Technical Appendix

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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

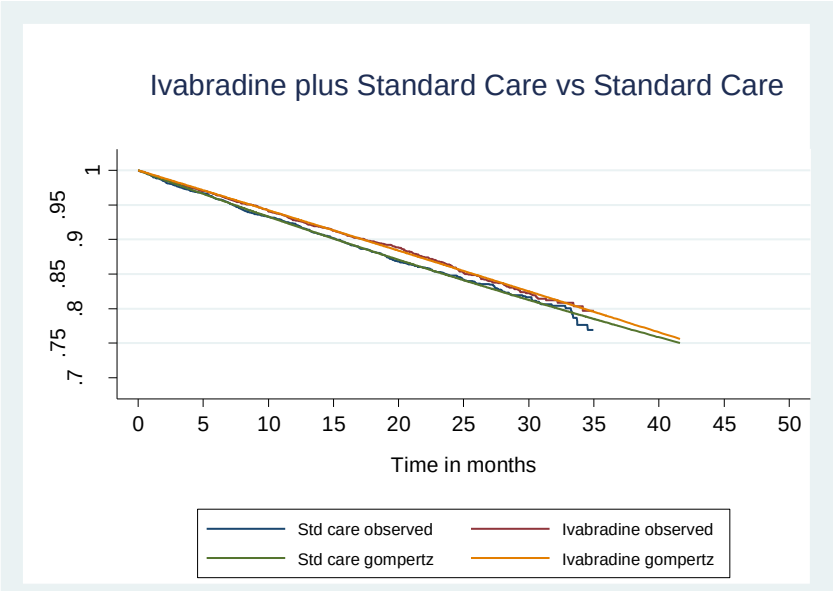
Figure 1) and the plausibility of predicted survival in the extrapolated, post-trial period [2]. This model also generates the most conservative (least favourable) estimate of patient long term survival and, hence, the most conservative incremental differences in mortality for ivabradine versus standard 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

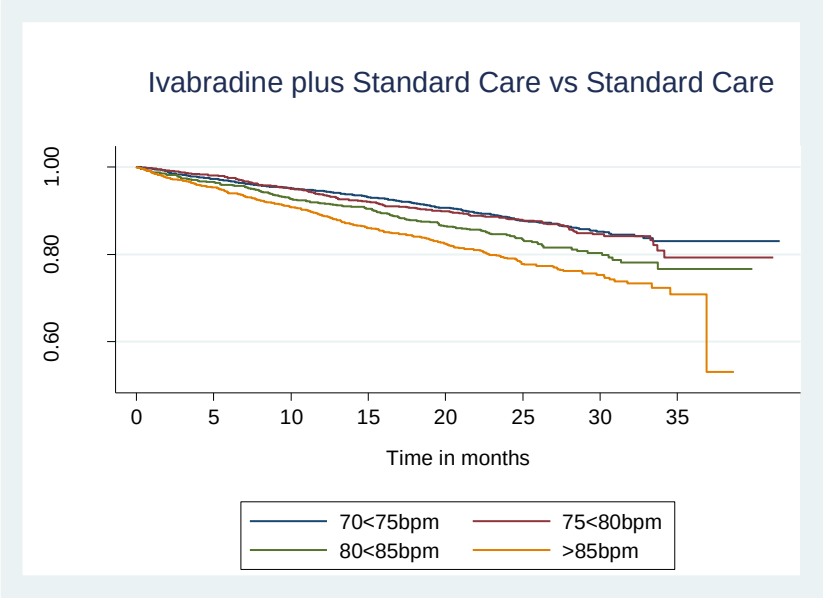
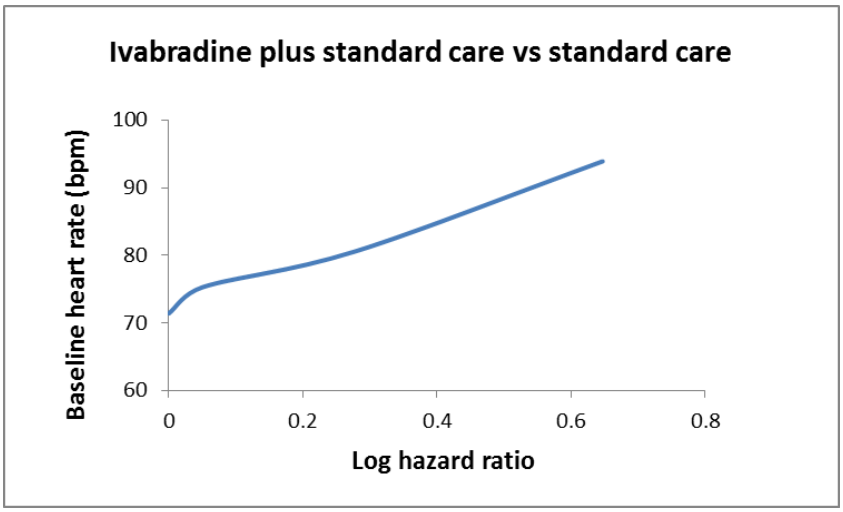


Figure 3 Mean baseline heart rate vs log hazard ratio CV mortality



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

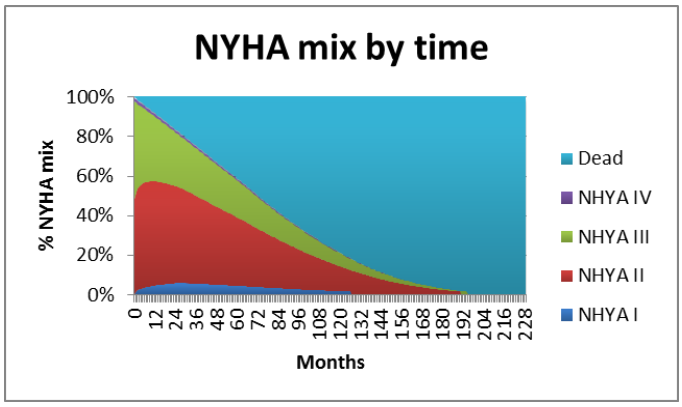
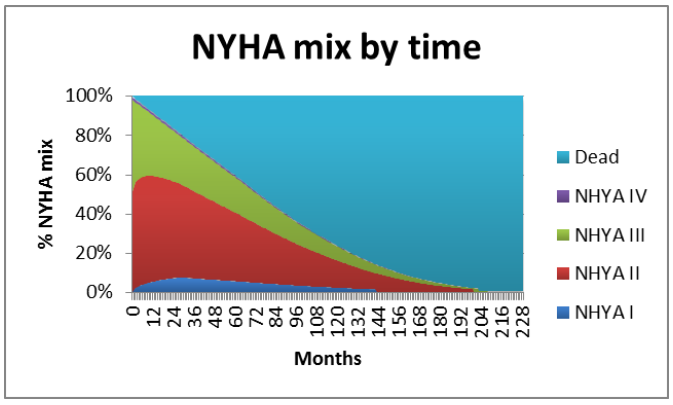


Figure 5 Ivabradine: predicted proportion of patients by NYHA class over time



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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