in the sensitivity analysis.

Question	Aidelsburger, 2008	Blomstrom. 2008	Boersma, 2006
8. Was an incremental analysis of the outcomes and costs of alternatives performed?	Yes – ICER results are published for the base case scenario comparison as well as results from the various sensitivity analyses undertaken.	Yes – Incremental analysis was performed in each of the three country settings as well as a comparison with previous studies	Yes – the authors conducted an incremental analysis including comparisons between valsartan and placebo throughout, and stating the incremental cost for treatment with valsartan.
9. Was a sensitivity analysis performed?	Yes - Sensitivity analysis undertaken and results are reported for modifications of cost parameters, device longevity and discount rate.	Yes – sensitivity analysis results are presented and it was noted that the largest effect on the ICER was as a result of altering the survival assumptions.	No – no sensitivity analysis was performed.
10. Did the presentation and discussion of the results include all, or enough, of the issues that are of concern to purchasers?	Yes – although authors do point out that the cost-effectiveness of the device is highly dependent upon the longevity of the device – a further consideration for decision makers.	Yes – well discussed summary of the results, suitable for use in the three Nordic healthcare settings.	Yes – good discussion of results in an appropriate way for Dutch setting.
11. Were the conclusions of the evaluation justified by the evidence presented?	Yes – the discussion of the resulting evidence supports the cautious conclusions reached concerning the cost-effectiveness.	Yes – conclusions are supported by the evidence; the authors are able to recommend CRT as a cost-effective treatment over traditional OMT for patients with moderate to severe heart failure.	Yes – the conclusions regarding the cost-effectiveness of valsartan are supported by the evidence provided. The authors were able to conclude incremental cost of €368 for valsartan vs. placebo.

Question	Aidelsburger, 2008	Blomstrom. 2008	Boersma, 2006
12. Can the results be applied to the local population?	Yes – transferable information is relevant and available for use in the current setting	Yes – the results are based on CARE-HF trial data mixed with locally sourced cost data so the approach used would be comparable. Obviously costs vary greatly from location to location so this would have to be a consideration, but the results certainly offer a useful reference point.	No – Dutch focussed study with costs and other estimates extracted from Dutch sources.

Table 86 quality assessment for each cost-effectiveness study identified continued (studies 4-6)

Question	Caro, 2007	Colombo, 2008	Heerey, 2006
1. Was a well-defined question posed in an answerable form?	Yes – to assess the economic and health consequences in the UK of implanting CRT devices into patients with NYHA class iii-iv heart failure.	Yes- the study (based on CHARM) assesses the cost-effectiveness of candesartan with standard care from the perspective of NHS in Italy	Yes – A cost utility analysis from the healthcare perspective was performed using HF patients who received a biventricular pacing device.
2. Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where and how often)?	Yes – Brief description of pharmacologic alternatives to CRT along with the issues which they fail to address.	Yes – discussion of alternatives to valsartan are provided.	No – Little data was available in terms of comparators so this is not really plausible in terms of evaluation. Comparisons and cost-effectiveness were made and assessed to OMT
3. Was there evidence that the programme's effectiveness had been established?	Yes – references clinical evidence to support the fact that CRT reduces hospitalisations and improves the patients QoL.	Yes – the discussion regarding the clinical effectiveness and efficacy of candesartan through CHARM trials and the potential need to conduct the Italian specific analysis.	Can't tell – not enough information available. A previous CU analysis of cardiac resynchronization vs. MT places the ICER of biventricular pacemakers at $107,800, so borderline cost-effective as it is above the widely accepted limit of $100,000. Results were also sensitive to a number of variables so the question of its cost-effectiveness remains.

Question	Caro, 2007	Colombo, 2008	Heerey, 2006
4. Were all the important and relevant outcomes and costs for each alternative identified?	Yes – breakdown of relevant costs considered along with the cost sources are provided, analysis was carried out from the UK perspective using 2004 costs.	Yes- Italian perspective was used. However, breakdown of cost was provided by each CHARM trial together with CHARM overall results.	Yes – on the whole costs and effects were well described. The analysis was performed with a societal perspective in mind with randomly selected patients from the Cleveland Clinic Foundation.
5. Were outcomes and costs measured accurately in appropriate units (e.g. hours of nursing time, number of physician visits, years-of-life gained) prior to evaluation?	Yes – appropriate use of units and reporting of costs throughout. Costs per QALY and ICERs also reported	Yes – appropriate units used throughout. Two analyses were reported: cost consequence and cost-effectiveness analysis. Costs stated in €.	Yes – all costs and outcomes were reported in suitable units. Cost data was presented in 2004 $US. ICERs and cost per QALYs were also reported
6. Were the outcomes and costs valued credibly?	Yes – additional costs of the CRT device implantation relative to MT are reported and the relative benefits are also discussed.	Yes- the clinical effectiveness was used from CHARM trials. Unit costs and resource use cost was used from Italian government sources.	Yes comparison were made to MT alone and resulting cost savings in terms of hospital admissions etc. were discussed
7. Were outcomes and costs adjusted for different times at which they occurred (discounting)?	Yes –for the base case scenario, costs and benefits were discounted at 3.5%	Yes – discounting was applied at a rate of 3% and this was varied in the sensitivity analysis.	Yes – Costs and benefits were both discounted at 3% annually as recommended by the US panel for cost-effectiveness in health and medicine

Question	Caro, 2007	Colombo, 2008	Heerey, 2006
8. Was an incremental analysis of the outcomes and costs of alternatives performed?	Yes – ICERs and costs relative to MT are discussed, as well as a comparison to ICERs generated elsewhere, including COMPANION and CARE-HF.	Yes – the incremental analysis was conducted for all three subgroups.	Yes – Incremental costs and ratios are presented for two follow-up time points; 1 and 5 years.
9. Was a sensitivity analysis performed?	Yes – Results of the sensitivity analysis are tabulated and discussed throughout.	Yes – sensitivity analysis was performed by increasing length of non-CV stay, adding GP visit for an adverse event, varying length of stay for all hospital admission, and changing discount rate for costs (0% and 8%).	Yes – PSA was performed by altering the costs and probabilities of the outcomes being modelled.
10. Did the presentation and discussion of the results include all, or enough, of the issues that are of concern to purchasers?	Yes/No - Costs are reported in 2004 British pounds but only direct medical costs were considered in the analysis. Summary results provided are useful in the UK setting.	Yes – good discussion of results for Italian perspective	Yes – discussions explore the fact that the ICERs generated are within the thresholds of cost-effectiveness and results/study population data is also similar to other clinical trials; MIRACLE and MUSTIC.
11. Were the conclusions of the evaluation justified by the evidence presented?	Yes - an ICER below £20,000 was presented and this is accepted as being cost-effective in the UK. Furthermore, increased cost-effectiveness was noted with longer simulations. Not surprising perhaps as the bulk of the CRT costs have to be met immediately with the benefits being realised over time.	Yes – the conclusions are supported by the evidence provided. For Italy, candesartan was cost-effective at €713 LYG for CHARM alternative, dominant for CHARM added, and CHARM reduced. The results are consistent with Germany, France, and UK.	Yes – Conclusions and recommendations are supported by the results and the discussion put forward by the authors.

Question	Caro, 2007	Colombo, 2008	Heerey, 2006
12. Can the results be applied to the local population?	Yes – results are suitable for use with the local population of interest.	No – Italian focussed study with costs and other estimates extracted for Italian NHS.	Yes – study population taken from US centres.

Table 87 quality assessment for each cost-effectiveness study identified continued (studies 7-9)

Question	Linde, 2010	Mark, 2006	McKenna, 2010
13. Was a well-defined question posed in an answerable form?	Yes – an assessment of the cost-effectiveness of CRT compared with optimal medical therapy in patients with New York Heart Association (NYHA) II heart failure (HF) or NYHA I with previous HF symptoms.	Yes – cost-effectiveness analysis of defibrillator therapy or amiodarone in chronic stable heart failure.	Yes – a systematic review and economic evaluation of the clinical effectiveness and cost-effectiveness of aldosterone antagonists for post-myocardial infarct heart failure.
14. Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where and how often)?	Can't say – no obvious discussion of alternatives to CRT.	No – no discussion of alternatives.	Yes – good discussion of competing alternatives and current recommendations regarding these interventions.
15. Was there evidence that the programme's effectiveness had been established?	Yes – discussion of existing analysis of the clinical and cost-effectiveness of CRT-P and CRT-D. It is noted the cost-effectiveness of CRT in patients with asymptomatic or mild-HF (NYHA I/II) needs to be determined. The authors refer to the main study which uses REVERSE trial. This study considered CRT and OMT. Authors also refer to European study which used REVERSE-EU when looking at CRT-P and CRT-D.	Yes – the authors refer to the SCD-HeFT which compared the use of ICDs and amodiarone with placebo, and supports the use of ICDs.	Yes – the authors include discussion of trials and the effectiveness of two aldosterone antagonists currently licensed for HF in the UK.

Question	Linde, 2010	Mark, 2006	McKenna, 2010
16. Were all the important and relevant outcomes and costs for each alternative identified?	Yes – proportion in state model with Monte Carlo simulation used to capture underlying disease processes of patients with costs and utilities being assigned to each health state. The utility values and non-drug costs used in the model are reported. 10 year time horizon used.	Can't say – a societal perspective was used, non-medical costs were not assessed. Lifetime time-horizon used.	Yes – the model evaluates costs from a UK NHS perspective. Costs are expressed in £s with a base year of 2008-9. A two-part Markov model was used with a lifetime time-horizon. Part I is a short term model which captures costs and outcomes in first 3 months post-MI; Part II is a long term model which captures long term costs and outcomes after 3 months.
17. Were outcomes and costs measured accurately in appropriate units (e.g. hours of nursing time, number of physician visits, years-of-life gained) prior to evaluation?	Yes – appropriate units used throughout.	Yes – good discussion of measurements of resource use and the calculation of within-trial costs. Data was taken from the SCH-HeFT trial.	Yes – appropriate units were used throughout, costs per QALY and ICERs reported throughout.
18. Were the outcomes and costs valued credibly?	Yes – discount rates were applied and costs are well documented throughout analysis discussion.	Yes – appropriate units used throughout, costs are reported in $.	Yes – good discussion of costs and comparisons across competing alternatives.
19. Were outcomes and costs adjusted for different times at which they occurred (discounting)?	Yes – discounting was applied to costs and benefits at a rate of 3.5%, and an appropriately sourced exchange rate was used in all costs conversions.	Can't tell – no explicit use of opportunity costs, all costs valued in 2003 USD.	Yes – costs and outcomes were discounted annually at a rate of 3.5%.

Question	Linde, 2010	Mark, 2006	McKenna, 2010
20. Was an incremental analysis of the outcomes and costs of alternatives performed?	Yes – incremental analysis used for both costs and benefits, and additionally, the authors considered the impact of changes in the period of which the REVERSE data was extrapolated.	Yes – both survival and costs were discounted by 3%.	Yes – cost-effectiveness was assessed using incremental cost-effectiveness ratios, and ICERs are well documented throughout.
21. Was a sensitivity analysis performed?	Yes – a PSA was conducted as well as cost-effectiveness acceptability curves and various deterministic analyses to consider the effect of changes in parameter values and modelling assumptions on findings.	Yes – an incremental analysis was conducted by the authors and the resulting ICERs are tabulated by subgroup.	Yes – sensitivity analysis was included, and the results are included in discussion of the results.
22. Did the presentation and discussion of the results include all, or enough, of the issues that are of concern to purchasers?	Yes – good discussion summarising results, including comparison of ICERs in this paper with those derived from the CARE-HF study. Results and discussion appropriate for EU setting.	Yes – sensitivity analysis was conducted, and some discussion of the results is included by the authors	Yes – discussion of results includes references to costs per QALY and ICERs throughout. The authors note that in all but one case, eplerenone appeared to be the most cost-effective for post-MI HF.
23. Were the conclusions of the evaluation justified by the evidence presented?	Yes – results and conclusions are supported, authors concluded that at European WTP thresholds, CRT is cost-effective for patients with mildly symptomatic HF and for asymptomatic patients with left ventricular dysfunction and previous symptoms of HF.	Yes – the authors performed cost-effectiveness analysis of amiodarone therapy (survival in amiodarone and placebo arms were equivalent). CE ratios of ICD were expressed as incremental lifetime costs required to add 1 extra year of life with ICD relative to medical therapy alone. The authors concluded on an ICER of $38,389 per LYS for ICD vs. medical therapy.	Yes – the conclusions were well supported by the evidence, and the authors were able to conclude on an ICER of £4457 per QALY for eplerenone vs. standard care. This was consistently under the £20,000-30,000 threshold.

Question	Linde, 2010	Mark, 2006	McKenna, 2010
24. Can the results be applied to the local population?	Yes – Transferable information is available as this was run in Europe (multicentre European population including UK); NYHA classes used so comparison can be made easily in this aspect. To sum-up comparison to UK can be made.	Yes – Although caveats exist as this is a US based study so costs etc. need to be scrutinised to ensure relevance to UK setting, demographically patients can be viewed as similar to UK setting.	Maybe – conclusions by authors state that a contemporary trial comparing eplerenone and spironolactone would be needed to evaluate efficacy; however they also state that this might not be sensible from a CE and clinical standpoint. That said there is value in the information presented to assist UK decision makers.

Table 88 quality assessment for each cost-effectiveness study identified (studies 10-12)

Question	McMurray, 2006	Perez, 2011	Pourvourville, 2008
1. Was a well-defined question posed in an answerable form?	Yes – the study evaluates the cost-effectiveness of candesartan with standard care in patients with heart failure (NYHA II-IV) and LVEF (with three subgroups LVEF <40% not receiving ace inhibitor, <40% receiving an ace inhibitor, LVEF >40%).	Yes – an cost utility evaluation to compare lifetime costs and health outcomes of rate control versus rhythm control	Yes – cost-effectiveness analysis of aldosterone blockade with eplerenone in patients with heart failure after acute myocardial infarction in the French context: the EPHESUS study.

Question	McMurray, 2006	Perez, 2011	Pourvourville, 2008
2. Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where and how often)?	Yes – the analysis was compared with conventional treatment of HF (incl. combination of diuretics, digoxin, ace inhibitor, beta blocker, and spironolactone). The current analysis takes the perspective of a third party payer in France and Germany, and NHS in UK.	Yes- Both rate and rhythm controls were comprehensively summarised. Various drug regimens included in each controls were listed and described.	Yes – discussion of results from RALES trial which consider post-AMI patients with severe HF and various interventions.
3. Was there evidence that the programme's effectiveness had been established?	Yes – the discussion regarding the clinical effectiveness and efficacy of candesartan through CHARM trials.	No- Authors reported that there wasn't any published data that describes health care utilisation and costs of the management	No – EPHESUS study used to compare eplerenone and standard treatment vs. standard treatment alone for patients with AMI and HF. The results from this were used to model the expected life-years gained.
4. Were all the important and relevant outcomes and costs for each alternative identified?	Yes – economic evaluation was reported by three different perspectives – France, Germany, and UK. Complete breakdown of costs was also reported	The costs and quantities were extracted from the Healthcare Cost and Utilization Project database, a published cost-effectiveness analysis, average wholesale prices from 2009 Red Book, a pharmacy chain drug discount programme, and a local pharmacist-run anticoagulation clinic. The study took a third-party payer perspective; however, the societal perspective is the reference standard.	Can't say – only direct medical costs were included in the model, taking a French partial societal perspective. The sources of direct costs are well documented. The estimation models were based around two separate databases.

Question	McMurray, 2006	Perez, 2011	Pourvourville, 2008
5. Were outcomes and costs measured accurately in appropriate units (e.g. hours of nursing time, number of physician visits, years-of-life gained) prior to evaluation?	Yes- appropriate unit used throughout. Incremental cost and incremental LYG were reported. Costs were reported in €.	There were no unit costs reported for outcomes and costs. However, additional data was referred to Appendices which are not part of the original study publication	Can't say – costs were measured in appropriate units throughout, all costs are in 2003 €. In terms of health outcomes, changes in life-years gained are considered but there is little reference to QoL.
6. Were the outcomes and costs valued credibly?	Yes – the clinical effectiveness was used from CHARM trials, unit costs were used from relevant national formularies, DRG and per diem hospital bed day were used to calculate other resource use cost.	Yes- As listed above, all the costs were extracted from published sources.	Yes – costs in the follow-up period are documented for eplerenone vs. placebo.
7. Were outcomes and costs adjusted for different times at which they occurred (discounting)?	Yes- discounting was applied at a rate of 3%.	Yes- All costs were adjusted to 2009 US dollars by using the medical Consumer Price Index.	Yes – costs and outcomes were discounted annually at a rate of 5%.
8. Was an incremental analysis of the outcomes and costs of alternatives performed?	Yes – the incremental analysis was conducted for all three subgroups.	Yes- The ICERs were calculated by the individual costs and QALYs reported for each treatment therapy.	Yes – incremental analysis was conducted comparing eplerenone and placebo, using both databases, applying a 5% discount and no discount. ICERs are stated for each of these.

Question	McMurray, 2006	Perez, 2011	Pourvourville, 2008
9. Was a sensitivity analysis performed?	Yes – sensitivity analysis was performed by increasing length of non-CV stay, adding GP visit for an adverse event, varying length of stay for all hospital admission, and changing discount rate for costs (3.5%).	Yes- A deterministic and probabilistic sensitivity analyses were conducted to test whether results were robust to variance in the model inputs.	Yes – stochastic sensitivity analysis was conducted to obtain an acceptability curve which is included.
10. Did the presentation and discussion of the results include all, or enough, of the issues that are of concern to purchasers?	Yes – good discussion of results for all three jurisdictions. The authors concluded that candesartan is clinically and economically effective adjunctive treatment for patients providing a 'win-win' scenario for both patient and health care provider	Yes- The study reported various issues linked to the model assumptions and few study limitations. The model assumed that patients with rate control will be remained in that state, but in real-life patients can get into sinus-rhythm. The model patients assumed to have same symptomatic profile	No – due to adoption of within-trial analysis, full cost-effectiveness analysis is not available. In addition, indirect costs were excluded from the analysis although the authors suggest this may not have a significant effect on results.
11. Were the conclusions of the evaluation justified by the evidence presented?	Yes – the conclusions are supported by the evidence provided. For the UK, the authors reported candesartan was cost-effective in CHARM added, with highest ICER in CHARM alternative at €2,547 per LYG.	Yes- The conclusions were justified, but there were several limitations as described above.	Yes – conclusions are supported by the evidence. The authors conclude on a cost per life-year gained of €15,382 for eplerenone vs. placebo.
12. Can the results be applied to the local population?	Yes – three party payer perspective including UK.	No- the study concluded to recommend rate control for 65 year old patients with AF and HF, but may not be applicable for other patient groups. And, considering the limitations and uncertainty in refractory patients, the study also recommends rhythm control in these patients.	Maybe – French context of the EPHESUS trial. Large multicentre trial so potential relevance to UK population. Also focus on within-trial results as opposed to full CE analysis must be taken into account.

Table 89 quality assessment for each cost-effectiveness study identified (studies 13-16)

Question	Pradelli, 2009	Ribeiro, 2009	Rosen, 2010	Steckler, 2006
1. Was a well-defined question posed in an answerable form?	Yes – to evaluate the cost-effectiveness and cost utility of valsartan in addition to standard therapy for the treatment of patients with chronic heart failure with low left ventricular injection fraction (LVEF) in Italy.	Yes – to evaluate the cost-effectiveness of ICD in HF patients under the perspective of the Brazilian Public Healthcare System (PHS)	Yes - The study aimed to investigate the cost-effectiveness of high-dose vs. low-dose statin therapy for HF patients	Yes - This paper investigates the effectiveness and cost-effectiveness of prophylactic pacemaker implantation to facilitate beta-blocker use in HF patients.
2. Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where and how often)?	Yes – reference to first-line therapy based on ACE inhibitors for patients with NYHA class II-IV HF and reduced LVEF and additional combinations.	Yes – descriptions of other models and assessment techniques is quite detailed with several references to the MADIT-II trial as well as the lack of comparison or CE studies that consider data from developing countries.	Yes - Comparisons are difficult to make as there is not much literature in this specific area of comparison. Nevertheless, there was support for the base case assumptions from other trials and the alternative mortality scenario also compared favourable to clinical data even though this reversed the outcome of the model findings.	Yes – descriptions of other studies/models provided in detail and a comparison of these results to their own is well described with mention of the different approaches taken by each of the other trials discussed.
3. Was there evidence that the programme's effectiveness had been established?	Yes – good discussion of existing analysis of valsartan as an effective treatment for reducing cardiovascular morbidity in patients with HF, reference to Val-HeFT study.	Yes – it is accepted that the benefits of ICD implantation for the target population is associated with a marked reduction in total death from HF. However, the cost is preventative on a large scale.	No – Low dose statin use is reported elsewhere in this indication, however this is not the case for the higher dose and there has been a trend to exclude patients with HF from statin related studies in the past.	Yes – Authors describe the trials used to populate the various parameters in the model and discuss the development of the Markov Model from a previously published decision tree model.

Question	Pradelli, 2009	Ribeiro, 2009	Rosen, 2010	Steckler, 2006
4. Were all the important and relevant outcomes and costs for each alternative identified?	Yes – Markov based patient level simulation. Costs evaluated from Italian Health Service perspective – these included both drug costs and expenses for hospitalisation due to worsening heart failure.	Yes – costs and effects were well described as well as the relevant sources they were taken from. The analysis was conducted from Brazilian PHS perspective.	Yes – Outcomes and cost variations were well explored along with differing treatment effects borrowed from various trial datasets such that the cost-effectiveness switched favourability depending on which mortality data was used. Analyses were conducted in $US from the payer perspective using 2006-2007 values.	Can't Tell – Seems to focus on the patient perspective. Nevertheless, that said, costs are well described, as is the Markov Model and its development from the original decision tree along with model inputs from the various trials used to populate the model. Patient cohort for this model is described as hypothetical.
5. Were outcomes and costs measured accurately in appropriate units (e.g. hours of nursing time, number of physician visits, years-of-life gained) prior to evaluation?	Yes – appropriate units are used throughout, costs themselves are not particularly well documented except those that are sourced.	Yes – Suitable units were used throughout and the authors employed the use of QALYs to present the cost-effectiveness results. Costs were expressed as international dollars applying the purchasing power parity (PPP) conversion rate	Yes – appropriate use of units throughout. Costs per LYS and per QALY reported.	Yes – BUT no use of QALYs when presenting data, however authors report incremental values and values for life years saved; other units were also well reported, namely costs, and hospital visits/time was recorded as a frequency per month , presumably for rate calculations.

Question	Pradelli, 2009	Ribeiro, 2009	Rosen, 2010	Steckler, 2006
6. Were the outcomes and costs valued credibly?	Can't say – brief discussion of the some of the direct costs included in the model but no clear discussion of the opportunity costs associated.	Can't Tell – ICD cost in Brazil is proportionally more elevated than in developed countries and as such ICD therapy was associated with a high ICER. Utilities were not available from a study in Brazilian patients and as such values were borrowed from the Beaver Dam Study, a method also adopted by other authors. Opportunity costs not expressly discussed in detail.	Yes – Quality of life data and cost data were based on literature, other input data was trial based. The authors question the robustness of their results and highlight the dependence upon which mortality data is used as the overall cost is very sensitive to this and reverses the recommendation of which dose is cost-effective.	Can't tell - Costs etc. all valued correctly and references are given for all the costs included, however no specific mention of opportunity costs
7. Were outcomes and costs adjusted for different times at which they occurred (discounting)?	Yes – costs and benefits were discounted annually at a rate of 3.5%.	Yes - Discount rates for both costs and effects were set at 3% per year over a 20-year time horizon from a public third party payer perspective.	Yes - Both cost and benefits were discounted annually at 3%	Yes- future costs and benefits discounted at annual rate of 3%.
8. Was an incremental analysis of the outcomes and costs of alternatives performed?	Yes – incremental analysis was conducted.	Yes - Incremental cost-effectiveness estimates were generated by the study.	Yes – both incremental costs and ICERs were presented in the paper	Yes - Incremental cost-effectiveness was calculated for various different scenarios and the results were presented as incremental cost-effectiveness per life year saved. QALYs were not reported.

Question	Pradelli, 2009	Ribeiro, 2009	Rosen, 2010	Steckler, 2006
9. Was a sensitivity analysis performed?	Yes – sensitivity analysis was performed with the results presented graphically in a cost-effectiveness plane and cost-effectiveness acceptability curve.	Yes – one-way and two-way sensitivity analyses were performed on various parameters, results are tabulated and displayed graphically.	Yes – probabilistic and one-way sensitivity analyses were conducted as well as an investigation into the sensitivity of the model to the price of Atorvastatin after year 5 in the model to reflect patent expiration.	Yes – Sensitivity analyses were performed where various cost and benefit elements were varied to asses their impact on the overall CE.
10. Did the presentation and discussion of the results include all, or enough, of the issues that are of concern to purchasers?	Yes – continual reference to cost per QALY and ICERs throughout discussion of the results.	Yes – results and their significance are discussed in detail and are comparable to those generated by other studies. Due to high cost and the Brazilian setting, authors recommend use of ICD therapy only for those patients that are at high risk of ventricular arrhythmias. In other scenarios ICD use would have to be carefully considered.	Yes – from a payer perspective all relevant data was presented as well as a detailed discussion of the limitations.	Yes – The results presented by the authors would be useful to decision makers despite not reporting QALYs explicitly there is enough information for decision makers to work with.

Question	Pradelli, 2009	Ribeiro, 2009	Rosen, 2010	Steckler, 2006
11. Were the conclusions of the evaluation justified by the evidence presented?	Yes – the authors concluded that over a 10 year time horizon, a 23 month treatment course with valsartan in combination with standard therapy for all Italian patients with chronic heart failure and low LVEF is expected to be less costly than standard therapy alone, as well as being more clinically effective. This is supported by the analysis.	Yes – see point above. ICD implant use relative to optimal medical therapy (OMT) was associated with a cost-effectiveness ratio of PPP $50,345 per QALY with a more favourable cost-effectiveness for patients at higher risk.	Yes – conclusions based on the model well reported and discussed	Yes – The model reports that using a pacemaker prophylactically to facilitate beta-blocker therapy in patients who are currently denied access to them may present a cost-effective method of reducing death and hospitalisations from HF. An ICER of $6,100 per year of life saved is associated with the pacemaker-carvedilol strategy over a 20-year time span with both costs and benefits discounted.
12. Can the results be applied to the local population?	Yes – although it is important to remember that this is an Italian modelling study and so specificity to Italy must not be forgotten when attempting to draw conclusions relevant to the UK setting.	Yes – Authors have been careful to note the paucity of data for the Brazilian and developing world settings in this area with costs and resource used data being generated from a cohort study of ambulatory patients in south-eastern Brazil.	Yes – model based on the TNT (Treating to New Targets) trial HF subpopulation (n=781)	Yes – Base case consideration were based on the US Carvedilol Hear t Failure Study and other trial data was included as necessary, all from relevant population cohorts.

Table 90 quality assessment for each cost-effectiveness study identified (studies 17-20)

Question	Szucs, 2006	Taylor, 2009	Yao, 2007	Yao, 2008
1. **Was a well-defined question posed in an answerable form?**	Yes- the study assess the cost-effectiveness of eplerenone in patients with heart failure after MI in a Swiss setting	Yes – an economic evaluation of valsartan for post-MI patients in the UK who are not suitable for treatment with ACE inhibitors.	Yes – An evaluation of the cost-effectiveness (CE) of CRT-P vs. Medical Therapy (MT) and an incremental CE analysis of CRT-ICD vs. CRT-P. CRT-ICD may well appear cost-effective vs. MT but the incremental benefit of ICD in addition to CRT-P could well be beyond the UK willingness to pay threshold.	Yes – long term cost-effectiveness analysis of nebivolol compared with standard care in elderly patients with heart failure.
2. **Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where and how often)?**	Yes- the analysis was retrospective and was based on the results of a clinical trial EPHESUS, which compared eplerenone (25mg or 50mg) with placebo once daily. This current cost-effectiveness analysis doesn't provide any description of competing alternatives to the drug.	No – no discussion of alternatives to valsartan, authors highlight valsartan is only angiotensin II antagonist licensed for the management of post-MI patients with left ventricular systolic dysfunction, heart failure, or both.	Yes – Perhaps not comprehensive. However, previous evaluations have provided varying estimates of CE for CRT-P and CRT-ICD relative to MT but none have addressed the incremental CE of CRT-P vs. CRT-ICD.	Yes – discussion of existing analysis of cost-effectiveness of *β*-blockers, highlighting it may even be cost saving to society.

Question	Szucs, 2006	Taylor, 2009	Yao, 2007	Yao, 2008
3. Was there evidence that the programme's effectiveness had been established?	Yes- the cost-effectiveness results were shown similar to the original EPHESUS study. The treatment effects of the eplerenone was shown to be effective in terms of primary and secondary end points.	No – some discussion regarding the clinical effectiveness and efficacy of valsartan through VALIANT trial. No discussion of existing cost-effectiveness analysis of valsartan.	Yes – Previous studies have highlighted its effectiveness but not with respect to the comparison being made here. Authors provided overview of CARE-HF trial, the RCT used to populate the model.	Yes – the SENIORS trial compared nebivolol with standard care, demonstrating the direct health benefits of nebivolol compared with standard care in elderly patients with HF. All clinical input values were estimated using individual patient data from the SENIORS trial.
4. Were all the important and relevant outcomes and costs for each alternative identified?	Yes- the effectiveness was measured by LYG and QALYs. Because there was no single data source to estimate life expectancy three different data sources were used to estimate survival. Costs for all hospitalisation were identified also like; total costs by type of service, ER visit, diagnostic procedure/test, concomitant medication and eplerone by their corresponding mean utilisation values for the first, second and third year of randomisation. All costs expected from a payee perspective.	Yes – UK NHS perspective used. Excel based Markov model used along with data from the VALIANT clinical trial. For placebo, 3 other trials were used. A breakdown of the unit costs used in the model is provided. 10 year time horizon used.	Yes – Markov Model with Monte Carlo simulation captured both short term (changes in health states, costs and consequences of device implantation) and long term effects of successful implantation. Again success rates were taken from CARE-HF trial. Utility scores, costs and probabilities for each stage reported in paper.	Yes – individual patient-level simulation based on Markov framework used. Unit costs and transition probabilities well documented, economic analysis conducted from NHS perspective. Lifetime horizon used.

Question	Szucs, 2006	Taylor, 2009	Yao, 2007	Yao, 2008
5. Were outcomes and costs measured accurately in appropriate units (e.g. hours of nursing time, number of physician visits, years-of-life gained) prior to evaluation?	Yes- as described above. Effectiveness measured using two metrics: LYG and QALYs; Costs for the eplerenone reported as an estimate of HF 3.88/day (public price)	Yes – appropriate units used throughout, cost per QALY and ICERs also reported. Costs stated in £ or $ with base year identified.	Yes – appropriate use of units is consistent throughout.	Yes – appropriate units were used throughout, all costs are expressed as € with base case exchange rate reported
6. Were the outcomes and costs valued credibly?	The effectiveness outcomes were taken from an RCT (EPHESUS); Life expectancy estinmates were obtained from epidemiology studies conducted in different databases and adjusted to specific Swiss life-expectancies. Unit cost data for hospitalisation were derived by "all patient diagnostic related groups (AP-DRG)"; Costs for outpatient procedures and tests were derived from the national tariff code (TARMED)	Can't say – good discussion throughout of associated costs yet no explicit discussion of the opportunity cost of valsartan.	Can't Tell – Cost for procedures etc. are displayed and a statement about future costs being discounted by 3.5% annually but no mention of opportunity costs as a consideration.	Yes – good discussion throughout costs section.
7. Were outcomes and costs adjusted for different times at which they occurred (discounting)?	The costs were discounted by 3%; All life years lost estimates were discounted using rates from 0-6%	Yes – discounting was applied at a rate of 3.5% and this was varied in the sensitivity analysis.	Yes – Both costs and benefits were discounted at 3.5% annually.	Yes – both costs and benefits were discounted annually at a rate of 3.5%.

Question	Szucs, 2006	Taylor, 2009	Yao, 2007	Yao, 2008
8. Was an incremental analysis of the outcomes and costs of alternatives performed?	Yes-Incremental cost-effectiveness of the eplerenone compared with placebo was calculated across three data sets.	Yes – the authors conducted an incremental analysis including comparisons between valsartan and placebo throughout, and stating the incremental cost per QALY gained for treatment with valsartan.	Yes – this was designed as an incremental CE comparison of CRT-P and CRT-ICD. Mean incremental costs, QALYs, incremental QALYs and ICERs are reported for various scenarios, deviating from the base case. Incremental cost-effectiveness is reported per QALY and per LY gained.	Yes – the authors conducted an incremental analysis of costs and benefits, supported with cost-effectiveness acceptability curves.
9. Was a sensitivity analysis performed?	Yes- Sensitivity analyses were performed to test the variability of results (like, the costs per life-year saved). The discount rate was increased from 3 to 6%.	Yes - both one-way sensitivity analysis and PSA were included and the results are tabulated in detail. The findings support the conclusion that valsartan is a cost-effective intervention.	Yes – the author presented results for a variety of scenarios varying battery life, starting age and follow-up time. Considerations were also made employing different combinations with MT relative to MT on its own.	Yes – sensitivity analysis was conducted with respect to age starting treatment, discount rates and number of outpatient specialist visits on the cost and cost-effectiveness results. A PSA was conducted across key input values.
10. Did the presentation and discussion of the results include all, or enough, of the issues that are of concern to purchasers?	Yes- the study reported various limitations of the analyses, which include concerns about cost and outcome adjustments to Swiss healthcare settings. However, the study reported issues with extrapolation of costs beyond the scope of the clinical trial. The ICER went up by 50% in US when extrapolated, which could be the case in Switzerland.	Yes – good discussion of results in an appropriate way for UK setting.	Yes – from a UK perspective the analysis would be useful to decision makers. The conclusion presented by the authors makes a recommendation of CRT-P + MT at the £30,000 threshold.	Yes – good discussion of findings in base case and following sensitivity suitable for use in a UK setting.

Question	Szucs, 2006	Taylor, 2009	Yao, 2007	Yao, 2008
11. Were the conclusions of the evaluation justified by the evidence presented?	Yes- The analyses results are similar to those of the cost-effectiveness study, conducted by the original EPHESUS investigators.	Yes – the conclusions regarding the cost-effectiveness of valsartan are supported by the evidence provided. The authors were able to conclude on ICER of £5338 per QALY gained for valsartan vs. placebo.	Yes - as mentioned in previous point	Yes – the conclusions derived from the results follow naturally and are well supported. The authors concluded on an ICER of €3296 per QALY saved for nebivolol vs. standard care.
12. Can the results be applied to the local population?	Yes- the study reported the patient population of the EPHESUS study is comparable to a Swiss AMI population wrt age, co-morbidity, and concomitant medication. But also reported that patients are only partly representative of the total collective of corresponding patients in Switzerland. Eplerenone is shown be cost-effective in increasing life-years of patients with AMI-HF.	Yes – UK focused study so potential relevance to UK population is immediately apparent.	Yes – results are comparable as patients were recruited from 82 European centres (as per CARE-HF protocol) and these results were combined with UK cost data.	Yes – Markov model constructed with a UK healthcare perspective, taking data from CARE-HF and COMPANION trials. Costs converted to Euros using a £1=€1.47 exchange rate. Potential relevance to UK setting is immediately apparent.

Appendix 12: Search strategy for section 6.4 (Measurement and valuation of health effects)

The following information should be provided.

The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS Economic Evaluation Database (NHS EED)
- EconLIT.

The following databases were searches:

- Medline and Medline (R) in process (with OVID as the search provider)
- Embase (OVID SP)
- Cochrane library
- NHS EED (CRD database)
- Econlit (OVID SP)

The date on which the search was conducted. All searches were carried on the 6th January 2012.

The date span of the search.

Searches were limited to publications from 2000 onwards.

The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Medline and Medline in process

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
---

1 heart failure/ or heart failure, diastolic/ or heart failure, systolic/ (74145)
2 Cardiomyopathy, Dilated/ (11789)
3 Shock, Cardiogenic/ (5679)
4 exp Ventricular Dysfunction/ (21466)
5 Cardiac Output, Low/ (5116)
6 (hf or chf).ti,ab. (26368)
7 ((heart or cardiac or myocardial or coronary) adj2 (failure or decompensation)).ti. (40596)
8 heart decompensation.ti,ab. (93)
9 ((congestive or chronic) adj2 "heart failure").ti,ab. (37884)
10 ((dilated or congestive) adj2 cardiomyopath$).ti. (5656)
11 "cardiogenic shock".ti. (2063)
12 ((ventricular or ventricle$) adj2 (failure or insufficien$ or dysfunction$)).ti. (5097)
13 (("left ventricular" or "left ventricle") adj2 (failure or insufficien$ or dysfunction$)).ti,ab. (14305)
14 lvsd.ti,ab. (255)
15 or/1-14 (142958)
16 quality of life.ti. (31396)
17 (hql or hrql or hrqol).ti,ab. (7054)
18 quality-adjusted life years/ (5271)
19 quality of life index.ti,ab. (927)
20 quality adjusted life year$.ti,ab. (4287)
21 (qaly$ or qald$ or qale$).tw. (3772)
22 qwb.tw. (150)
23 quality of well being.tw. (292)
24 quality of wellbeing.tw. (7)
25 (hui or hui 2 or hui2 or hui 3 or hui3).tw. (721)
26 (time trade off or time tradeoff or tto).tw. (956)
27 (utilit$ adj2 (value$1 or cost$1 or health or analys$ or index)).ti,ab. (4270)
28 health state$1.tw. (2940)
29 "Value of Life"/ (5190)
30 (hye or healthy year$1 equivalent$).ti,ab. (54)
31 standard gamble$.ti,ab. (588)
32 (euroqol or euroquol or EQ 5D or eq5d).tw. (2658)
33 visual analog$ scale$.tw. (21993)
34 or/16-33 (71510)
35 15 and 34 (928)
36 limit 35 to (english language and yr="2000 -Current") (696)

Embase

Database: Embase <1996 to 2012 Week 03>
Search Strategy:
---

1 *heart failure/ or *acute heart failure/ or *cardiogenic shock/ or diastolic dysfunction/ or *forward heart failure/ or exp *heart ventricle failure/ or *high output heart failure/ or *systolic dysfunction/ (50079)
2 exp *congestive heart failure/ (14263)
3 *congestive cardiomyopathy/ (4509)
4 (hf or chf).ti,ab. (32228)
5 ((heart or cardiac or myocardial or coronary) adj2 (failure or decompensation)).ti. (40635)
6 heart decompensation.ti,ab. (40)
7 ((congestive or chronic) adj2 "heart failure").ti,ab. (32832)
8 ((dilated or congestive) adj2 cardiomyopath$).ti. (4433)
9 "cardiogenic shock".ti. (1460)
10 ((ventricular or ventricle$) adj2 (failure or insufficien$ or dysfunction$)).ti. (4624)
11 (("left ventricular" or "left ventricle") adj2 (failure or insufficien$ or dysfunction$)).ti,ab. (13165)
12 lvsd.ti,ab. (454)
13 or/1-12 (103670)
14 quality of life.ti. (36640)
15 (hql or hrql or hrqol).ti,ab. (9230)
16 quality of life index.ti,ab. (1028)
17 quality adjusted life year$.ti,ab. (5218)
18 (qaly$ or qald$ or qale$).ti,ab. (5266)
19 qwb.tw. (137)
20 quality of well being.tw. (254)
21 quality of wellbeing.tw. (15)
22 (hui or hui 2 or hui2 or hui 3 or hui3).ti,ab. (768)
23 (time trade off or time tradeoff or tto).ti,ab. (1054)
24 (utilit$ adj2 (value$1 or cost$1 or health)).ti,ab. (4896)
25 health state$1.ti,ab. (3383)
26 (hye or healthy year$1 equivalent$).ti,ab. (40)
27 standard gamble$.ti,ab. (603)
28 (euroqol or euroquol or EQ 5D or eq5d).ti,ab. (3910)
29 visual analog$ scale$.ti,ab. (24900)
30 *visual analog scale/ (326)
31 or/14-30 (75360)
32 13 and 31 (1118)
33 conference.so. (614543)
34 conference paper/ (429380)
35 33 or 34 (1042382)
36 32 not 35 (817)
37 36 (817)
38 limit 37 to (English language and yr="2000 -Current") (651)

Cochrane library

ID	Search	Hits
#1	MeSH descriptor Heart Failure, this term only	4651
#2	MeSH descriptor Heart Failure, Diastolic, this term only	12
#3	MeSH descriptor Heart Failure, Systolic, this term only	45
#4	MeSH descriptor Cardiomyopathy, Dilated, this term only	416
#5	MeSH descriptor Shock, Cardiogenic, this term only	139
#6	MeSH descriptor Ventricular Dysfunction explode all trees	1578
#7	MeSH descriptor Cardiac Output, Low, this term only	331
#8	((heart or cardiac or myocardial or coronary) NEXT (failure or decompensation)):ti	5130
#9	((congestive or chronic) NEXT ("heart failure")):ti,ab	4099
#10	((dilated or congestive) NEXT cardiomyopath*):ti	294
#11	("cardiogenic shock"):ti	87
#12	((ventricular or ventricle) NEXT (failure or insufficienc* or dysfunction)):ti	447
#13	(lvsd or hf or chf or "heart decompensation"):ti,ab	2566
#14	(("left ventricular" or "left ventricle") NEXT (failure or insufficienc* or dysfunction*)):ti,ab	943
#15	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #11 OR #12 OR #13 OR #14)	9741
#16	quality of life:ti	6259
#17	(hql or hrql or hrqol):ti,ab	1084
#18	MeSH descriptor Quality-Adjusted Life Years, this term only	2423
#19	quality of life index:ti,ab	3191
#20	quality adjusted life year*:ti,ab	1552
#21	(qaly* or qald* or qale*):ti,ab	482
#22	(hui or "hui 2" or hui2 or "hui 3" or hui3):ti,ab	68
#23	("time trade off" or "time tradeoff" or tto):ti,ab	107
#24	utilit* NEAR/2 value*:ti,ab	53

#25	utilit* NEAR/2 cost*:ti,ab	731
#26	utilit* NEAR/2 health:ti,ab	172
#27	health state*:ti,ab	5694
#28	MeSH descriptor Value of Life, this term only	142
#29	(hye or "healthy year* equivalent*"):ti,ab	0
#30	standard gamble*:ti,ab	87
#31	(euroqol or euroquol or eq5d or "eq 5d"):ti,ab	656
#32	visual analog* scale*:ti,ab	11861
#33	(#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 OR #31 OR #32)	29252
#34	(#15 AND #33)	464
#35	(#34), from 2000 to 2012	360

NHS EED

Search		Hits	
1		MeSH DESCRIPTOR Heart Failure EXPLODE ALL TREES	418
	2	MeSH DESCRIPTOR Cardiomyopathy, Dilated EXPLODE ALL TREES	11
	3	MeSH DESCRIPTOR Shock, Cardiogenic EXPLODE ALL TREES	5
	4	MeSH DESCRIPTOR Ventricular Dysfunction EXPLODE ALL TREES	95
	5	MeSH DESCRIPTOR Cardiac Output, Low EXPLODE ALL TREES	19
	6	(((heart or cardiac or myocardial or coronary) NEAR2 (failure or decompensation))):TI	402
	7	(hf or chf):TI	10
	8	((((congestive or chronic) NEAR2 "heart failure")))	532
	9	(((dilated or congestive) NEAR2 cardiomyopath*)):TI	2
	10	("cardiogenic shock"):TI	4
	11	(((ventricular or ventricle*) NEAR2 (failure or insufficien* or dysfunction*))):TI	31

12	((("left ventricle") NEAR2 (failure or insufficien* or dysfunction*)))))	1
13	((("left ventricular") NEAR2 (failure or insufficien* or dysfunction*)))))	137
14	(lvsd)	21
15	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	884
16	IN NHSEED WHERE PD FROM 2000 TO 2012	60

Econlit

Database: Econlit <1961 to December 2011>

Search Strategy:

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1 ((heart or cardiac or myocardial or coronary) adj2 (failure or decompensation)).mp,tw. (53)

2 (chf or hf).mp,tw. (52)

3 ((congestive or chronic) adj2 "heart failure").mp,tw. (28)

4 heart decompensation.mp,tw. (0)

5 ((dilated or congestive) adj2 cardiomyopath$).mp,tw. (1)

6 "cardiogenic shock".mp,tw. (0)

7 ((ventricular or ventricle$) adj2 (failure or insufficien$ or dysfunction$)).mp,tw. (1)

8 (("left ventricular" or "left ventricle") adj2 (failure or insufficien$ or dysfunction$)).mp,tw. (1)

9 lvsd.mp,tw. (0)

10 or/1-9 (104)

11 limit 10 to yr="2000 - 2011" (79)

Details of any additional searches (for example, searches of company databases [include a description of each database]).

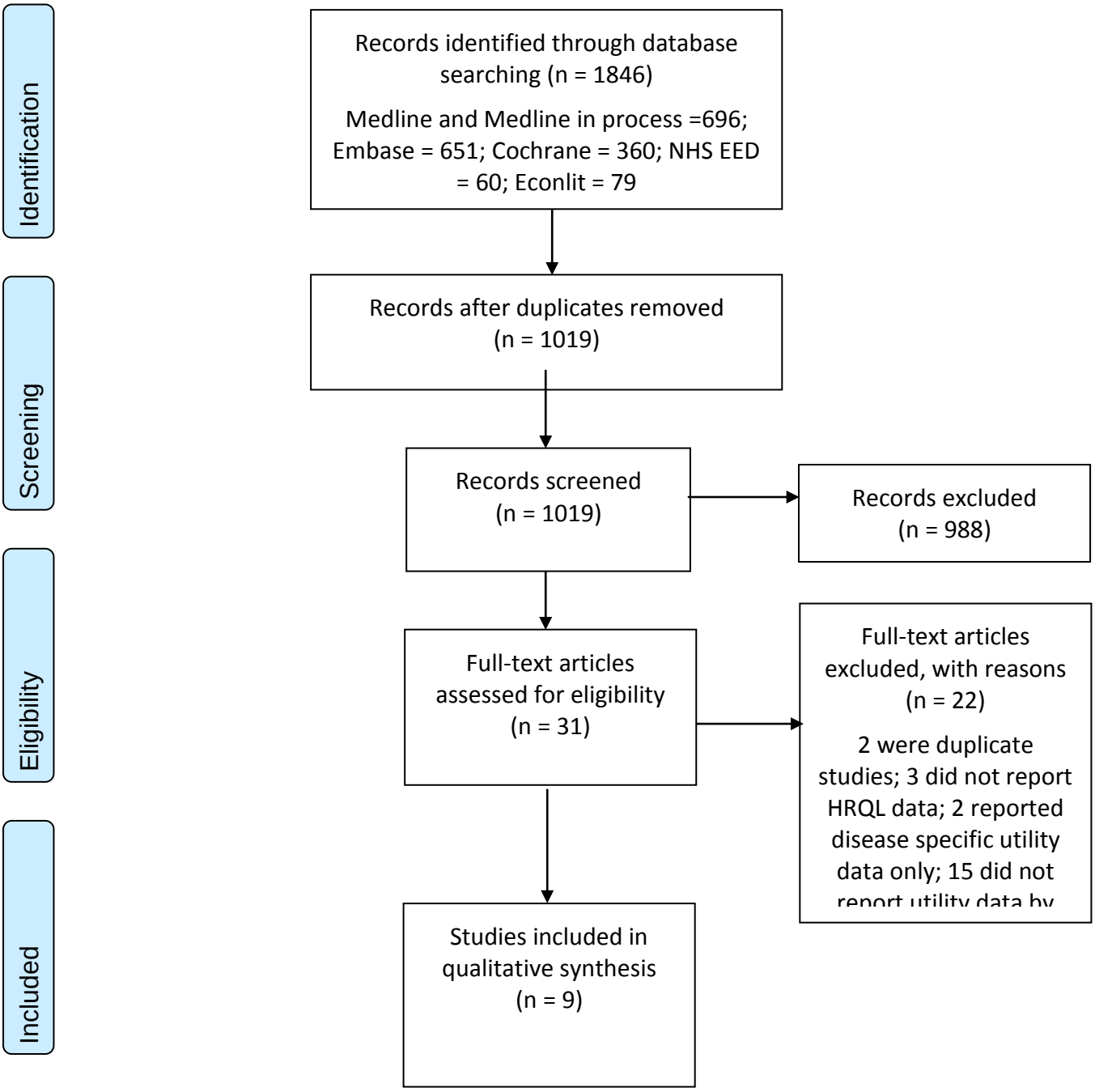
The inclusion criteria were as follows:

- Target population: Adult patients with chronic heart failure
- Type of studies: Generic measures of utility (EQ 5D, SF-36, HUI)
- Utility level by NYHA class
- Utility measure obtained using TTO or Standard Gamble method

The exclusion criteria were as follows:

- Studies published prior to 2000
- Studies not in the English language
- References to studies from conference abstracts

Figure 1: PRISMA flow diagram for systematic review of HRQL studies



The data abstraction strategy.

Study author, year, population, recruitment method, interventions, HRQL measure used, sample size, NYHA classes included and mean HRQL score by NYHA class were all extracted. Extractions were carried out by a systematic reviewer. All extracted data was then validated by a second reviewer.

Table 91: Details of included HRQL studies

Study Author	Year	Population	Recruitment	Interventions	HRQL Measures	Sample Size (n)*	NYHA Class	Health States Appropriate?	Mean Score (SD) [CI]	Appropriate for CE analysis?
Alehagen U	2008	Sweden - Elderly patients with symptoms of HF inc. dyspnea, peripheral oedema + tiredness	Patients who contacted primary care clinics in rural municipalities in SE Sweden (1995-96)	NR	SF-36 & TTO	323	I-III & self classified sI-sIV	NYHA functional class as the basis for assessment is sensible given that it is a well-known, reliable method for assessing functional status & issued in routine clinical practice.	TTO: I=0.75 [0.72-0.78]; II=0.71 [0.66-0.741]; III=0.56 [0.49-0.63]; sI=0.77 [0.74-0.80]; sII=0.68 [0.65-0.72]; sIIIa=0.61 [0.55-0.68]; sIIIb+sIV=0.50 [0.38-0.62]	Yes - Statistically significant correlation between NYHA class and the dimensions of SF-36 validates results. QALY weights linked to NYHA

Study Author	Year	Population	Recruitment	Interventions	HRQL Measures	Sample Size (n)*	NYHA Class	Health States Appropriate?	Mean Score (SD) [CI]	Appropriate for CE analysis?
										classes could be a useful tool to policymakers
Bennett SJ	2002	USA - All patients with HF, diagnosed by LVIDD ≥5.5 or FSS ≤18% or LVEF ≤40% or abnormal ventricular wall motion, 18yr+,	Convenience sample of patients enrolled in the adult medicine or heart clinics affiliated with an urban county hospital	NR	SF-12 (also CHQ and LHFQ)	211	I -IV	Disease specific questionnaire may be more appropriate in this case as these are more able to distinguish between the different NYHA classes	SF-12 Physical component: I=45.86; II=33.45; III=27.96; IV=24.80, Mental component: I=52.99; II=48.12; III=40.95; IV=38.83	Maybe - Merits to using SF-12 when wishing to compare patients with HF to other groups. SF-12 is also less complex and less time consuming to administer

Study Author	Year	Population	Recruitment	Interventions	HRQL Measures	Sample Size (n)*	NYHA Class	Health States Appropriate?	Mean Score (SD) [CI]	Appropriate for CE analysis?
Eurich DT	2006	USA & Canada - Patients with HF. All patients were at least 30yo with LVEF <0.40	Patients were recruited through the Cardiovascular Outcomes Research Consortium across 14 medical centre outpatient departments	None	EQ-5D - UK, US and VAS scoring (also reports on KCCQ and RAND12)	298	I-IV	Disease specific measures may provide better insight into HRQL for certain disease related events such as dyspnoea in the case of KCCQ. That said EQ-5d would result in the best overall perspective and is a chosen method as far as NICE is concerned	NYHA Class Improvement: UK: +2=0.79(0.14); +1=0.70(0.24); 0=0.71(0.22); -1=0.65(0.25) US: +2=0.82(0.06); +1=0.77(0.16); 0=0.77(0.16); -1=0.74(0.17) VAS: +2=77.50(10.61); +1=62.10(21.32); 0=65.74(20.62); -1=60.38(22.31)	Yes - Wealth of information presented in paper, relevance to UK is stated. Disease specific measure may be the most responsive for short periods of study as they are more specific but the generic measures provide further information for which the KCCQ,

Study Author	Year	Population	Recruitment	Interventions	HRQL Measures	Sample Size (n)*	NYHA Class	Health States Appropriate?	Mean Score (SD) [CI]	Appropriate for CE analysis?
										for example, would not be suitable
Göhler A	2009	Subset of patients with HF from multicentre RCT, EPHESUS trial	Data obtained from EPHESUS trial	Aldosterone antagonist, eplerenone	EQ-5D	1395	I-IV	NYHA functional class is an established proxy for HF progression and can be linked to utilities when used as health states in a Markov model. NYHA based	I= 0.855 [0.845-0.864]; II=0.771 [0.761-0.781]; III=0.673 [0.665-0.690; IV=0.532 [0.480-0.584].	Yes - Goal of study was to provide a set of empirically derived utility weights that can be easily linked to common disease

Study Author	Year	Population	Recruitment	Interventions	HRQL Measures	Sample Size (n)*	NYHA Class	Health States Appropriate?	Mean Score (SD) [CI]	Appropriate for CE analysis?
								estimates are also less sensitive to interaction with population age.		proxies and can be used to represent health states in future Markov models.
Havranek EP	2004	USA & Canada - Patients with HF. A subset of patients from the OVERTURE trial. LVEF ≤30%	Mail and telephone interviews of patients enrolled at investigator sites took part in this health preference sub-study	Omapatrilat vs. Enalapril	TTO (also VAS and DASI)	153	II-IV	Favourable comparison with previous literature. TTO method might be more transparent and easier to follow for HF patients	II = 0.82 (0.24); III-IV = 0.70 (0.34)	Maybe - Suggestion that this relationship between TTO and VAS values seems to be different so perhaps "in trial" utility measurements might

Study Author	Year	Population	Recruitment	Interventions	HRQL Measures	Sample Size (n)*	NYHA Class	Health States Appropriate?	Mean Score (SD) [CI]	Appropriate for CE analysis?
										be best to examine HF trial results
Kirsch J	2000	UK - HF patient sample drawn from SmithKline Beecham UK workforce and members of the SBRSA	Face to face interviews were held	None	TTO	64	I-IV	Continuing debate over reliability and validity of NYHA classification, but widely used for economic evaluations in HF.	2-year TTO: I=0.934(0.089); II=0.782(0.244); III=0.553(0.361); IV=0.372(0.407) 10-year TTO: I=0.930(0.093); II=0.765(0.183); III=0.509(0.351); IV=0.284(0.404)	Maybe - Concerns over the differentiating capabilities for the worst health states and potential violations of constant proportionality in these states. Authors suggest more work

Study Author	Year	Population	Recruitment	Interventions	HRQL Measures	Sample Size (n)*	NYHA Class	Health States Appropriate?	Mean Score (SD) [CI]	Appropriate for CE analysis?
										is needed to be certain of conclusions
Kurtalic S	2011	Bosnia Hertzegovina - Previously diagnosed HF patients, who were hospitalised and ambulatory treated at the Clinic for International Medicine of University Clinical Centre in Tuzla, Bosnia Hertzegovina,	Sectional study of 120 patients hospitalised and ambulatory treated compared to 10 subjects without heart failure. Further details not reported	NR	SF-36	120 with HF and 10 healthy controls	I-IV	NYHA class is defined as the appropriate classification for HF severity	Control group=98.6 (0.0); I=90.76 (4.51); II=70.14 (10.64); III=36.45 (9.52); IV=25.41 (5.91)	

Study Author	Year	Population	Recruitment	Interventions	HRQL Measures	Sample Size (n)*	NYHA Class	Health States Appropriate?	Mean Score (SD) [CI]	Appropriate for CE analysis?
		during 2010								
Pressler SJ	2011	USA - HF patients recruited from primary care and heart clinics affiliated with a Midwestern university medical centre between 9/1998 and 8/2000	Telephone interviews at baseline, 4, 8 and, 24 weeks	None	HUI-3 & SF-12 (also LHFQ and CHQ)	211	I-IV	NYHA system has demonstrated validity and interrater reliability. In this case only baseline scores are given per NYHA class	Baseline (mean): I= 0.76; II=0.56; III=0.35; IV=0.24	Maybe - HUI-3 was able to distinguish between the different classes on the NYHA scale and demonstrated satisfactory reliability and validity in this sample. Disease specific measures might be better at assessing changes in the health states

Study Author	Year	Population	Recruitment	Interventions	HRQL Measures	Sample Size (n)*	NYHA Class	Health States Appropriate?	Mean Score (SD) [CI]	Appropriate for CE analysis?
Soriano N	2010	Spain - HF patients admitted to hospital in all regions of Spain; clinicians from each Centre were invited to participate such that no regions were missed	6 pen and paper questionnaires, one at each visit (before discharge and at 1, 3, 6, 9, and 12 months after discharge)	NR	SF-36 (also MLHFQ)	670~ (drop-out rates reduce 'n' at each visit)	I-IV	NYHA class as differentiation for HF patients is robust enough. Not enough detail as to SF-36 scores per NYHA class reported	Evolution Physical Component Score: NYHA I-II: Baseline=38; M1=39.3; M3=40.3; M6=38.9; M9=40.6; M12=40. NYHA III-IV:Baseline= 33.7; M1=36.5; M3=37.9; M6=38; M9=38.3; M12=38.7.	Maybe - The generic SF-36 has the advantage of covering a broader set of dimensions in terms of HRQL. Agreement with other studies.

*Sample size is those that completed the study questionnaire; HF = Heart Failure; ~ This value represent the number of questionnaires completed prior to discharge

Appendix 13: Resource identification, measurement and valuation (section 6.5)

No specific resource use search was undertaken.

Appendix 14: Literature review of recent HF studies – Search strategy

(removed as non-relevant).

Appendix 15: SHIfT Study - additional Information

Methodology – additional information

9.1.1.1 Definition of analysis sets for SHIfT and the SHIfT PRO sub-study

SHIfT: Definition of the Analysis Sets

The analysis sets of patients were defined according to the ICH E9 guidelines (1998), in accordance with the intention-to-treat principle. A summary of the analysis sets is provided in Table 92. **Randomised Set (RS)** (based on the intention-to-treat principle) was defined as all included patients with a randomisation number allocated by Interactive Randomisation Service (IRS) and to whom a therapeutic unit had been dispensed.

The **RS_{BBdose}** was defined as all patients of the RS receiving at least half of target daily dose of beta-blockers at randomisation. "At least half target daily dose" was attained if the dose was equal to or superior to the following total daily dose for each beta-blocker (as defined by the European Society of cardiology guidelines (Swedberg, 2005) except for metoprolol tartrate which does not appear in the guideline):

- Carvedilol: 25 mg.
- Metoprolol succinate: 95 mg.
- Bisoprolol: 5 mg.
- Nebivolol: 5 mg.
- Metoprolol tartrate: 75 mg (half target dose indicated by Waagstein, 1993).

The **Safety Set** was defined as all patients having received at least one dose of study drug.

Table 92: Analysis Sets

Analysis sets and subsets		Ivabradine	Placebo	All
Randomised Set	n	**3241**	**3264**	**6505**
RS_{BBdose}	n (%)	**1581 (48.8)**	**1600 (49.0)**	**3181 (48.9)**
Safety Set	n (%)	**3232 (99.7)**	**3260 (99.9)**	**6492 (99.8)**
Subgroups of RS				
Age < 65 years	n (%)	1976 (61.0)	2055 (63.0)	4031 (62.0)
Age ≥ 65 years	n (%)	1265 (39.0)	1209 (37.0)	2474 (38.0)
Age ≥ 75 years*	n (%)	369 (11.4)	353 (10.8)	722 (11.1)
Male	n (%)	2462 (76.0)	2508 (76.8)	4970 (76.4)
Female	n (%)	779 (24.0)	756 (23.2)	1535 (23.6)
BB intake at randomisation	n (%)	2897 (89.4)	2923 (89.6)	5820 (89.5)
No BB intake at randomisation	n (%)	344 (10.6)	341 (10.4)	685 (10.5)
Ischaemic HF	n (%)	2215 (68.3)	2203 (67.5)	4418 (67.9)
Non-ischaemic HF	n (%)	1026 (31.7)	1061 (32.5)	2087 (32.1)
NYHA class II	n (%)	1585 (48.9)	1584 (48.5)	3169 (48.7)
NYHA class III / IV	n (%)	1655 (51.1)	1679 (51.5)	3334 (51.3)
No history of diabetes	n (%)	2268 (70.0)	2258 (69.2)	4526 (69.6)

History of diabetes	n (%)	973 (30.0)	1006 (30.8)	1979 (30.4)
History of hypertension	n (%)	2162 (66.7)	2152 (65.9)	4314 (66.3)
No history of hypertension	n (%)	1079 (33.3)	1112 (34.1)	2191 (33.7)
Heart rate ≥ 77 bpm	n (%)	1657 (51.1)	1700 (52.1)	3357 (51.6)
Heart rate < 77 bpm	n (%)	1583 (48.9)	1561 (47.9)	3144 (48.4)

% = % of the Randomised Set

** non pre-specified subgroup*

PRO-SHIfT sub-study: Definition of Analysis sets

- Included set PRO (IS PRO), defined as all patients randomised in the main study and consented to participate in the PRO sub-study
- Full Analysis Set EQ-5D (FAS EQ-5D): All patients of the IS PRO who had taken at least one dose of the study treatment and who have one baseline and at least one post-baseline reliable assessment of EQ-5D VAS (reliable value means that the value is not missing and is not ambiguous)
- Full Analysis Set KCCQ (FAS KCCQ) All patients of the IS PRO who had taken at least one dose of the study treatment and who have one baseline and at least one post-baseline reliable assessment of KCCQ

9.1.1.2 Definitions of the individual components of the primary composite endpoint in the SHIfT study

Hospitalisation (EVC Charter p15)

- Hospitalisation was defined as any attendance at hospital requiring completion of the hospital admission procedures and/or at least an overnight stay or until death of the patient. An event leading to the prolongation of an ongoing hospitalisation, with or without the transfer of the patient in a specialised hospital department, was considered as a hospitalisation. The adjudication process specified if the hospitalisation was considered planned or unplanned. A hospitalisation was considered unplanned when triggered by a clinical event. An unplanned hospitalisation could be delayed from the causal event.

Hospitalisation for worsening heart failure (EVC Charter p15)

Satisfying the outcome “hospitalisation for worsening HF” was dependent on the patient simultaneously satisfying the following four pre-specified criteria:

1. Patient should be hospitalised (see definition above), AND
2. New or increasing symptoms of HF (e.g. dyspnoea, fatigue), AND
3. New or increasing signs of HF including signs of fluid retention (e.g. pulmonary rales, peripheral oedema, raised jugular venous pressure, weight gain), or objective evidence of heart failure (such as for instance pulmonary oedema/congestion in chest X-ray), AND

4. A significant change in the treatment to improve HF defined by: initiation of intravenous diuretics or other intravenous medications (excluding cardiac glycosides) or mechanical ventilation or mechanical support (intra-aortic balloon pump, ventricular assist device).

In the presence of the criteria listed above, HF was adjudicated even in the presence of other causes for hospital admission, related or not to the episode of worsening HF (e.g. pneumonia, anaemia, atrial fibrillation). In the case of concomitant occurrence of MI and worsening HF, the cause considered by EVC members as being the main reason for hospital admission was adjudicated. Planned or unplanned hospitalisation for heart transplant was adjudicated as unplanned hospitalisation for worsening HF. Patients with cardiogenic shock fulfilled the definition of HF.

Cardiovascular death (EVC Charter p17-18):

- Death due to HF; death due to MI, arrhythmic death or presumed arrhythmic death, OR
- Other CV death – e.g., a stroke, ruptured aneurysm, or pulmonary embolism, OR
- Death of unknown cause – corresponded to non-violent or traumatic deaths for which it was not possible to specify whether they were CV or not. At the time of the final statistical analysis, death of unknown cause was considered as CV death.

9.1.1.3 Definitions of the secondary outcomes in the SHIfT study

The definitions for the secondary outcomes in the SHIfT study are presented in Table 93.

Table 93: Definitions of the secondary outcomes

Definition of secondary outcome	Definition
Individual components of the primary composite outcome	
Hospitalisation for worsening HF	As for the primary outcome,
CV death (including death from unknown cause)	As for the primary outcome,
Non-composite outcomes	
Death from any cause	This consisted of all deaths: • CV deaths; • Non-CV deaths; • Deaths of unknown cause.
Death from HF	Death occurring from worsening or uncontrolled HF: • with or without hospitalisation; • HF was considered a major factor leading to death;

Definition of secondary outcome	Definition
	• Even if the terminal event is an arrhythmia and unless there is an obvious other cause for the death.
Hospitalisation for any cause	See 'Hospitalisation',
Unplanned hospitalisation for any cause	See 'Hospitalisation',
Hospitalisation for CV reason (including hospitalisation for undetermined cause)	• Hospitalisation for worsening HF (see above, in this table); • Hospitalisation for MI (see below in this table); • Other CV hospitalisation: must be caused by a fully documented CV cause; eg, unstable angina, stroke, arrhythmia, hospitalisation related to a vascular procedure/operation, ruptured aneurysm, pulmonary embolism, hypotension, syncope, hypertensive emergency; • Hospitalisation for undetermined cause: corresponded to hospitalisations for which it was not possible to specify whether they were CV or not. At the time of the final statistical analysis, hospitalisation of undetermined cause was considered as CV hospitalisation.
Unplanned hospitalisation for CV reason	See • 'Hospitalisation', • Hospitalisation for CV reason (see above, in this table).
Secondary composite outcome	
First event among CV death (including death from unknown cause), hospitalisation for non-fatal MI or hospitalisation for worsening HF	• CV death: as for the primary outcome, • Hospitalisation for non-fatal MI: based on typical increase of biochemical markers of myocardial necrosis and at least one of ischaemic symptoms, ECG changes or coronary artery intervention; for further information see EVC Charter p16. • Hospitalisation for worsening HF: as for the primary outcome
Other secondary criteria	
Heart rate	Resting heart rate was measured on 12-lead ECG at each scheduled visit during the study. All measurable assessments in sinus rhythm during the study were analysed, whether the patient was on treatment or not.
NHYA classification	At each visit, the investigator questioned the patient about his/her HF symptoms to evaluate the disease by the functional capacity of the patient (NYHA classification).
Global assessments	• At pre-specified visits, patients were requested to complete the PaGA (patient global assessment) and the investigator was requested to complete the PhGA (physician global assessment). These pre-specified visits were at Month 4, 12, 24, and termination visit (PhGA assessments at Month 36 48 visits were added in Amendment No. 6). • The patients were asked, 'Since treatment started, please evaluate the change in your heart condition by making a

Definition of secondary outcome	Definition
	cross in one of the boxes below'. The boxes were labeled: markedly improved, moderately improved, slightly improved, no change, slightly worsened, moderately worsened, markedly worsened. The patient completed the questionnaire in a separate room, before meeting the physician and a member of the investigator's team put the sealed envelope containing the questionnaire into the medical file. • The investigators were asked, 'According to your clinical evaluation, how do you find your patient today in comparison to before treatment started?' The choices in the e-CRF (to be completed at the end of the planned visit after the patient had left) were labelled as for the patient's questionnaire. • The investigator and the patient did not discuss this evaluation together.

Abbreviations: CV, cardiovascular; HF, heart failure; MI, myocardial infarction; NYHA, New York Heart Association; PaGA, patient global assessment (ie, questionnaire completed by patient); PhGA, physician global assessment (ie, questionnaire completed by investigator); ECG, electrocardiogram; eCRF, electronic clinical report form

Source: SHIfT CSR p58, p64, p65; Swedberg et al 2010b p877; EVC Charter p16, 17

9.1.1.4 Background therapy – additional information

Table 94: Background therapy at randomisation (main trial population and licensed population)

Background therapy	Heart rate ≥70 bpm at baseline (N =6505)		Heart rate ≥75 bpm at baseline (N = 4150)	
	Ivabradine n (%)	Placebo n (%)	Ivabradine n (%)	Placebo n (%)
beta-blocker intake				
beta-blocker intake at randomisation	N = 3241 2897 (89.4)	N = 3264 2923 (89.6)	N = 2052 1794 (87.4)	N= 2098 1845 (87.9)
ESC recommended beta-blocker or metoprolol tartrate[a]	**N = 2897** 2842 (98.1)	**N = 2923** 2871 (98.2)	[redacted]	[redacted]
At least half of the target daily dose Yes No	**N = 2842** 1581 (55.6) 1261 (44.4)	**N = 2871** 1600 (55.7) 1271 (44.3)	N = 1767 974 (55.1) 793 (44.9)	N = 1818 1012 (55.7) 806 (44.3)
Target daily dose	**N = 2842**	**N = 2871**	N = 1767	N = 1818

Yes	743 (26.1)	745 (26.0)	467 (26.4)	471 (25.9)
No	2099 (73.9)	2126 (74.1)	1300 (73.6)	1347 (74.1)
Reasons why not at target daily dose	**N = 2099**	**N = 2126**	[redacted]	[redacted]
Hypotension	933 (44.5)	952 (44.8)	[redacted]	[redacted]
Fatigue	676 (32.2)	670 (31.5)	[redacted]	[redacted]
Pulmonary dyspnoea	284 (13.5)	302 (14.2)	[redacted]	[redacted]
Dizziness	267 (12.7)	245 (11.5)	[redacted]	[redacted]
Cardiac decompensation	180 (8.6)	187 (8.8)	[redacted]	[redacted]
Bradycardia	134 (6.4)	125 (5.9)	[redacted]	[redacted]
Other	199 (9.5)	219 (10.3)	[redacted]	[redacted]
Concomitant treatments (other than beta-blockers)				
	N =3241	**N = 3264**	[redacted]	[redacted]
ACEI and/or ARB	2963 (91.4)	2960 (90.7)	1852 (90.3)	1896 (90.4)
Diuretics (excluding aldos. antagonist)	2719 (83.9)	2695 (82.6)	1743 (85.0)	1741 (84.0)
ACEI	2565 (79.1)	2551 (78.2)	[redacted]	[redacted]
Aldosterone antagonist[b]	1981 (61.1)	1941 (59.5)	1286 (62.7)	1271 (60.6)
Digitalis/digoxin	706 (21.8)	710 (21.8)	478 (23.3)	512 (24.4)
ARB	455 (14.0)	472 (14.5)	[redacted]	[redacted]
Cardiac devices at baseline				
	N = 3241	**N = 3264**	N = 2052	N = 2098
At least one device: pacemaker of CRT or ICD	110 (3.4)	134 (4.1)	66 (3.2)	94 (4.5)
ICD	92 (2.8)	115 (3.5)	[redacted]	[redacted]
Device with pacemaker function	46 (1.4)	42 (1.3)	[redacted]	[redacted]
Conventional pacemaker only	8 (0.2)	5 (0.2)	[redacted]	[redacted]
CRT	28 (0.9)	44 (1.4)	[redacted]	[redacted]
CRT and ICD	18 (0.6)	30 (0.9)	[redacted]	[redacted]

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CRT, cardiac resynchronisation therapy; ICD, implantable cardioverter defibrillator; RSBBDOSE, patients of the randomised set receiving at least half of target daily dose of beta-blockers at randomisation

Notes: a Concerning the 107 patients who were not taking one of the recommended -blockers, 59 were taking atenolol, 33 were taking betaxolol and the remaining patients were taking other types of beta-blockers. None of these patients were eligible for inclusion in the RSBBdose.

b Potassium-sparing diuretic

Source: SHIfT CSR Table (10.4.1.3) 2 p95, Table (10.4.1.3) 4 p96, Table (10.4.1.3) 6 p97

Table 95 Background treatments after randomisation (main trial population and licensed population)

Background therapy	Heart rate ≥70 bpm at baseline (n = 6,505)		Heart rate ≥75 bpm at baseline (n = 4,150)	
	Ivabradine N = 3241 % on drug	**Placebo N = 3264 % on drug**	Ivabradine N = 2052 % on drug	Placebo N = 2098 % on drug
Beta-blockers				
After 6 months	88.7	89.7	[redacted]	[redacted]
After 12 months	88.6	89.8	[redacted]	[redacted]
After 18 months	89.0	90.0	[redacted]	[redacted]
After 24 months	87.9	91.4	[redacted]	[redacted]
After 30 months	87.7	90.1	[redacted]	[redacted]
ACEi and/or ARB[a]				
After 6 months	90.9	90.2	[redacted]	[redacted]
After 12 months	90.8	90.4	[redacted]	[redacted]
After 18 months	91.4	90.1	[redacted]	[redacted]
After 24 months	91.2	91.6	[redacted]	[redacted]
After 30 months	90.3	92.5	[redacted]	[redacted]
Diuretics (excluding aldosterone antagonist)[a]				
After 6 months	83.7	83.1	[redacted]	[redacted]
After 12 months	82.5	82.8	[redacted]	[redacted]
After 18 months	82.6	82.1	[redacted]	[redacted]
After 24 months	82.8	83.5	[redacted]	[redacted]
After 30 months	84.9	83.1	[redacted]	[redacted]
Aldosterone antagonist[a,b]				
After 6 months	60.3	58.8	[redacted]	[redacted]
After 12 months	60.0	58.3	[redacted]	[redacted]
After 18 months	58.4	57.6	[redacted]	[redacted]
After 24 months	56.4	56.4	[redacted]	[redacted]
After 30 months	54.9	53.5	[redacted]	[redacted]
Cardiac devices implanted after randomisation				
At least one device: pacemaker of CRT or ICD	4.1	4.5	-	-
New ICD	2.6	3.3		
New device with pacemaker function	2.2	1.7		
New conventional pacemaker only	0.9	0.3		
New CRT	1.5	2.4		
New CRT and ICD	0.9	1.5		

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CRT, cardiac resynchronisation therapy; ICD, implantable cardioverter defibrillator

Notes: [a] Expressed as a proportion of assessable patients
[b] Potassium-sparing diuretic

Source: SHIfT CSR Table (10.6) 1 p104, Table (10.6) 3 p106, Table (10.6) 4 p107

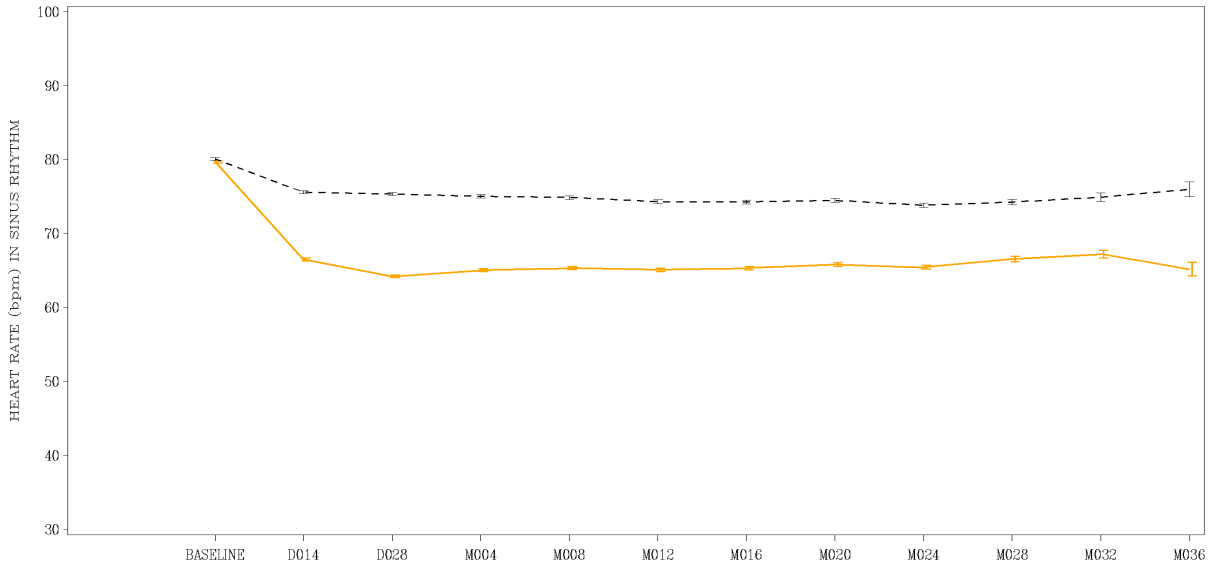
Results – additional information

Heart rate

Change in heart rate from baseline (main trial population; ≥70 bpm)

The mean heart rate in each treatment group is plotted at each visit for patients in sinus rhythm in Figure 24: Mean heart rate by visit in patients in sinus rhythm (randomised patients). The mean heart rate at baseline was around 80 bpm. The profiles in the mean heart rate during the study for each treatment group showed an expected initial decrease followed by a stable plateau. In view of the very small number of observations, the results are not given after Month 36.

Figure 24: Mean heart rate by visit in patients in sinus rhythm (randomised patients)



number of patients with a value observed at baseline and at the considered visit

Ivabradine	3240	3181	3147	3028	2880	2727	2479	2215	1732	1020	530	156
Placebo	3261	3203	3182	3070	2893	2765	2479	2199	1724	1028	535	183

Source: SHIfT CSR Figure (11.3.1) 1 p133

Safety - additional information

Additional analysis of safety for the main trial population (≥70 bpm) is presented in the following order:

(iii) All clinical events
(iv) Clinical events related to heart failure
(v) Severe adverse events
(vi) Treatment–related adverse events
(vii) Deaths

Detailed analysis of safety: main trial population (≥70 bpm)

(iii) All clinical events

In total, 17,496 AEs were reported in 4,806 patients (74.0%), with similar frequencies in the ivabradine and placebo arms (8,498 events in 74.7% of patients *vs* 8,998 events in 73.4% of patients, respectively). Table 96 shows the AEs 'on treatment' by system organ class (SOC) and preferred term. The analogous table for AEs 'during the study' (i.e. after first intake of study drug until database closure) by SOC is reported in the SHIfT CSR, Table (12.1.1) 1, p144.

The principal SOCs associated with AEs reported at higher incidence rates in the ivabradine group than in the placebo groups were Investigations (14.0% *vs* 10.0%) and eye disorders (6.1% *vs* 3.2%). The most frequently reported AEs in both groups were (ivabradine *vs* placebo): Cardiac failure (21.7% *vs* 26.0%), Atrial fibrillation (8.3% *vs* 6.7%) and blood pressure inadequately controlled (7.1% *vs* 6.1%).

Atrial fibrillation has been proposed to be added as an identified risk in the SPC. Patients developing AF were identified as having the following characteristics:

- older (mean age 64.3 years) than the overall population (mean age 60)
- more likely to be in NYHA class III or IV and to have a previous history of atrial fibrillation (approximately one quarter of these patients)

When considering serious AF, the difference between the ivabradine and placebo group was less marked (3.9% *vs* 3.3%). Importantly, the higher incidence of AF in the ivabradine group did not translate into worse outcomes. On the contrary, the incidence of primary endpoint in such patients was markedly lower in the ivabradine group than in the placebo group (52.4% *vs* 61.8%). Similarly, the incidence of AEs relating to central nervous system haemorrhage and cerebrovascular accidents was not higher in the ivabradine group as compared to placebo (2.2% *vs* 2.9%). The same observation can be made for the most frequent preferred term ischaemic stroke (1.1% with ivabradine and 1.4% with placebo).

Table 96: Adverse events 'on treatment' by system organ class and preferred term (at least 1% of patients in either group) (safety set)

System organ class Preferred term	**Ivabradine** **N = 3232** **n (%)**	**Placebo** **N = 3260** **n (%)**
All	**2414 (74.7)**	**2392 (73.4)**
Cardiac disorders	**1332 (41.2)**	**1357 (41.6)**
Cardiac failure	701 (21.7)	846 (26.0)
Atrial fibrillation	267 (8.3)	217 (6.7)
Bradycardia	148 (4.6)	28 (0.9)
Ventricular extrasystoles	144 (4.5)	138 (4.2)
Angina pectoris	133 (4.1)	142 (4.4)
Angina unstable	118 (3.7)	126 (3.9)
Acute myocardial infarction	62 (1.9)	54 (1.7)
Ventricular tachycardia	60 (1.9)	70 (2.2)
Myocardial infarction	57 (1.8)	51 (1.6)
Supraventricular extrasystoles	41 (1.3)	50 (1.5)
Sinus tachycardia	40 (1.2)	102 (3.1)
Atrial flutter	37 (1.1)	35 (1.1)
Atrioventricular block first degree	35 (1.1)	37 (1.1)
Infections and infestations	**632 (19.6)**	**731 (22.4)**
Pneumonia	120 (3.7)	132 (4.1)
Respiratory tract infection	44 (1.4)	32 (1.0)
Upper respiratory tract infection	34 (1.1)	54 (1.7)
Respiratory tract infection viral	31 (1.0)	35 (1.1)
Urinary tract infection	28 (0.9)	41 (1.3)
Influenza	67 (2.1)	70 (2.2)
Bronchitis	41 (1.3)	39 (1.2)
Bronchitis acute	68 (2.1)	85 (2.6)
Nasopharyngitis	66 (2.0)	70 (2.2)
Investigations	**451 (14.0)**	**325 (10.0)**
Heart rate decreased	181 (5.6)	45 (1.4)
Transaminases increased	46 (1.4)	42 (1.3)
Blood creatinine increased	55 (1.7)	47 (1.4)
Metabolism and nutrition disorders	**448 (13.9)**	**480 (14.7)**
Diabetes mellitus inadequate control	135 (4.2)	141 (4.3)
Diabetes mellitus	34 (1.1)	37 (1.1)
Hyperuricaemia	47 (1.5)	52 (1.6)
Hypokalaemia	33 (1.0)	26 (0.8)
Hyperkalaemia	29 (0.9)	56 (1.7)
Hypercholesterolaemia	33 (1.0)	34 (1.0)
Vascular disorders	**437 (13.5)**	**425 (13.0)**
Blood pressure inadequately controlled	228 (7.1)	198 (6.1)
Hypotension	62 (1.9)	87 (2.7)
Hypertensive crisis	27 (0.8)	33 (1.0)
General disorders and administration site conditions	**313 (9.7)**	**287 (8.8)**
Sudden death	111 (3.4)	119 (3.7)
Sudden cardiac death	73 (2.3)	68 (2.1)
Gastrointestinal disorders	**306 (9.5)**	**314 (9.6)**
Gastritis	38 (1.2)	40 (1.2)
Diarrhoea	33 (1.0)	35 (1.1)

Nervous system disorders	**305 (9.4)**	**376 (11.5)**
Ischaemic stroke	35 (1.1)	47 (1.4)
Syncope	27 (0.8)	39 (1.2)
Dizziness	55 (1.7)	47 (1.4)
Headache	44 (1.4)	58 (1.8)
Respiratory, thoracic and mediastinal disorders	**253 (7.8)**	**291 (8.9)**
COPD	65 (2.0)	78 (2.4)
Cough	42 (1.3)	44 (1.4)
Musculoskeletal and connective tissue disorders	**199 (6.2)**	**242 (7.4)**
Osteoarthritis	27 (0.8)	45 (1.4)
Eye disorders	**197 (6.1)**	**104 (3.2)**
Phosphenes[a]	89 (2.8)	16 (0.5)
Renal and urinary disorders	**181 (5.6)**	**226 (6.9)**
Renal failure	63 (2.0)	83 (2.6)
Renal failure chronic	29 (0.9)	49 (1.5)
Blood and lymphatic system disorders	**142 (4.4)**	**152 (4.7)**
Anaemia	96 (3.0)	100 (3.1)
Injury, poisoning and procedural complications	**131 (4.1)**	**170 (5.2)**
Fall	41 (1.3)	45 (1.4)
Hepatobiliary disorders	**104 (3.2)**	**117 (3.6)**
Neoplasms benign, malignant and unspecified	**102 (3.2)**	**82 (2.5)**
Reproductive system and breast disorders	**94 (2.9)**	**75 (2.3)**
Psychiatric disorders	**89 (2.8)**	**105 (3.2)**
Surgical and medical procedures	**89 (2.8)**	**102 (3.1)**
Skin and subcutaneous tissue disorders	**81 (2.5)**	**114 (3.5)**
Ear and labyrinth disorders	**39 (1.2)**	**24 (0.7)**
Endocrine disorders	**33 (1.0)**	**36 (1.1)**
Immune system disorders	**4 (0.1)**	**7 (0.2)**
Congenital, familial and genetic disorders	**3 (0.1)**	**4 (0.1)**
Pregnancy, puerperium and perinatal conditions	**1 (< 0.1)**	**1 (< 0.1)**
Social circumstances	**1 (< 0.1)**	**1 (< 0.1)**

Abbreviation: COPD, chronic obstructive pulmonary disease
Note: [a] Phosphenes refers to transient enhanced brightness in a limited area of the visual field
Source: SHIfT CSR Table (12.1.2.1) 1 p146, Table (12.1.2.2) 1 p148

(iv) Clinical events related to heart failure

A total of 3,148 clinical events were considered as 'foreseeable' in this population, i.e. deaths, sudden deaths, or clinical events related to heart failure, and these were reported in 29% of patients: 887 patients (27.4%) in the ivabradine group and 1,024 (31.4%) in the placebo group. Cardiac failure was reported in 21.7% *vs* 26.0% respectively. Other more frequent events in this analysis were congestive cardiac

failure (0.7% *vs* 0.8% respectively), acute pulmonary oedema (0.6% *vs* 0.8% respectively) and cardiogenic shock (0.5% in both groups).

(v) Severe adverse events

The analysis of patients having at least one severe AE 'on treatment' is summarised by SOC in Table 97 (for at least five patients in either group). For the preferred terms associated with each SOC, see the SHIfT CSR Table (12.1.2.3) 2, p153. The incidence rates were slightly lower in the ivabradine group, and most commonly related to Cardiac disorders (mainly cardiac failure or MI) and 'General disorders and administration site conditions' (mainly sudden deaths, cardiac or not).

A few preferred terms were reported at slightly higher frequencies in the ivabradine group than in the placebo group, notably: Atrial fibrillation (0.9% *vs* 0.5%) and Ventricular fibrillation (0.7% *vs* 0.3%).

Table 97: Severe adverse events 'on treatment' by system organ class (at least five patients in either group) (safety set)

System organ class	Ivabradine N = 3232 n (%)	Placebo N = 3260 n (%)
All	**773 (23.9)**	**820 (25.2)**
Cardiac disorders	415 (12.8)	820 (25.2)
General disorders and administration site conditions	191 (5.9)	190 (5.8)
Infections and infestations	53 (1.6)	76 (2.3)
Nervous system disorders	51 (1.6)	76 (2.3)
Respiratory, thoracic and mediastinal disorders	46 (1.4)	55 (1.7)
Neoplasms benign, malignant and unspecified	38 (1.2)	27 (0.8)
Gastrointestinal disorders	30 (0.9)	32 (1.0)
Vascular disorders	23 (0.7)	39 (1.2)
Injury, poisoning and procedural complications	20 (0.6)	23 (0.7)
Renal and urinary disorders	19 (0.6)	18 (0.6)
Metabolism and nutrition disorders	16 (0.5)	19 (0.6)
Hepatobiliary disorders	7 (0.2)	15 (0.5)
Surgical and medical procedures	10 (0.3)	14 (0.4)
Musculoskeletal and connective tissue disorders	9 (0.3)	7 (0.2)
Eye disorders	5 (0.2)	5 (0.2)
Psychiatric disorders	7 (0.2)	3 (0.1)
Investigations	4 (0.1)	5 (0.2)

Source: SHIfT CSR Table (12.1.2.3) 2 p153

(vi) Treatment–related adverse events

Adverse events were recorded by the investigator as doubtfully, possibly or probably related to the study product. The analysis of treatment-related AEs by SOC is

summarised in Table 98. For the preferred terms associated with each SOC, see the SHIfT CSR Table (12.1.2.3) 3, p155. The incidence rates can be seen to be generally higher in the ivabradine group, most notably for Cardiac disorders, Investigations and Eye disorders. The differences between the two groups were mainly due to known AEs associated with ivabradine treatment, such as Asymptomatic bradycardia, Symptomatic bradycardia, Phosphenes, Dizziness and Blurred vision

A total of 45 patients (1.4%) in the ivabradine group reported at least one treatment-related AE that was considered as severe, *vs* 32 patients (1.0%) in the placebo group. These events mainly concerned cardiac disorders (0.8% *vs* 0.4% respectively) such as Cardiac failure, Cardiac conduction disorders and Symptomatic bradycardia.

Table 98: Treatment-related adverse events by system organ class (at least five patients in either group) (safety set)

System organ class	Ivabradine N = 3232 n (%)	Placebo N = 3260 n (%)
All	**574 (17.8)**	**271 (8.3)**
Cardiac disorders	196 (6.1)	83 (2.6)
Investigations	171 (5.3)	53 (1.6)
Eye disorders	120 (3.7)	25 (0.8)
Nervous system disorders	42 (1.3)	37 (1.1)
Gastrointestinal disorders	38 (1.2)	26 (0.8)
General disorders and administration site conditions	31 (1.0)	15 (0.5)
Skin and subcutaneous tissue disorders	10 (0.3)	18 (0.6)
Vascular disorders	15 (0.5)	8 (0.3)
Ear and labyrinth disorders	10 (0.3)	6 (0.2)
Metabolism and nutrition disorders	3 (0.1)	12 (0.4)
Respiratory, thoracic and mediastinal disorders	10 (0.3)	7 (0.2)
Renal and urinary disorders	7 (0.2)	5 (0.2)

Source: SHIfT CSR Table (12.1.2.3) 3 p155

(vii) Deaths

The analysis of patients dying ‘on treatment’ by SOC is summarised in Table 2. For the preferred terms associated with each SOC, see the SHIfT CSR Table (12.2.2.2) 1, p172. The analogous data for deaths ‘during the study’ (i.e. after first intake of study drug until database closure) by SOC can be found in the same table.

A total of 828 on-treatment AEs with a fatal outcome were reported (12.8%), slightly fewer in the ivabradine group than in the placebo group. For 152 cases the death was reported more than two days after ceasing treatment (77 in the ivabradine group and 75 in the placebo group). Fatal events on treatment were most frequently sudden deaths (3.4% on ivabradine *vs* 3.7% on placebo) or sudden cardiac death (2.3% on ivabradine *vs* 2.1% on placebo).

Table 99: Adverse events 'on treatment' with fatal outcome by system organ class (safety set)

System organ class	Ivabradine N = 3232 n (%)	Placebo N = 3260 n (%)
All	**400 (12.4)**	**428 (13.1)**
General disorders and administration site conditions	188 (5.8)	190 (5.8)
Cardiac disorders	147 (4.6)	148 (4.5)
Nervous system disorders	21 (0.7)	27 (0.8)
Infections and infestations	9 (0.3)	14 (0.4)
Neoplasms benign, malignant and unspecified	14 (0.4)	16 (0.5)
Respiratory, thoracic and mediastinal disorders	7 (0.2)	13 (0.4)
Gastrointestinal disorders	7 (0.2)	7 (0.2)
Injury, poisoning and procedural complications	2 (0.1)	6 (0.2)
Vascular disorders	0 (0.0)	3 (0.1)
Hepatobiliary disorders	2 (0.1)	1 (< 0.1)
Renal and urinary disorders	1 (< 0.1)	1 (< 0.1)
Surgical and medical procedures	1 (< 0.1)	1 (< 0.1)
Metabolism and nutrition disorders	1 (< 0.1)	0 (0.0)
Psychiatric disorders	0 (0.0)	1 (< 0.1)

Source: SHIfT CSR Table (12.2.2.2) 1 p172

Appendix 16: Table 100: Major morbidity/mortality trials in HF

	VS Placebo											*VS* Treatment	
	SHIfT 2010	**CONSENSUS 1987**	**SOLVD 1991**	**CHARM Added 2003**	**MERIT HF 1999**	**COPERNICUS 2001**	**CIBIS II 1999**	**BEST 2001**	**SENIORS 2005**	**CARE-HF 2005**	**RALES 1999**	**COMET 2003**	**ELITE II 2000**
Tested ttt	**Procoralan**	**Enalapril**		**Cande-sartan**	**Metop/ s CR/ER**	**Carvedilol**	**Bisoprolol**	**Bucindolol**	**Nebivolol**	**CRT**	**Spirono-lacton**	**Carvedilol vs Metoprolol**	**Losartan vs captopril**
1. PATIENTS POPULATION, METHODS													
n of pts; T-ttt, P-Pl group	6505, 3241 ttt 3264 Pl	253, 127 ttt 126 Pl	2569, 1285 ttt 1284 Pl	2548, 1276 ttt 1272 Pl	3991, 1990 ttt 2001 Pl	2289, 1156 ttt 1133 Pl	2647, 1327 ttt 1320 Pl	2708, 1354 ttt 1354 Pl	2128, 1067 ttt 1061 Pl	813 409 404	1663, 822 ttt 841 Pl	3029, 1511 Car 1518 Me	3152, 1578 Los 1574 Cap
Mean follow up, moths	**22.9**	**6.2**	**41.4**	**41**	**12**	**10.4**	**15.6**	**24**	**21**	**29.4**	**24**	**58**	**18.5**
Inclusion criteria	Age ≥18 y, NYHA class II–IV, EF ≤35, HR ≥70 bpm in sinus rythm	NYHA class IV	NYHA class I-IV, EF <35,	Age ≥18 y, NYHA class II–IV, EF ≤40, ttt with ACEI for last 30 days	Age 40–80 y, NYHA class II–IV, EF ≤40, HR >68 bpm, SBP >100 mm Hg	NYHA class III–IV, LVEF<25, HR>68bpm, SBP>85 mm Hg	NYHA class III–IV, LVEF ≤35, stable for 6 wk, HR>_60 bpm, SBP >100 mm Hg	NYHA class III–IV, LVEF ≤35, stable for 4 wk, HR >50 bpm, SBP>80 mm Hg	Age ≥70 y, NYHA class I–IV, hospitalisation or LVEF ≤35, stable for 6 wk, HR >60 bpm, SBP >90 mm Hg	Age.18 y, NYHA class III-IV, LVEF≤ 35%, QRS interval of at least 120 msec	Age ≥60 y, NYHA class III-IV, with class IV within 6 months before; LVEF <35	NYHA II–IV, EF <35, HR >60 bpm, SBP >85 mm Hg	Age ≥60 y, NYHA II–IV, EF <40 ACEi, ARB naive/ >3 mnth
Primary end point	CV death or hospitalisation for HF	6-month mortality	Mortality and hosp for HF	CV death or HF hosp	All cause death	All cause death	All cause death	All cause death	All cause death or CV hospitalisation	All cause death or CV hospitalisation	All cause death	All cause death	All cause death
EF,%	29	NA	25	28	28	20	28	23	36	35	25	26	31
Male, %	76	71	80	79	77	80	80	78	63	73	73	80	70
Mean age	60	70	61	64	64	63	61	60	76	66	65	62	71
HF of CAD origin , %	68	74	72	62	65	67	50	59	68	36	54	52	79
NYHA III-IV, %	51	100 -IV	33	76	60	100	100	100	41	100	100	51	48

	SHIFT 2010	CONSENSUS 1987	SOLVD 1991	CHARM Added 2003	MERIT HF 1999	COPERNICUS 2001	CIBIS II 1999	BEST 2001	SENIORS 2005	CARE-HF 2005	RALES 1999	COMET 2003	ELITE II 2000
2. HEART RATE													
Baseline HR, bpm	**80**	**80**	**80**	**73.4**	**82**	**83**	**81**	**81**	**79**	**70**	**81**	**81**	**75**
Follow up HR, bpm	Ttt: 64, Pl:75 at 1mo, 67 vs 75 at 32mo	NA	NA	NA	Ttt: 68 Pl: 80 at 6 mo	Ttt: 71 Pl:81 at 2mo	Ttt: 70 Pl:81 at 2mo	Ttt: 72 Pl:81 at 3mo	Ttt: 69 Pl:77 at 4mo	NA	NA	Car: 67.7 Met: 69.3 at 4 mo	NA
Change in HR, bpm	**-16 in ttt** **-5 in Pl** at 1 mo	NA	**NA**	NA	**-14 in ttt** **-3 in Pl** at 6 mo	**-12.5 in ttt** **-2.2 in Pl** at 2 mo	**-9.8 in ttt** **-0.2 in Pl** at 2 mo	**-9 in ttt** **-1 in Pl** at 3 mo	**-10.3 in ttt** **-1.5 in Pl** at 4 mo	NA	NA	**-13.3 in Car** **-11.7 in Met** at 4 mo	NS
3. BASELINE TREATMENT, %													
ACEIs, ARB,	91	ST	ST	100	96	97	96	91	82	95	94	98	ST
BBs	89	2	7	55	ST	ST	ST	ST	ST	74	10	ST	23
BB doses	26% on TD 56%≥50% TD				NA 64% on TD	37 mg 65% on TD (50mg)	8.3 mg 43% on TD (10mg)	76 mg NA	7.7 mg 68% on TD (50mg)			41.8 mg Car 75% on TD 85 mg Met 78% on TD	
Diuretics	84	98 (furosemid)	85	90	91	99	99	94	85	44	100	99	77
Digitalis	22	94	68	58	63	65	51	93	NA	45	72	61	50
Aldosterone antagonists	61	55	NA	17	NA	20	NA	NA	NA	59	ST	NA	NA

4. ANNUAL RISK IN PLACEBO POPULATION														
		SHIfT 2010	**CONSENSUS, 1987**	**SOLVD, 1991**	**CHARM, Added, 2003**	**MERIT HF 1999**	**COPERNICUS 2001**	**CIBIS II 1999**	**BEST 2001**	**SENIORS 2005**	**CARE-HF 2005**	**RALES 1999**	**COMET 2003**	**ELITE II 2000**
PL Annual total mortality		**8.5%**	**52%**	**15.6%**	**9.4%**	**11%**	**18.5%**	**13.1%**	**16.5%**	**10.4%**	**20.0%**	**23%**		
PL Annual CV mortality		**8.3%**	**NA**	**10.4%**	**7.9%**	**10.1%**	**NA**	**9.2%**	**14.5%**	**8.2%**	**NA**	**19%**		
5. MAIN OUTCOMES														
All-cause mortality	**abs/ risk, ttt**	16% (8.3%)*	26% (36%)	35.2% (12.4)	30% (8.9%)	7.2 % (7.2%)	11.2%, (11.4%)	12% (8.8%)	30% (15%)	15.8% (9.1%)	20% (9.7%)	35% (17.5%)	34% Car (8.3%)	17.7% Los (11.8%)
	abs/ risk, Pl	17% (8.5%)	44% (52%)	39.7% (15.6%)	32% (9.4%)	11% (11%)	16.7% (18.5%)	17% (13.1%)	33% (16.5%)	18.1% (10.4%)	30% (12.6%)	46% (23%)	40% Met (10%)	15.9% Cap (10.3%)
	ARR	1% **p=0.092**	18% **p=0.003**	4.5 % **p=0.003**	*2% NS*	3.8% **p=0.0062**	5.5% **p=0.0014**	5% **p=0.0001**	3% **NS**	2.3% **NS**	10% **p<0.002**	11% **p=0.001**	**6% p=0.002**	**-1.8% *NS***
	RRR	10%	26%	12%	8.5%	33%	32%	32%	8%	12%	36%	27%	17%	- 13%
CV mortality	**abs/ risk, ttt**	**14%** (7.3%)	NA	31.1% (9%)	24% (7%)	6.4% (6.4%)	NA	9% (7%)	25% (12.5%)	11.5% (6.9%)	NA	27% (13.5%)	29% Car (6%)	NA
	abs/ risk, pl	**15%** (8.3%)	NA	35.9% (10.4%)	27% (7.9%)	10.1% (10.1%)	NA	12% (9.2%)	29% (14.5%)	13.7% (8.2%)	NA	37% (19%)	40% Met (8.3%)	NA
	ARR	1% **p=0.128**	NA	4.8% **p=0.002**	3% **p=0.02**	3.7% **p=0.0003**	NA	3% **p=0.0049**	4% **p=0.04**	2.2% **NS**	NA	10% **p=0.001**	11% **p=0.0004**	NA
	RRR	9%	NA	14%	13%	37%	NA	26%	12%	16%	NA	28%	20%	NA

	SHIFT 2010	CONSENSUS, 1987	SOLVD 1991	CHARM Added	MERIT HF 1999	COPERNICUS 2001	CIBIS II 1999	BEST 2001	SENIORS 2005	CARE-HF 2005	RALES 1999	COMET 2003	ELITE II 2000
All Hospitalisation (annual event rates)	38% (19.8%) vs 42% (21.9%)* **p=0.003**	NA	NA	**S**	NA	NA	33% (25.3%)vs 39% (30%) **p=0.0006**	61% (30%) vs 65% (32%) **NS**	33.6% (24.4%) vs 34.3% (25.7%) **NS**	NA	NA	NS	41.8% Los (27.8%) vs 40.5% Cap (27%) NS
Primary endpoint	24% (12.5%) vs 29% (15.1%) **p<0.0001**	See all-cause mortality **p=0.003**	47.7% (13.9%) vs 57.3% (16.8%) **p<0.0001**	38% (14.1%) vs 42% (16.6%), **p=0.011**	See all-cause mortality **p=0.0062**	NA	See all-cause mortality **p=0.0001**	See all-cause mortality **NS**	31.1 (20.3%) vs 35.3% (23.9%) **p=0.039**	39% vs 55% **p<0.001**	See all-cause mortality **p=0.001**	See all-cause mortality **p=0.002**	See all-cause mortality **NS**
HF Hospitalisation	16% (8.3%) vs 21% (11%) **p<0.0001**	NA	NA	24.2% (7%) vs 28% (8.2%), **p=0.018**	NA	NA	18% (13.8%) vs 12% (9.2%) **p=0.0001**	42% (21%) vs 35% (17.5%) **p<0.001**	NA	18% vs 33% **p<0.001**	47% (26%) vs 79% (40%) **p<0.001**	NA	17.1% Los (11.4%) vs 18.6% Cap (12.4%) **NS**
CV Hospitalisation	30% (15.7%) vs 34% (17.7%) *p=0.0002*	NA	NA	NA	NA	NA	NA	NA	24% (16.3%) vs 26% (18.3%) **NS**	31% vs 46% **p<0.001**	NA	NA	NA
MI	NA	NA	3.1% (0.9%) vs 4.1% (1.2%) *P<0.07*	NA	NA	NA	*1% vs 1%* ***NS***	1% (0.5%) vs 1% (0.5%) **NS**	NA	NA	NA	NA	2% Los (1.3%) vs 1.8% Cap (1.2%) **no p value**
Sudden death	NA	11% vs 11% **p>0.25**	NA	NA	3.9% VS 6.6% **p=0.0002**	NA	4% (3%) vs 6% (4.6%) **p=0.0011**	13% (6.5%) VS 15% (7.5%) NS	4.1% (2.5%) vs 6.6% (4%) **no p value**	35% vs 32% no p-value	10% (5%) vs 13% (6.5%) **p=0.02**	14% Car (2.9%) vs 17% Met (3.5%) **no p value**	8.2% Los (5.5%) vs 6.4% Cap (4.3%) **no p value**
HF death	3% (1.6%) vs 5% (2.6%) **p=0.014**	17% vs 35% **p=0.001**	HF or Arrh 16.3 vs 19.5	NA	1.5% VS 2.9% **p=0.0023**	NA	4% (3%) vs 3% (2.3%) **NS**	9% (4.5%) VS 10% (5%) **NS**	NA	40% vs 47% **no p-value**	15% (7.5%) vs 22% (11%) **p<0.001**	NA	2.9% Los (1.9%) vs 3.4% Cap (2.3%) **no p value**