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# The cost effectiveness of ivabradine in the treatment of chronic heart failure from the UK National Health Service perspective

A Griffiths,[1] N Paracha,[1] A Davies,[1] N Branscombe,[2] M R Cowie,[3] M Sculpher[1,4]

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[1]ICON Health Economics, Oxford, UK
[2]Servier Laboratories Ltd, Suresnes, France
[3]Imperial College London, Royal Brompton Hospital, London, UK
[4]Centre for Health Economics, University of York, York, UK

**Correspondence to**
Professor Martin R Cowie, Imperial College London, Dovehouse Street, London SW3 6LY, UK;
m.cowie@imperial.ac.uk

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## ABSTRACT

**Objective** Ivabradine, a specific heart rate lowering therapy, has been shown in a randomised placebo-controlled study, Systolic HF Treatment with the $I_f$ Inhibitor Ivabradine Trial ($SHI_fT$), to significantly reduce the composite end point of cardiovascular death and hospitalisation for worsening heart failure (HF) in patients with systolic HF who are in sinus rhythm and with a heart rate ≥70 bpm, when added to optimised medical therapy (HR: 0.82, 95% CI 0.75 to 0.90, p<0.0001). We assessed the cost effectiveness of ivabradine, from a UK National Health Service perspective, based on the results of $SHI_fT$.

**Methods** A Markov model estimated the cost effectiveness of ivabradine compared with standard care for two cohorts of patients with HF (heart rate ≥75 bpm in line with the EU labelled indication; and heart rate ≥70 bpm in line with the $SHI_fT$ study population). Modelled outcomes included death, hospitalisation, quality of life and New York Heart Association class. Total costs and quality adjusted life years (QALYs) for ivabradine and standard care were estimated over a lifetime horizon.

**Results** The incremental cost per additional QALY for ivabradine plus standard care versus standard care has been estimated as £8498 for heart rate ≥75 bpm and £13 764 for heart rate ≥70 bpm. Ivabradine is expected to have a 95% chance of being cost-effective in the EU licensed population using the current National Institute for Health and Care Excellence cost effectiveness threshold of £20 000 per QALY. These results were robust in sensitivity analyses.

**Conclusions** This economic evaluation suggests that the use of ivabradine is likely to be cost-effective in eligible patients with HF from a UK National Health Service perspective.

## INTRODUCTION

Heart failure (HF) is a clinical syndrome characterised by the inability of the heart to pump enough blood to meet the body's demands. Symptoms include dyspnoea and fatigue which may limit exercise tolerance as well as fluid retention which may lead to peripheral oedema and pulmonary congestion. The British Heart Foundation (BHF) estimates that around 750 000 people in the UK have HF and there are approximately 25 000 new cases each year. Prognosis from HF is poor and the 5-year survival rate for patients with HF is estimated to be only 58%.[1–3]

Epidemiological and clinical studies indicate that a higher resting heart rate in sinus rhythm is associated with increased morbidity and mortality in the general population and in patients with cardiovascular (CV) disease. Heart rate reduction is associated with improved outcomes in patients with HF[4] and some of the beneficial effects of β-blockade may be attributed to heart rate reduction.[5] However, some patients cannot tolerate target dosages of β-blockers and, when resting heart rates remain elevated despite efforts to optimise β-blocker dose, there is potential benefit from further heart rate reduction.

Ivabradine is a pure heart rate lowering therapy, which acts by selective and specific inhibition of the cardiac pacemaker current via the $I_f$ channel. The effect of using ivabradine to slow the heart rate in patients with systolic HF, in addition to standard care medications including β-blockade, has been examined in a large, randomised, placebo-controlled trial: Systolic HF Treatment with the $I_f$ Inhibitor Ivabradine Trial ($SHI_fT$).[6] This trial assessed 6505 patients with symptomatic HF (New York Heart Association (NYHA) classes II to IV), sinus rhythm, and a left ventricular EF ≤35%, with a prior hospitalisation for HF within 12 months and a baseline resting heart rate ≥70 bpm despite optimised medical therapy. Ivabradine therapy was associated with a significant reduction in the number of primary composite end point events compared with standard care (CV death or hospitalisation for worsening HF; HR: 0.82; 95% CI 0.75 to 0.90, p<0.0001). This result was driven primarily by a reduction in HF hospitalisations (first event worsening HF HR: 0.74; 95% CI 0.66 to 0.83, p<0.0001) and HF death (HR: 0.74; 95% CI 0.58 to 0.94, p=0.014). There was also a reduction in overall CV mortality (HF and other CV mortality HR: 0.91; 95% CI 0.80 to 1.03, p=0.128), however, this result did not achieve statistical significance.

The ivabradine treatment effect was found to be consistent across most patient subgroups but was modified by baseline heart rate. In patients with a heart rate ≥75 bpm, a significant treatment effect was also demonstrated on CV mortality (HR: 0.83; 95% CI 0.71 to 0.97, p=0.02) as well as all-cause mortality (HR: 0.83; 95% CI 0.72 to 0.96).[7] Standard care treatment patterns in $SHI_fT$ appeared at least as good as clinical practice in the UK and elsewhere in Europe,[8] even though only 26% of patients achieved the target dose β-blockade

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considered to represent gold standard β-blocker therapy in patients with HF. While it is not expected that target dose β-blockade can be achieved in all patients in clinical practice, due to intolerance to therapy and contraindications to use, it is recognised that β-blockade lowers resting heart rate and the effect of ivabradine is modified by resting heart rate.

Adoption of new treatment is influenced by an assessment of the relative efficacy and safety of the treatment, and by whether an intervention is likely to represent value for money, assessed using economic evaluation which systematically compares the costs and benefits of a new therapy relative to existing care. A cost effectiveness analysis was developed to compare ivabradine plus standard care versus standard care alone using resource use and clinical outcomes reported in $SHI_fT$. The model has been designed to be adapted to a population consistent with the European licensed indication (heart rate ≥75 bpm). The model also presents results for an average population which has been optimised on β-blocker therapy according to current clinical practice, as well as for a subgroup population treated with target dose β-blockade given interest in the treatment effect of ivabradine on top of target dose β-blockade.

## METHODS

### Overview

A Markov model has been used to estimate the costs and clinical outcomes for two cohorts of patients with HF treated with either ivabradine or standard care in line with the EU labelled indication (heart rate ≥75 bpm).

HF is a chronic, progressive disease requiring lifelong therapy and consequently the cost effectiveness analysis considers a lifetime time horizon, although alternative time horizons, including an analysis which modelled costs and outcomes only for the $SHI_fT$ trial follow-up period, have been considered in scenario analyses. An annual discount rate of 3.5% has been applied to costs and outcomes consistent with the National Institute for Health and Care Excellence (NICE) recommendations.[9] The cost effectiveness of ivabradine is expressed in terms of the incremental cost per quality adjusted life year (QALY) gained, and the analysis has been taken from a UK National Health Service (NHS) perspective. In order to determine whether ivabradine represented value for money, the incremental cost effectiveness ratio (ICER) was compared with the NICE cost effectiveness threshold range of £20 000 to £30 000 per QALY.[9] A summary of key model assumptions may be found in table 1.

**Table 1** Key model assumptions

| Parameter description | Base case value |
|---|---|
| Model structure | Two state Markov cohort model |
| Modelled cycle length | 1 month |
| Time horizon | Lifetime |
| Costs and effects discount rate per annum | 3.50% |
| Parametric survival model CV mortality | Gompertz |
| Extrapolation CV mortality post trial | Gompertz |
| Regression model hospitalisation | Poisson |
| Regression model NYHA class | Generalised ordered logistic |
| Regression model QoL | Multilevel model |
| Drug costs per month (£) | |
| Standard care average cost per month | 9.54 |
| Ivabradine average cost per month | 42.10 |
| Other therapy related costs (£) | |
| ECG unit cost | 31.28 (12.01–44.30) |
| CV specialist visit unit cost | 118.81 (89.48–138.97) |
| Hospitalisations cost per event ( £) | |
| HF diagnosis (general ward) | 2307.98 |
| HF diagnosis (cardiac ward) | 3295.12 |
| Other CV diagnosis (general ward) | 1942.44 |
| Other CV diagnosis (cardiac ward) | 1729.60 |
| Non-CV diagnosis (general ward) | 2643.56 |
| Admission type given hospitalisation | |
| Proportion of hospitalised patients admitted in cardiac specialist ward versus general ward | 50% (40–60%) |
| Other resource use | |
| Ongoing HF management costs per month | 26.77 |

Regression equations reported in online supplementary technical appendix.
Ivabradine average dose=6.7794 mg, British National Formulary list price £40.17 per pack.
HF hospitalisation weighted average of HRG (Health Resource Group) codes: EB03H–EB03I.
Cardiovascular hospitalisation weighted average HRG codes: EA03Z–EB10Z.
All-cause hospitalisation HRG weighted average codes AA02Z–WA23Y.
CV, cardiovascular; HF, heart failure; NYHA, New York Heart Association; QoL, quality of life.

### Mortality and hospitalisation

The cost-effectiveness analysis captures the monthly risk of clinical events (CV mortality, hospitalisation) using risk equations developed from $SHI_fT$ individual patient data (n=6505). These equations have been designed to predict outcomes according to the treatment received and patients' baseline characteristics including heart rate. The treatment effect of ivabradine is assumed to be multiplicative to the underlying risk of these events which has been based on the data from standard care patients in $SHI_fT$. The change in efficacy of ivabradine associated with baseline heart rate, identified in previous clinical analyses,[7] is captured in the risk equations using a treatment interaction term (treatment×baseline heart rate). The risk equations consequently allow costs and outcomes to be predicted for the subgroup of patients with a heart rate ≥75 bpm, consistent with the European licence indication. This approach was taken in preference to developing risk equations based solely on individual patient data from subjects who met the European licence criteria (baseline heart rate ≥75 bpm (n=4154)) in order to avoid breaking randomisation and reducing the predictive power of the risk equations due to the smaller sample size.

The risk of non-CV mortality has been estimated using age and sex adjusted UK national life table data with CV mortality removed.[10]

### NYHA class

The most commonly used classification of HF severity is the NYHA classification of functional capacity which assigns patients to one of four classes depending on patient symptoms.[11] In each monthly cycle, the patients who remained alive were distributed into one of the four NYHA classes using a risk equation developed from $SHI_fT$ individual patient data. NYHA class has been captured in the cost effectiveness analysis primarily to determine the potential quality of life of patients over time, since NYHA class was found to strongly predict patients' quality of life. In the post-trial period the proportion of patients in each NYHA class is assumed to remain fixed (although in absolute terms numbers in each category vary according to survival estimates). This approach was taken because an extrapolation based on $SHI_fT$ data predicted that the proportion of patients with minimal or mild symptoms would increase over time, consistent with trends in $SHI_fT$ observed data, which for the long-term were not considered clinically plausible.

### Patients' quality of life

The $SHI_fT$ patient reported outcomes substudy collected quality of life (QoL) data using the EuroQoL (EQ-5D) questionnaire, which was administered to patients in countries with a validated questionnaire (n=5313). The EQ-5D is a generic instrument designed to capture patient reported outcomes across five health domains (self-care, mobility, usual activities, pain/discomfort, anxiety/depression).[12] QoL weights (utility values) may be derived from the EQ-5D using country-specific values of different health statuses; UK values were used in this study regardless of the country of origin of the QoL data. Utility values typically measure patient QoL on a scale, where 0 represents death and 1 represents full health, although negative values are feasible.[13] Measurements from the same individual are much more likely to be correlated than estimates from different individuals and it is important to take into account such correlation when analysing data with repeated measures to increase precision and avoid bias. EQ-5D data have been analysed using multilevel modelling, a regression technique appropriate for repeated observations across individuals. The regression equation was designed to predict patient utility according to treatment allocation, baseline characteristics, NYHA class (time varying) and a hospitalisation episode.

### Resource use and costs

The cost per month for ivabradine therapy (£42.10 per month) was estimated using British National Formulary (BNF) list prices (5 mg/7.5 mg=£0.72 per tablet, 2.5 mg (half a 5 mg tablet=£0.36)) multiplied by the distribution of patients taking each dose in $SHI_fT$ (approximately 7% 2.5 mg, and 93% 5 mg or 7 mg). An additional one-off titration visit and ECG has been included as an administration cost for ivabradine patients. It was assumed that, once titrated, patients would be monitored at routine clinical assessments, hence further ongoing administration costs were not included for ivabradine.[14] Standard therapy use (£9.54 per month) was also estimated, using BNF list prices and the proportion of patients treated with each therapy in $SHI_fT$ (β-blockers (89%), ACE inhibitors and/or angiotensin receptor blockers (ARBs) (91%), aldosterone antagonists (60%) and diuretics (83%)). The analysis includes costs for hospitalisations by admission type (HF, other CV and non-CV) estimated from UK NHS data.[14] Unit costs were reported for a 2011 cost year, inflation-adjusted where necessary using the health component of the UK consumer price index.[15] Resource use quantities and unit costs are summarised in table 1.

### Sensitivity analysis

A series of one-way sensitivity analyses on parameter values and structural assumptions have been undertaken to test the robustness of model results to changes in individual model parameters while remaining assumptions were held constant. NICE recommends that a range of sensitivity analyses should be undertaken to reflect alternative assumptions for the treatment effect for the intervention of interest, particularly regarding the modelled benefit in the post-trial period. In our analyses we have explored the ivabradine treatment effect using a range of sensitivity analyses. These include variation of ivabradine's treatment effect within 95% CIs (CV mortality, hospitalisation and QoL), variation in the duration of the effect (gradual reduction until no further benefit of therapy is assumed over a 5-year and a 10-year range while assuming lifelong costs) and restricting the ivabradine treatment effect to HF mortality and HF hospitalisation end points only (rather than to the broader CV mortality and all-cause hospitalisation end point).

Other sensitivity analyses for mortality included the use of alternative distributions (exponential and Weibull) for the parametric survival analysis and the use of alternative external data to predict mortality in the post-trial period.[16 17] Sensitivity analyses conducted on the hospitalisation end point included doubling and halving the rate of hospitalisation and applying alternative UK data for hospitalisation length of stay (National HF Audit and Hospital Episode Statistics data[18 19]). Quality of life estimates were explored using alternative utility estimates from external sources.[20] The distribution of patients in each NYHA class in the post-trial period was explored using a modelled scenario in which patients' symptoms were assumed to deteriorate over time (5% of patients were redistributed each year into NYHA classes associated with more severe HF symptoms).

Probabilistic sensitivity analysis has been used to assess overall parameter uncertainty in the model. In this analysis point estimates for each parameter have been replaced with values sampled from statistical distributions and the ICER has been recalculated using the new resampled values.[21] This process has been repeated 1000 times to predict the likelihood that ivabradine would be cost-effective at different cost effectiveness thresholds (the value the decision maker is willing to pay for each additional QALY).

### Subgroup analyses

Subgroup analyses have been performed for subgroup populations identified from the clinical study protocol. These included age (< or ≥75 years old); HF duration (categoried by quartile cut points); NYHA class; LVEF (categoried by quartile cut points); prior ischaemia; prior diabetes and β-blocker use.

## RESULTS

### Base case analysis

A parametric model based on a Gompertz distribution was established as the best fit of the observed data based on statistical evidence (Akaike and Bayesian information), a visual review of Kaplan-Meier survival plots versus predicted curves and the plausibility of predicted survival in the extrapolated, post-trial period (see online supplementary technical appendix). The parametric survival analysis predicted that mean survival for ivabradine patients with a heart rate ≥75 bpm would be 5.61 years compared with 5.86 years for standard care patients. Ivabradine was expected to improve patient survival duration by 0.25 years (approximately 3.0 months) compared with standard care. Our analysis suggests that, over 1 year, approximately 225 patients would need to be treated to prevent one HF death.

Quality of life scores for the base case analysis ranged from 0.82 to 0.46 for standard care patients and from 0.84 to 0.47 for ivabradine patients (based on NYHA classes I–IV, and no hospitalisation event). QoL increased, on average, by 0.014 due to ivabradine therapy itself. However, hospitalisations were associated with a substantial temporary QoL loss, which varied according to NYHA class (−0.04 to −0.29; NYHA I–IV). Ivabradine therapy was also associated with a reduction in hospitalisations and hence also avoided the potential QoL loss associated with these events, see table 2. Overall, in a lifetime analysis, ivabradine plus standard care was associated with a gain of 0.28 QALYs (approximately 3.4 quality adjusted life months) versus standard care alone.

The model predicted that, over a lifetime, ivabradine would be £2376 more expensive per patient compared with standard

**Table 2** Utility values predicted for $SHI_fT$ population heart rate ≥75 bpm

| Description | Utility value |
|---|---|
| No hospitalisation | |
| NYHA I | 0.82 |
| NYHA II | 0.74 |
| NYHA III | 0.64 |
| NYHA IV | 0.46 |
| Hospitalisation | |
| NYHA I | −0.04 |
| NYHA II | −0.07 |
| NYHA III | −0.10 |
| NYHA IV | −0.29 |
| Ivabradine | 0.01 |

Regression equation for quality of life estimates reported in online supplementary technical appendix.
Utility values estimated using EQ-5D data; UK tariff values.
NYHA, New York Heart Association.

care alone. The additional drug therapy and follow-up costs (£3341 per patient) were offset by an important reduction in expected hospitalisation costs (£965 per patient). In HF, with a heart rate ≥75 bpm, ivabradine would be expected to reduce the rate of HF hospitalisation from approximately 18 hospitalisations per 1000 patient months (standard care) to 13 hospitalisations per 1000 patient months (ivabradine plus standard care); 20 patients would need to be treated to prevent one HF hospitalisation.

The incremental cost per additional QALY for ivabradine plus standard care versus standard care has been estimated as £8498 for heart rate ≥75 bpm and £13 764 for heart rate ≥70 bpm.

### Subgroup analyses

The cost per QALY increased by 20% in patients on target dose β-blocker therapy due to their lower risk of mortality and hospitalisation and a slightly lower heart rate compared with patients not on target dose therapy. Despite this increase, ivabradine remains cost-effective at existing NICE cost effectiveness threshold values. The ICER for patients on target dose β-blocker therapy is estimated as £10 374 per QALY (heart rate ≥75 bpm) and £16 578 per QALY (heart rate ≥70 bpm).

### Deterministic sensitivity analysis

The Tornado diagram in figure 1 shows the effect on the estimated ICER if one model assumption is altered while other assumptions/parameter values remain at base case values. The ICER remains below £20 000 in virtually all scenarios. The ICER was sensitive to changes in the treatment effects of ivabradine at the upper bound 95% CI for CV mortality (HR 0.80 to 1.03). However, the risk equations were developed using data from the total $SHI_fT$ population (heart rate ≥70 bpm), therefore, this scenario analysis overestimates the upper bound HR and ICER estimate for the licensed indication (heart rate ≥75 bpm). A scenario analysis which modelled costs and outcomes only for the $SHI_fT$ trial follow-up period resulted in an ICER of £15 175. This estimate was less favourable than the base case estimate because the short time horizon did not take into account long-term benefits associated with ivabradine.

### Probabilistic sensitivity analysis

Probabilistic sensitivity analysis indicates that, using a cost effectiveness threshold of £20 000 per QALY, ivabradine plus standard care has a greater than 0.95 probability of being cost-effective versus standard care alone in a population with a heart rate ≥75 bpm (figure 2), and over 0.70 probability in a population ≥70 bpm.

## DISCUSSION

The cost effectiveness analysis suggests that ivabradine plus standard care has a high probability of being cost-effective versus standard care alone in patients with HF who are in sinus rhythm with left ventricular systolic dysfunction and have a baseline heart rate either ≥75 bpm or ≥70 bpm. The cost effectiveness of ivabradine is driven by important reductions in HF mortality and hospitalisation and associated costs of care as well as improvements in QoL.

Probabilistic sensitivity analyses suggest that, at the current lower bound NICE cost effectiveness threshold range, ivabradine plus standard care therapy has a 0.95 probability of being cost-effective versus standard care alone in a population consistent with the European licensed indication (heart rate ≥75 bpm), and over a 0.70 probability in the entire $SHI_fT$ study population (heart rate ≥70 bpm). The cost effectiveness results were robust to a range of sensitivity analyses that tested alternative assumptions for parameter values and model structure. Our analyses also indicated that ivabradine would be expected to remain effective in a range of patient subgroups including those on target dose β-blockade. A separate budget impact analysis undertaken by NICE indicated that the total budget impact of ivabradine in the UK would be expected to be approximately £4400 per 100 000 people.[22]

The cost effectiveness analysis has been developed using individual patient data from a pivotal, large scale randomised controlled trial $SHI_fT$. Model results have been shown to be robust and calibrate well against observed patient data.

It is acknowledged that that the cost effectiveness result for patients on target dose β-blockade may appear to contradict simple univariable analyses based on $SHI_fT$ data that indicated that ivabradine was not associated with a statistically significant treatment effect on either mortality or the rate of hospitalisation in these patients. $SHI_fT$ patients on target dose β-blockade were found to be generally healthier and at a low risk of mortality and hospitalisation. Furthermore, there were only 15 HF deaths (standard care) and 10 HF deaths with ivabradine plus standard care in patients on target dose therapy with heart rate ≥75 bpm (n=938). While the HR of patients on target dose therapy (HR: 0.68) was close to the HR observed in the base case population (HR: 0.62), the underlying clinical event rate was insufficient to provide statistical significance. It is also noted that the baseline characteristics of patients on target dose β-blockade in the ivabradine treatment group differed from those patients on target dose therapy in the standard care treatment group. In isolation, univariable analyses may consequently provide a misleading picture of the ivabradine treatment effect given a low underlying clinical event rate, small sample size in this subgroup and no correction for clinical differences at baseline between patients. A strength of this study is that it is based on multivariable risk equations which take into account the change in efficacy of ivabradine by baseline heart rate and adjust for differences in key prognostic risk factors. Our analyses indicated that there was no evidence that the treatment effect of ivabradine was altered by β-blocker use, ischaemia or age once differences in baseline heart rate had been taken into account ($p>0.05$). This suggested that, if patient heart rate remained high despite target β-blocker dose, ivabradine has a beneficial effect. Although the underlying clinical event rate in patients on target dose β-blocker therapy may be low, ivabradine is nevertheless

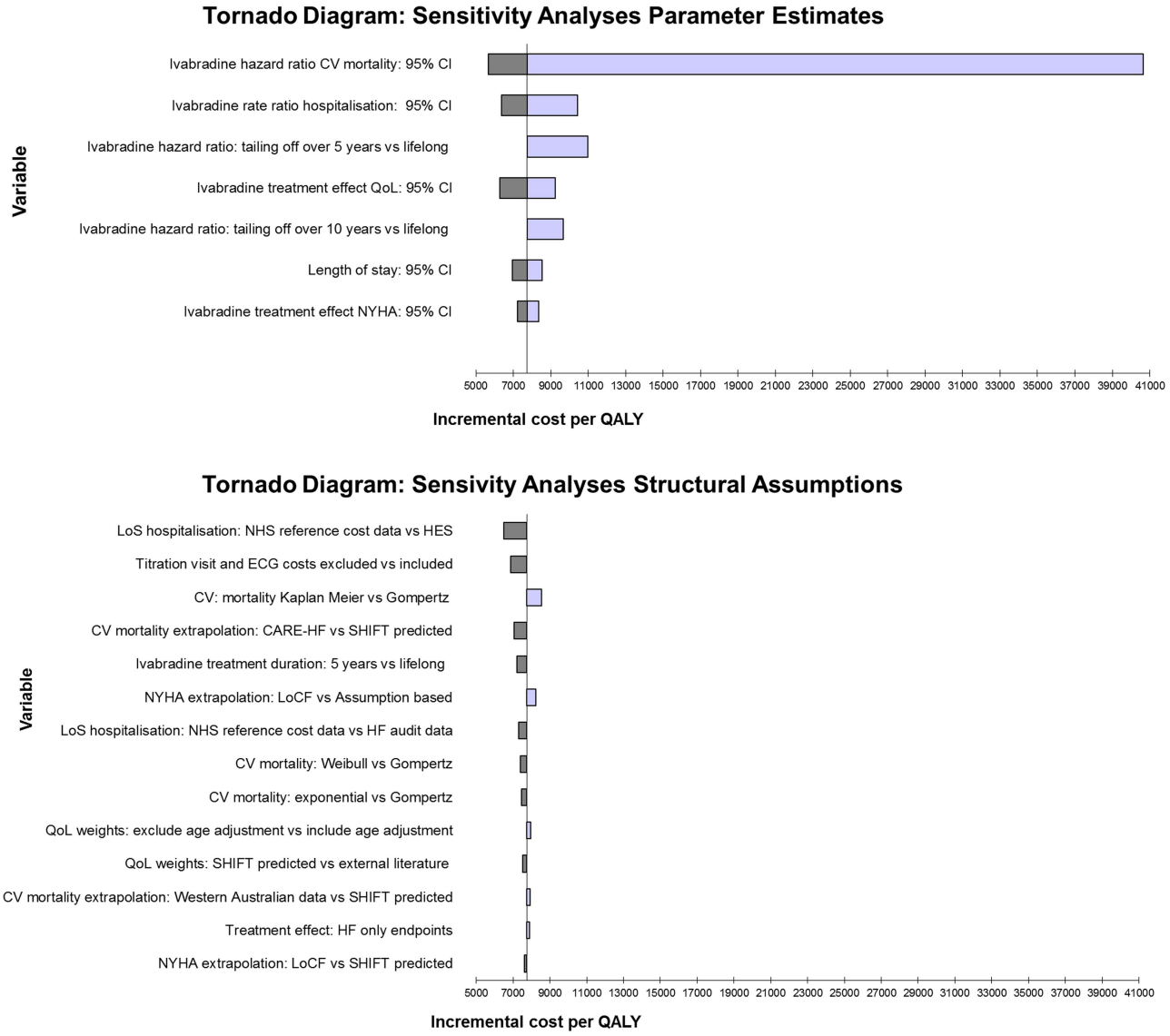


**Figure 1** One way sensitivity analyses for patients with heart failure (HF), heart rate ≥75 bpm (£).

expected to reduce mortality and hospitalisations in such patients relative to standard care.

These analyses were designed to derive the most likely estimate of effect for ivabradine in specific patient subgroups including those patients on target dose β-blocker therapy based on available evidence from $SHI_fT$. An alternative approach to determining the clinical effect of ivabradine on top of target dose β-blockade would be to conduct a randomised trial in this population. However, such a trial would have to be large, as those patients who tolerate target dose β-blockade in $SHI_fT$ appeared to be the healthiest, lowest-risk patients hence the underlying event rate in these patients is likely to be low.

In summary, from a UK NHS perspective, ivabradine in combination with optimised standard care therapy, including β-blockade,

**Table 3** Base-case results in patients with heart rate ≥75 bpm and ≥70 bpm

| Population | Technologies | Total costs (£) | Total LYs | Total QALYs | Incremental costs (£) | Incremental LYs | Incremental QALYs | ICER (£) incremental LYs | ICER (£) incremental QALY |
|---|---|---|---|---|---|---|---|---|---|
| Heart rate ≥75 bpm | Standard care | 9446 | 5.61 | 3.99 | – | – | – | – | – |
| | Ivabradine plus std care | 11 822 | 5.86 | 4.27 | 2376 | 0.25 | 0.28 | 9363 | 8498 |
| Heart rate ≥70 bpm | Standard care | 9312 | 5.89 | 4.23 | | – | – | – | – |
| | Ivabradine plus standard care | 11 796 | 6.03 | 4.41 | 2484 | 0.14 | 0.18 | 17 875 | 13 764 |

ICER, incremental cost effectiveness ratio; LY, life years; QALY, quality adjusted life years.

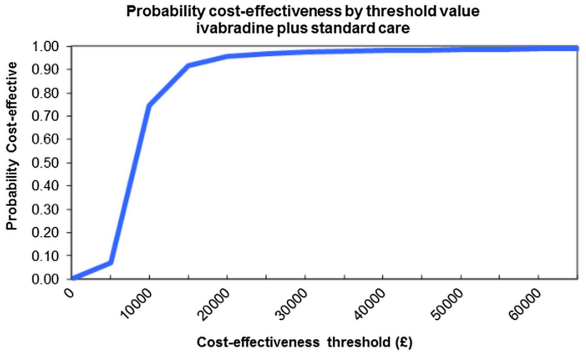


**Figure 2** The cost effectiveness acceptability curve for patients with heart failure (HF), heart rate ≥75 bpm (£).

has a high probability of being cost-effective versus standard care alone in patients with HF, who are in sinus rhythm with left ventricular systolic dysfunction and a baseline heart rate either ≥75 bpm or ≥70 bpm. In support of this, the single technology appraisal of ivabradine by NICE concluded that this analysis was robust and unlikely to overestimate the cost effectiveness, leading to a recommendation that patients in England and Wales should have access to this therapy if indicated. [9]

## Key messages

**What is already known about this subject?**
Ivabradine, a specific heart rate lowering therapy, has been shown in a randomised placebo-controlled study, Systolic HF Treatment with the If Inhibitor Ivabradine Trial ($SHI_fT$), to significantly reduce the composite end point of cardiovascular death and hospitalisation for worsening heart failure (HF) in patients with systolic HF who are in sinus rhythm and with a heart rate ≥70 bpm, when added to optimised medical therapy.

**What does this study add?**
We assessed the cost effectiveness of ivabradine, from a UK National Health Service (NHS) perspective, based on the results of $SHI_fT$. The incremental cost per additional quality adjusted life year (QALY) for ivabradine plus standard care versus standard care has been estimated as £8498 for heart rate ≥75 bpm and £13 764 for heart rate ≥70 bpm. Ivabradine is expected to have a 95% chance of being cost-effective in the EU licensed population using the current National Institute of Health and Care Excellence (NICE) cost effectiveness threshold of £20 000 per QALY.

**How might this impact on clinical practice?**
These results should encourage clinicians to prescribe ivabradine to appropriate patients, as it has a clinical effect that represents good value for money when added to optimised medical therapy.

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**Competing interests** MRC reports receiving consultancy and speaking fees from Servier. ICON Health Economics was contracted to undertake the analysis and has supported AG, NP, AD and MS through salary or consultancy payments. NB is a Servier employee.

**Ethics approval** $SHI_fT$ trial provided the data for this analysis: approval from all countries' ethical approval bodies as per GCP.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** Further data are available in the online supplementary appendix. Requests for additional data should be sent to Servier laboratories for discussion with the Executive Steering Committee of the $SHI_fT$ Study.



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# Technical Appendix

## Contents

# 1. Introduction

This document provides a detailed summary of methods and the risk equations used to populate the ivabradine UK cost-effectiveness analysis. This analysis was designed to assess whether ivabradine in combination with standard therapy would be cost-effective from an NHS perspective versus standard care alone in UK chronic heart failure (HF) patients [New York Heart Association (NYHA) class II to IV with systolic dysfunction, in sinus rhythm, baseline heart rate ≥75 bpm].

# 2. Overview

The SHIFT cost-effectiveness analysis captures the risk of clinical events (mortality, hospitalisation, NYHA class and patient quality of life) using risk equations developed from SHIFT individual patient data [patients with baseline heart rate ≥70bpm (n=6505)]. These equations have been designed to predict outcomes according to the treatment received and patient baseline characteristics including baseline heart rate.

The treatment effect of ivabradine on CV mortality, hospitalisation and NYHA class is assumed to be multiplicative to the underlying risk of these events (estimated from standard care patients in SHIFT). The improvement in efficacy of ivabradine associated with increasing baseline heart rate, identified in previous clinical analyses, is captured in the risk equations using a treatment interaction term (treatment*baseline heart rate). The risk equations consequently allow costs and outcomes to be predicted for the subgroup of patients with a heart rate ≥75bpm, consistent with the European licence indication. This approach was taken in preference to developing risk equations

based solely on individual patient data from subjects who met the European licence criteria [baseline heart rate ≥75bpm (n=4154)] in order to avoid breaking randomisation and reducing the predictive power of the risk equations due to the smaller sample size.

# 3. Mortality

### 3.1. Mortality: standard care

The risk of non-cardiovascular (non-CV) mortality has been estimated using age and sex adjusted UK national life table data with CV mortality removed [1]. This method was selected in preference to using the risk of non-CV death estimated from SHIFT data since national data provides a larger, UK-specific data source, although, SHIFT data have been applied in sensitivity analyses.

SHIFT standard care data is used to estimate the underlying risk of CV mortality in patients who do not receive ivabradine therapy. CV mortality consists of HF and other non-heart failure CV death. However, the cost-effectiveness model also captures HF deaths independently, as a separate endpoint, to facilitate a sensitivity analysis in which the ivabradine treatment effect is applied to HF mortality only (i.e. no treatment effect is modelled on non-heart failure CV death), see Section 10.2. The base case analysis applies the ivabradine treatment effect to CV mortality and the parametric survival model developed to predict CV mortality is consequently reported in this document.

In the ivabradine economic analysis parametric survival estimates are used to predict the risk of CV mortality in both the within-trial and post-trial, extrapolated, period. Whilst it is recognised that patient survival in the within-trial period may be

obtained from observed Kaplan-Meier data, parametric survival analysis is used to predict mortality within-trial in order to:

- Permit specific exploration of the interaction between treatment and baseline heart rate evidenced in SHIFT and provide cost-effectiveness results relevant to the licensed indication (patients with a baseline heart rate ≥75 bpm).
- Provide an estimate of the underlying baseline risk of CV mortality without ivabradine (i.e. the natural history of HF) and explore differences in the underlying baseline mortality risk due to patient heterogeneity, thus permitting subgroup analyses.
- Adjust for potential differences in baseline characteristics in non-randomised subgroups.
- Extrapolate CV mortality beyond the SHIFT study period

Six parametric survival models (exponential, Weibull, Gompertz, log-logistic, lognormal, gamma distribution) were fitted to SHIFT mortality data. A parametric model based on a Gompertz distribution was considered the best fit of the observed data based on statistical evidence (AIC and BIC criteria, see Table 1), a visual review of Kaplan-Meier survival plots versus predicted curves (see

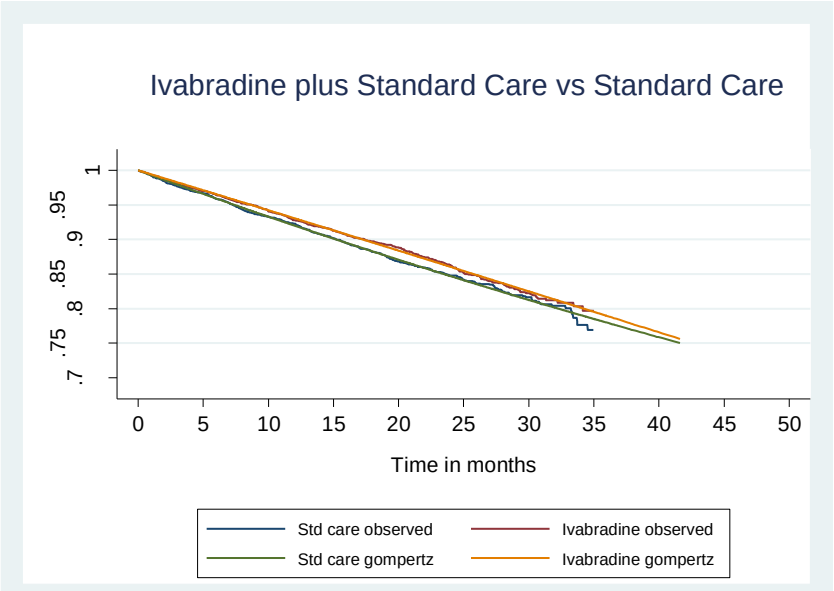
Figure 1) and the plausibility of predicted survival in the extrapolated, post-trial period [2]. This model also generates the most conservative (least favourable) estimate of patient long term survival and, hence, the most conservative incremental differences in mortality for ivabradine versus standard care alone relative to the six survival models tested. Parametric survival models based on the exponential and Weibull distributions, the next best fitting parametric models, and Kaplan Meier data,

are also included in the model for sensitivity analyses to explore the impact of parametric modelling assumptions on survival predictions, see Section 10.2.

**Table 1 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 |
| **Log-logistic** | 6505 | -3632.42 | -3373.61 | 27 | 6801.23 | 6984.30 |
| **Gamma** | 6505 | -3628.90 | -3368.94 | 28 | 6793.87 | 6983.72 |

**Figure 1 CV mortality: Kaplan-Meier versus Parametric survival model (Gompertz distribution)**




The CV mortality risk equation adjusts for a series of baseline patient characteristics. These variables are included to generate different estimates of mortality, depending on the characteristics of the population. 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 baseline variables considered for inclusion in the risk equation were derived from the SHIFT clinical study protocol, a previous HF risk equation published by Levy et al. 2006 [3], as well as clinical advice, and include:

- Baseline socio-demographic and clinical characteristics [age, sex, NYHA class, HF duration, left ventricular ejection fraction (LVEF), smoking status, alcohol use, diabetes, race, body mass index (BMI)]
- Baseline use of HF medications [beta-blockers, angiotensin-converting-enzyme (ACE) inhibitors, aldosterone antagonists, loop diuretics (dose/kg/day), angiotensin II receptor antagonists, cardiac glycosides, allopurinol]
- Baseline 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 independent variables were reviewed to confirm whether they showed evidence of a linear relationship with the outcome and a series of tests were used to ascertain the best functional form. Linear, quadratic and fractional polynomial functions were tested in addition to other standard transformations including centring

on the mean. In the final regression model five continuous variables were centred on the mean (age, BMI, heart rate, systolic blood pressure and sodium) and two continuous variables were treated as categorical variables (LVEF and HF duration), both categorised using quartile cut-points.

The relationship between baseline heart rate and time to CV mortality was given particular consideration. Patients were divided into baseline heart rate strata (70-74, 75-79, 80-84, ≥85 bpm), see Figure 2. The logrank 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 3. In order to maximise 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, linear variable in the final regression model.

**Figure 2 CV mortality: Kaplan-Meier survival curves by heart rate category**

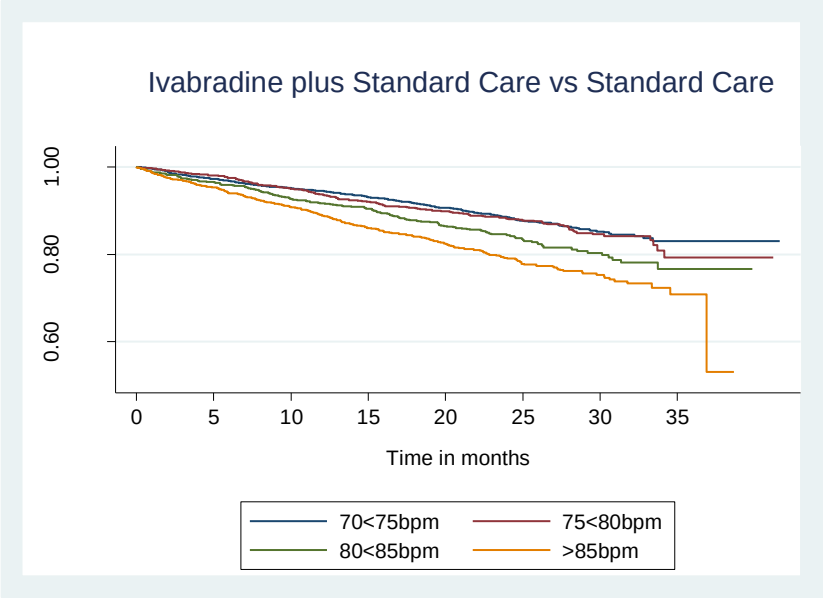
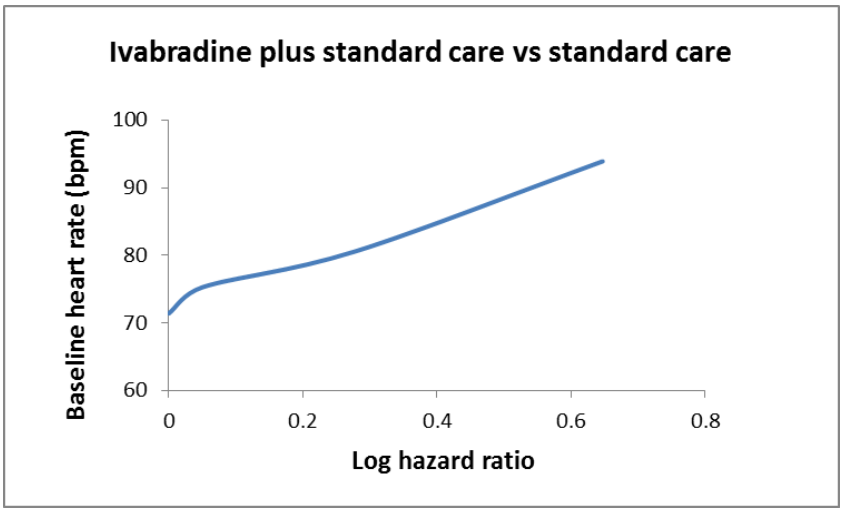



**Figure 3 Mean baseline heart rate vs log hazard ratio CV mortality**




All binary and categorical variables were reviewed to confirm whether 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:

- 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/past smoking habit’ versus ‘no’ due to overlapping KaplanMeier plots for ‘yes/past smoking habit’; 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%) at baseline to include this as a potential predictor in the final analysis, whilst a large proportion (~90%) of patients used ACE inhibitors/angiotensin receptor blockers (ARBs). The latter variable was retained in the final analysis since it was considered to be a clinically important predictor of patient outcomes.

An initial set of variables was identified using backwards stepwise elimination (p-value 0.1) and cross validated using forwards stepwise selection. This stepwise selection process was manually corroborated and additionally compared to alternative selection methods based on AIC criteria.

The correlation matrix for the initial regression model produced by the stepwise elimination process was reviewed. Those variables which appeared strongly correlated were further analysed for evidence of collinearity; the fit of the model was tested with and without the variable of interest using a log-likelihood test, and the direction and magnitude of effect for all other variables were reviewed. 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.

Variables which showed evidence of a borderline association with CV mortality ($p \geq 0.05 < 0.10$) 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 the model or improved the estimate of effect for other relevant variables the variable was retained. All variables included in the final CV regression model 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 4. It is noted that the direction of effect for use of some HF medications (aldosterone, digitalis and loop diuretics) was not as expected and medication use was associated with poorer outcomes (e.g. aldosterone HR 1.28, 95% CI 1.11-1.48, $p<0.001$). However, it is plausible that patients taking these medications were of poorer health than the average SHIFT patient and this effect has been captured by the regression analysis. Aldosterone, for example, was not recommended in a CHF indication at the time of SHIFT. Whilst it is recognised that these variables may not be capturing the true effect of the medication in question, they were nonetheless retained, since they were strong predictors of CV mortality outcomes and significantly improved the overall model fit.

The PH assumption for all variables included in the final regression model was tested statistically using Schoenfeld residuals and visually by plotting -ln[-ln(survival)] curves against ln (time), neither assessment indicated deviation from the PH assumption for included variables.

Cox-Snell residuals were evaluated to check the overall model goodness of fit. The predictive power of the final model was also tested using the Harrell's concordance measure. The final model showed concordance of >70% (95% confidence interval (CI) 0.68-0.72) and was consequently considered to be a good predictor of CV mortality [4].

### 3.2. Mortality: ivabradine treatment effect

***Overview***

In the SHIFT cost-effectiveness analysis ivabradine plus standard care is modelled to reduce CV mortality relative to standard care alone. The treatment effect is modelled to be multiplicative with respect to the underlying risk of CV death (captured in the regression model as a hazard ratio). Non-CV mortality is modelled to be equivalent between ivabradine plus standard care and standard care alone in all scenarios and no treatment benefit for ivabradine is modelled for this endpoint. Ivabradine is modelled to reduce CV mortality rather than only HF mortality for the following reasons:

- Ivabradine demonstrated a statistically significant reduction in CV mortality in the sub-population of interest (patients with a heart rate ≥75 bpm)
- Ivabradine is already licensed for other CV indications and has the potential to

affect other CV mortality endpoints

- HF death is captured within the CV mortality endpoint.

***Treatment effect modification***

The variables reviewed for treatment effect modification (treatment interaction) reflected those variables that had been identified to potentially modify ivabradine's treatment effect in earlier clinical analyses [baseline age, ischaemic heart disease, category of beta-blocker use, heart rate [5]]. Treatment interaction with other baseline variables and interactions between baseline variables have not been considered in order to prevent the generation of spurious results.

Multi-variable analyses indicated that ivabradine's treatment effect appeared to be modified by baseline heart rate (p=0.07). Once differences in baseline heart rate were taken into account there was no statistical evidence that ivabradine's treatment effect diminished with increased beta-blocker use, increasing age or ischaemic heart disease.

***Proportional hazard assumption***

The base case analysis uses a proportion hazard (PH) parametric survival model (Gompertz distribution), hence, the relative treatment effect of ivabradine plus standard care versus standard care alone is assumed to remain constant (proportional) over time. The PH assumption was assessed using a statistical test based on the correlation of Schoenfeld residuals and the rank order of failure events (evidence of correlation suggests PH violation) and visually by plotting -ln [-ln(survival)] curves

against ln(time) (evidence of non-parallelism in the plots by treatment indicating PH violation). These tests showed no evidence of PH violation.

**Table 2 CV mortality: Gompertz parametric regression model ≥70bpm (treatment variable only)**

| Parameter | 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 3 CV mortality: Gompertz parametric regression model ≥75bpm (treatment variable only)**

| Parameter | 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 4 CV mortality: Gompertz parametric regression model ≥70bpm**

| 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 | <0.0001 | -0.5389 | -0.2063 |
| **Aldosterone use** | 1.2823 | 0.2486 | 0.0743 | 0.0010 | 0.1031 | 0.3942 |
| **Digitalis use** | 1.3225 | 0.2795 | 0.0747 | <0.0001 | 0.1332 | 0.4259 |
| **Loop diuretic (dose/kg/day)** | 1.1215 | 0.1147 | 0.0298 | <0.0001 | 0.0562 | 0.1731 |
| **Lipid medications** | 0.7946 | -0.2299 | 0.0672 | 0.0010 | -0.3616 | -0.0983 |
| **Systolic Blood Pressure (mmHg)*** | 0.9902 | -0.0099 | 0.0022 | <0.0001 | -0.0142 | -0.0055 |
| **NYHA III (vs II)** | 1.3030 | 0.2647 | 0.0705 | <0.0001 | 0.1264 | 0.4029 |
| **NYHA IV (vs II)** | 2.7614 | 1.0157 | 0.1648 | <0.0001 | 0.6928 | 1.3386 |
| **HF duration ≥0.6<2 yrs vs <0.6 yrs** | 1.5099 | 0.4120 | 0.1074 | <0.0001 | 0.2015 | 0.6225 |
| **HF duration ≥2<4.8 yrs vs <0.6 yrs** | 1.7334 | 0.5501 | 0.1066 | <0.0001 | 0.3412 | 0.7591 |
| **HF duration ≥4.8 yrs vs <0.6 yrs** | 1.9833 | 0.6848 | 0.1033 | <0.0001 | 0.4822 | 0.8873 |
| **LVEF ≥26%<30% vs <26%yrs** | 0.8644 | -0.1457 | 0.0929 | 0.1170 | -0.3278 | 0.0364 |
| **LVEF ≥30%<33% vs <26%yrs** | 0.7121 | -0.3395 | 0.0893 | <0.0001 | -0.5145 | -0.1645 |
| **LVEF ≥33% vs <26%yrs** | 0.5895 | -0.5285 | 0.0921 | <0.0001 | -0.7091 | -0.3480 |

| Description | HR | Coefficient | SE | p-value | 95% LCI | 95% UCI |
|---|---|---|---|---|---|---|
| **Heart rate bpm*** | 1.0229 | 0.0226 | 0.0040 | <0.0001 | 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 | <0.0001 | 0.0137 | 0.0262 |
| **Prior stroke** | 1.2753 | 0.2432 | 0.1057 | 0.0210 | 0.0361 | 0.4503 |
| **Sodium (mmol/L)*** | 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 | <0.0001 | -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*

# 4. NYHA class

The most commonly used classification of severity of CHF symptoms is the NYHA classification of functional capacity. This system assigns patients to one of four functional classes, depending on patient symptoms. The distribution of patients in each NYHA class over time is estimated in the cost-effectiveness analysis using a generalised ordered logistic regression developed from SHIFT data [6]. A generalised ordered logistic regression is similar to a standard logistic regression but allows for an outcome variable with more than two response categories (i.e. NYHA class I-IV), see Table 6 and

Table 7. The NYHA regression model considers treatment and time variables but, for simplicity, does not consider other patient baseline characteristics.

**Table 5 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 6 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 7 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 |

# 5. Hospitalisation

## 5.1. Hospitalisation: standard care

The probability of all-cause hospitalisations each month is predicted from a Poisson regression model developed using SHIFT individual patient data. The Poisson regression model estimates the rate of hospitalisation per person month [7], which is converted into a monthly transition probability for final implementation.

HF hospitalisations and CV hospitalisations are captured in the cost-effectiveness analysis independently to permit sensitivity analysis of ivabradine's treatment effect on these endpoints and to allow appropriate resource use to be applied to different types of hospitalisation.

The rate of hospitalisation did not appear to vary over time in SHIFT consequently the Poisson model predicts hospitalisations to occur at a constant rate, although the rate predicted varies according to treatment allocation and patient characteristics. The independent variables considered for inclusion in the risk equation were consistent with those variables considered for the CV mortality risk equation (see Section 3.1**Error! Reference source not found.**) plus geographical region (Western Europe, Eastern Europe, Latin America and Asia).

Variables were initially identified using backwards stepwise elimination (p-value of <0.1) and corroborated using forwards stepwise selection The methods used to select variables for the final regression model were comparable to those used for the CV mortality risk equation, see Section 3.1. The final regression model is detailed in Table 8.

### 5.2. Hospitalisation: ivabradine treatment effect

***Overview***

Ivabradine is modelled to reduce all-cause hospitalisations relative to standard care using a rate ratio derived from the Poisson regression model. In the base case analysis ivabradine is modelled to reduce all-cause hospitalisations rather than only CV or HF hospitalisations because:

- Ivabradine demonstrated a statistically significant reduction in all-cause hospitalisation in the main study population (patients with a baseline heart rate ≥70 bpm) and in the sub-population of interest (patients with a heart rate ≥75 bpm)
- HF and CV hospitalisations are implicitly captured within the all-cause hospitalisation endpoint [5]

***Hospitalisation: treatment effect modification***

The variables reviewed for treatment effect modification included those variables found to predict hospitalisation rates and with prior clinical evidence of potential treatment interaction (baseline heart rate, beta-blocker use and age). There was strong evidence that patient baseline heart rate modified ivabradine's treatment effect on the rate of hospitalisation (p=0.01). However, similar to CV mortality, once differences in baseline heart rate had been taken into account, there was no statistically significant evidence that ivabradine's treatment effect was modified by either beta-blocker use or age.

**Table 8 Rate of all-cause hospitalisation: Poisson regression model**

| Parameter | Rate ratio | 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 European vs Western** | 0.7157 | -0.3345 | 0.0666 | 0.0000 | -0.4650 | -0.2040 |
| **Latin American vs Western** | 0.7041 | -0.3508 | 0.0900 | 0.0000 | -0.5272 | -0.1745 |
| **Asian vs Western** | 0.5079 | -0.6775 | 0.1179 | 0.0000 | -0.9087 | -0.4464 |
| **LVEF ≥26%<30% vs <26%yrs** | 0.8120 | -0.2083 | 0.0665 | 0.0020 | -0.3387 | -0.0779 |
| **LVEF ≥30%<33% vs <26%yrs** | 0.7181 | -0.3312 | 0.0622 | 0.0000 | -0.4532 | -0.2092 |
| **LVEF ≥33% vs <26%yrs** | 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 |

| Parameter | Rate ratio | Coefficient | SE | p-value | 95% LCI | 95% UCI |
|---|---|---|---|---|---|---|
| **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 (mmol/L)*** | 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 |
| **Systollic Blood Pressure (mmHg)*** | 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*

# 6. Hospitalisation length of stay

## 6.1. Overview

Expert clinical advice indicated that SHIFT data may not offer a reliable estimate of hospitalisation admission duration for UK patients due to regional variation in treatment practice. In the base case analysis hospitalisation length of stay is based on a weighted average of elective and non-elective NHS reference cost data (2010-2011) [8]. Hospital Episode Statistics (HES) data and National HF Audit data have been applied in sensitivity analyses [9 10], see Section 10. Length of stay is modelled to vary according to admission type (HF, other CV and non-CV diagnosis), see Table 9.

**Table 9 Hospitalisation length of stay by diagnosis and data source**

| **Admission type** | **NHS reference costs (base case analysis)** | **HES data (sensitivity analysis)** | **National HF audit (sensitivity analysis)** |
|---|---|---|---|
| HF | 7.57 | 11.50 | 9.0 (median) |
| CV | 3.97 | 7.55 | - |
| Non-CV | 5.13 | 5.25 | - |

# 7. Quality of life

## 7.1. Quality of life: standard care

Patient quality of life was captured using the SHIFT patient reported outcome sub-study which collected EQ-5D estimates from patients in countries with a validated EuroQoL EQ-5D questionnaire at baseline, 4, 12, 24 and 36 months (heart rate ≥70bpm, n=5313). EQ-5D index scores were calculated using tariff values taken from UK population survey data [11] for all patients regardless of country of origin.

SHIFT EQ-5D data have been analysed using a mixed regression model, which is specifically designed for datasets with repeated observations across individuals. The variables considered as potential predictors of patient quality of life 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].

### 7.2. Quality of life: ivabradine treatment effect

***Overview***

The mixed regression model suggested that ivabradine was associated with a significant improvement in patient quality of life. In the cost-effectiveness analysis the treatment effect on quality of life has been modelled using an absolute increment for ivabradine plus standard care relative to standard care alone. The treatment effect is assumed to continue post-trial period and is modelled to be equivalent to that demonstrated within study.

***Treatment effect modification***

The variables reviewed for treatment effect modification in the quality of life risk equation reflect those variables with a prior clinical evidence of potential interaction with ivabradine and which were a significant predictor of patient quality of life (baseline age, heart rate). Interaction between hospitalisation and NYHA class was also considered due to strong clinical rationale. The potential interaction of treatment with other baseline variables, and interaction between baseline variables, was not considered in order to prevent the generation of spurious results. The regression model indicated that the treatment effect was not significantly modified by baseline heart rate ($p=0.13$). However, the interaction term for treatment and heart rate was retained since heart rate had been found to significantly modify

the ivabradine treatment effect for other clinical outcomes and a trend towards an interaction effect (albeit non-significant) was evident in data. There was statistically significant evidence that the reduction in quality of life due to a hospitalisation varied according to NYHA class. The final risk equation is reported in **Error! Reference source not found.**.

**Table 10 SHIFT EQ-5D: predicted utility values**

| Health State | Estimated utility value* |
|---|---|
| **NYHA I** | 0.823 |
| **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)** | 0.014 |

*Reported values estimated using SHIFT average characteristics in regression equation reported in Table 12.

**Table 11 Mixed regression model: treatment (patient heart rate ≥70 bpm)**

| | Coefficient | SE | P-value | 95% LCI | 95% UCI |
|---|---|---|---|---|---|
| **Treatment** | 0.0156 | 0.0053 | 0.0030 | 0.0053 | 0.0259 |
| **Constant** | 0.6995 | 0.0037 | <0.0001 | 0.6923 | 0.7068 |

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

**Table 12 EQ5D index score: Mixed regression model: treatment and baseline characteristics (patient heart rate ≥70 bpm)**

| Description | Coefficient | SE | p-value | 95% LCI | 95% UCI |
|---|---|---|---|---|---|
| **Treatment** | 0.0104 | 0.0047 | 0.0270 | 0.0012 | 0.0195 |
| **Age (years)*** | -0.0008 | 0.0002 | <0.0001 | -0.0012 | -0.0004 |
| **Female** | -0.0590 | 0.0057 | <0.0001 | -0.0702 | -0.0478 |
| **Hospitalisation within 30 days** | -0.2116 | 0.0320 | <0.0001 | -0.2744 | -0.1489 |
| **NYHA II vs I** | -0.0848 | 0.0089 | <0.0001 | -0.1023 | -0.0673 |
| **NYHA III vs I** | -0.1798 | 0.0094 | <0.0001 | -0.1982 | -0.1614 |
| **NYHA IV vs I** | -0.3656 | 0.0182 | <0.0001 | -0.4012 | -0.3300 |
| **Ischaemia** | -0.0365 | 0.0054 | <0.0001 | -0.0471 | -0.0258 |
| **Prior stroke** | -0.0243 | 0.0086 | 0.0050 | -0.0410 | -0.0075 |
| **HF duration ≥0.6<2 yrs vs <0.6 yrs** | -0.0191 | 0.0067 | 0.0040 | -0.0322 | -0.0061 |
| **HF duration ≥2<4.8 yrs vs <0.6 yrs** | -0.0394 | 0.0068 | <0.0001 | -0.0526 | -0.0262 |
| **HF duration ≥4.8 yrs vs <0.6 yrs** | -0.0456 | 0.0068 | <0.0001 | -0.0590 | -0.0322 |
| **Allopurinol** | 0.0220 | 0.0098 | 0.0260 | 0.0027 | 0.0413 |
| **BMI kg/m2*** | -0.0026 | 0.0005 | <0.0001 | -0.0035 | -0.0016 |
| **Heart rate bpm*** | -0.0021 | 0.0004 | <0.0001 | -0.0028 | -0.0014 |
| **Loop diuretics (dose/kg/day)** | -0.0158 | 0.0032 | <0.0001 | -0.0220 | -0.0096 |
| **Potassium (>5 mmol/L)** | -0.0142 | 0.0060 | 0.0190 | -0.0261 | -0.0023 |
| **Hosp30*nyha I** | 0.1403 | 0.0832 | 0.0920 | -0.0228 | 0.3035 |
| **Hosp30*nyha II** | 0.1792 | 0.0352 | <0.0001 | 0.1102 | 0.2482 |
| **Hosp30*nyha III** | 0.1281 | 0.0344 | <0.0001 | 0.0607 | 0.1955 |
| **Treatment*heart rate** | 0.0008 | 0.0005 | 0.1330 | -0.0002 | 0.0017 |
| **Cons** | 0.9082 | 0.0108 | <0.0001 | 0.8870 | 0.9293 |

***Footnotes:*** *LCI – lower confidence interval, UCI upper confidence interval*
**Variables centred on the mean*

# 8. Extrapolation

## 8.1. Extrapolation: standard care

Heart failure is a chronic progressive disease requiring lifelong therapy, hence the cost-effectiveness model is designed to predict costs and effects over a patient's lifetime consistent with NICE recommendations [12]. In the base case analysis parametric survival analysis is used to predict CV mortality for standard care patients in both the within-trial and the extrapolated, post-trial period (proportional hazard model, Gompertz distribution).

There is little external evidence to predict the distribution of patients in each NYHA class post-trial. The NYHA risk equation, which includes a time variable, predicts a (small) increase in the absolute number of patients in NYHA I and II over time, a pattern observed during the SHIFT study period. 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 HF 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 HF. The cost-effectiveness analysis consequently assumes that the proportion of patients in each NYHA class remains fixed post trial (although in absolute terms numbers in each category varies according to survival estimates, see Figure 4 and Figure 5). This approach is considered more conservative than extrapolation using predictions from SHIFT data, which would predict a high proportion of patients with minimal or mild symptoms in the long-term and result in a more favourable ICER estimate for ivabradine.

Hospitalisations are assumed to occur at a constant rate. The rate of all-cause hospitalisations post-trial is consequently modelled to be equivalent to that modelled within-trial. In the base case analysis 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 hospitalisation regression model predicted that for every 10 year increase in age from the SHIFT mean (60.4 years) the risk of all-cause hospitalisations increased by approximately 10%. An increase in underlying rate of hospitalisation due to population ageing, given the same relative treatment effect for ivabradine, would generate a larger absolute reduction in hospitalisations. In these circumstances the increase in hospitalisations associated with population ageing would drive a more favourable (lower ICER) for ivabradine. This potential benefit is not captured in the SHIFT cost-effectiveness analysis.

Post-trial patient quality of life in each NYHA class is also modelled to be equivalent to within-trial estimates and hence is also not modelled to change as patients age. This simplification may result in higher utility values being applied to patients in later cycles than would naturally be expected in an older population. This approach may favour ivabradine since additional survival time will be associated with a greater modelled QALY benefit. A sensitivity analysis, which models patient quality of life to deteriorate due to population ageing, is consequently included in the cost-effectiveness analysis, see Section 10.2.

### 8.2. Extrapolation: ivabradine treatment effect

The treatment effect of ivabradine on CV death, hospitalisation, NYHA class and QoL has been modelled to continue post trial and to be equivalent to that estimated in the within-trial period. Alternative assumptions have been tested in sensitivity analyses, see

Section 10.2.

**Figure 4 Standard care: predicted proportion of patients by NYHA class over time**

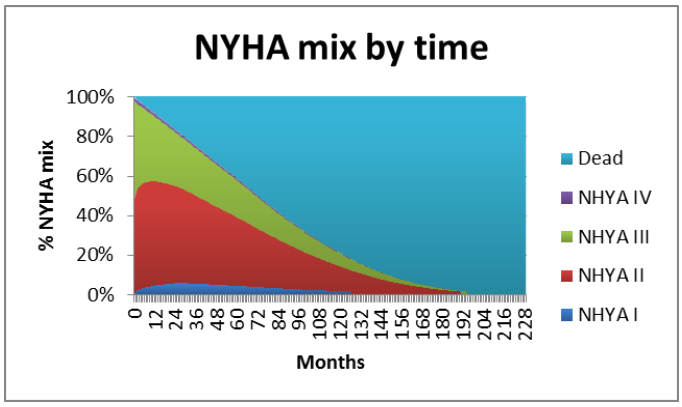
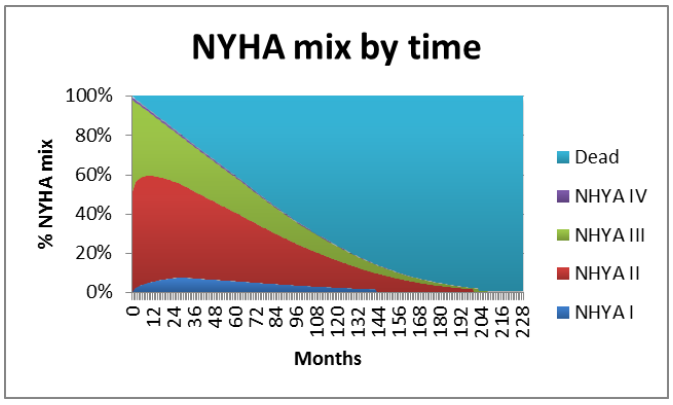



**Figure 5 Ivabradine: predicted proportion of patients by NYHA class over time**




# 9. Base case analysis

The base case results have been reported for a population consistent with the European licensed indication (patients with a baseline heart rate ≥75 bpm). 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 sequentially - one profile at a time - in each of the SHIFT adjusted risk equations in the cost-effectiveness analysis. In the

base case analysis estimates of costs and QALYs generated from each patient profile have been averaged to calculate incremental cost per life year gained and incremental cost per QALY gained for ivabradine plus standard care versus standard care alone. This approach was taken in preference to using the proportion of patients with each given characteristic (e.g. 0.24 for female) in the regression equations to provide a more accurate assessment of the incremental cost-effectiveness ratio (ICER).

# 10. One way sensitivity analyses

## 10.1. Parameter values

One way sensitivity analyses were conducted to test the effect of varying key parameter values within plausible ranges. These included:

- Hazard ratio CV mortality (95% confidence interval)
- Rate ratio hospitalisation (95% confidence interval)
- Utility increment ivabradine (95% confidence interval)
- Hospitalisation: cost per day
- Ivabradine monitoring/titration costs (inclusion/exclusion of titration visit and ECG costs)

### 10.2. Structural assumptions

A summary of the structural sensitivity analyses undertaken has been provided (base case assumptions 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 at 5 years)
- Continued treatment effect post trial versus reduction of treatment benefit post-trial period (hazard ratio/rate ratio linearly returns to 1 over 5-10 year range, drug costs cease once hazard ratio reaches 1)

**CV Mortality**

- Alternative parametric distribution (Gompertz, exponential, Weibull)
- Alternative survival modelling within-trial period (parametric vs Kaplan-Meier data)
- Alternative data source extrapolation of mortality post trial (SHIFT parametric model vs external data (CARE-HF))

**NYHA class**

- Alternative assumptions NYHA distribution post-trial (last observation carried forward *vs* increased proportion of patients in NYHA class III and IV)

**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 HF data, SHIFT data).

**Quality of Life**

- Alternative data source patient utility [SHIFT data vs external data (Gohler, 2009)]
- Alternative data: utility mixed regression model *vs* observed data
- Utility loss associated with population ageing excluded/included

**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

# 11. Probabilistic sensitivity analysis

The model is designed to quantify uncertainty probabilistically. Multivariable regression functions generated using SHIFT individual patient data are included in the model alongside a Cholesky decomposition to account for correlated parameters. Monte Carlo simulation is used to generate the resulting joint distributions of total costs and QALYs in the model [13]. The model outputs are also 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 [14].

The base case ICER is estimated by applying individual patient profiles sequentially into the risk equations one at time. 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 covariable values in the regression equations. Whilst there is some loss in accuracy in the ICER estimates generated

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.

## 12. Results

Results for the base case analysis, one-way sensitivity analyses and probabilistic sensitivity analyses are detailed in the primary publication and are not replicated in this document. Further details on the ivabradine cost-effectiveness model and Single Technology Appraisal (STA) may be found on the National Institute for Health and Care Excellence (NICE) website (www.nice.org.uk).

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