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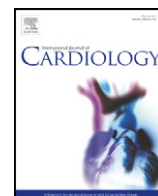
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Top ten risk factors for morbidity and mortality in patients with chronic systolic heart failure and elevated heart rate: The SHIFT Risk Model



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ABSTRACT

Aims: We identified easily obtained baseline characteristics associated with outcomes in patients with chronic heart failure (HF) and elevated heart rate (HR) receiving contemporary guideline-recommended therapy in the SHIFT trial, and used them to develop a prognostic model.

Methods: We selected the 10 best predictors for each of four outcomes (cardiovascular death or HF hospitalisation; all-cause mortality; cardiovascular mortality; and HF hospitalisation). All variables with $p < 0.05$ for association were entered into a forward stepwise Cox regression model. Our initial analysis excluded baseline therapies, though randomisation to ivabradine or placebo was forced into the model for the composite endpoint and HF hospitalisation.

Results: Increased resting HR, low ejection fraction, raised creatinine, New York Heart Association class III/IV, longer duration of HF, history of left bundle branch block, low systolic blood pressure and, for three models, age were strong predictors of all outcomes. Additional predictors were low body mass index, male gender, ischaemic HF, low total cholesterol, no history of hyperlipidaemia or dyslipidaemia and presence of atrial fibrillation/flutter. The c-statistics for the four outcomes ranged from 67.6% to 69.5%. There was no evidence for lack of fit of the models with the exception of all-cause mortality ($p = 0.017$). Similar results were found including baseline therapies.

Conclusion: The SHIFT Risk Model includes simple, readily obtainable clinical characteristics to produce important prognostic information in patients with chronic HF, systolic dysfunction, and elevated HR. This may help better calibrate management to individual patient risk.

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1. Introduction

In patients with chronic systolic heart failure (HF), despite modern pharmacological therapy, episodes of worsening heart failure (WHF) are common, and history of previous hospitalisation further increases the risk of subsequent admissions or death [1,2]. Recent European Society of Cardiology (ESC) guidelines recommend ivabradine to improve outcome for patients in sinus rhythm who remain symptomatic with reduced left ventricular ejection fraction (LVEF) and heart rate

≥ 70 bpm despite other evidence-based therapies, including beta-blocker [3]. This recommendation is based on the results of SHIFT (Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial), in which the patients enrolled had a hospital admission during the year preceding the trial enrolment.

Advances in therapies for HF create a continuous need for the construction of new models in contemporary HF trials. Objective prognostic information could guide decision-making in the management of HF in all or subsets of patients. Risk models also have a value in economic evaluations for projecting the potential benefit of a therapy that prevents non-fatal events and in identifying subgroups where the economic impact is greatest. Similarly, risk stratification can provide the opportunity to explore potential interactions between underlying risk and treatment effect. In some contexts, estimation of risk can be used to target individuals for more intensive monitoring and therapy. HF

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risk assessment is multifactorial and will inevitably involve multiple measurements. Some have argued that relatively simple risk scores, not needing computers, are needed [4]. However, with the growth in the use of electronic patient records and the universal availability of handheld devices capable of complex calculations, this argument no longer seems tenable. On the other hand, there are advantages in scores that utilize a modest number of readily available risk factors as well as more complex models.

Recent approaches to developing risk models in HF include that published by the CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity) investigators [5] and Seattle Heart Failure Model [6], which evaluates factors prognostic for HF and was developed and validated in independent cohorts. The MAGGIC (Meta-analysis Global Group in Chronic Heart Failure) collaborators have also recently developed a risk model for all-cause mortality based on 39,372 patients from a group of HF trials and registries conducted over a long period of time [7]. However, this approach has been a subject of debate because it includes a heterogeneous group of patients many of whom were recruited when heart failure treatment did not include all the modalities commonly used day.

The aim of the present study was to investigate the risk for the outcomes of death from all causes, death from cardiovascular causes, and death and/or hospitalisation for HF in symptomatic patients in sinus rhythm with chronic HF, left ventricular systolic dysfunction (LVSD) and heart rate ≥ 70 bpm (a level known to be a risk descriptor in HF), in whom therapy with ivabradine might be considered. Analyses are based on data from the Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial (SHIFT).

2. Methods

2.1. SHIFT study design

SHIFT was a randomised, double-blind, placebo-controlled trial in patients with moderate to severe HF and LVSD. The study design has been described in detail previously [8,9]. SHIFT included patients with symptomatic HF stable for at least 4 weeks, who had a hospitalisation due to WHF within the past 12 months, were in sinus rhythm with a resting frequency ≥ 70 bpm, and had an LVEF $\leq 35\%$. A total of 6505 patients were randomised and received ivabradine, a sinus node inhibitor, or placebo, on top of standard HF therapy. Median follow-up in the SHIFT trial was 22.9 (IQR 18–28) months. Hospitalisation for WHF during follow-up was defined as an admission with new or increasing symptoms and signs of HF including fluid retention or other objective evidence of HF, in combination with a change in treatment to improve HF. An endpoint validation committee adjudicated all pre-specified events including HF and cardiovascular death. All patients provided written informed consent for their participation in the study. The study complies with the Declaration of Helsinki and was approved by ethics committees in all participating countries.

2.2. Statistical methods

We reviewed baseline data collected in the SHIFT trial and identified all variables that could potentially be associated with adverse clinical outcomes (Table 1). In addition to demographic information, medical history, and basic measurements, we included laboratory measurements and baseline cardiovascular medications. The analysis focuses on the 6390 participants who had complete baseline data.

We studied four outcomes, namely a composite of cardiovascular death or hospital admission for HF (the primary outcome of SHIFT), all-cause mortality, cardiovascular mortality, and hospital admission for HF. All analyses are based on the time from randomisation until the first outcome for each endpoint or end of study, whichever came first. Follow-up was censored at time of death for deaths not included in the outcome analysed. Analyses were based on Cox proportional

Table 1
Baseline characteristics of the study population.

| Baseline characteristic | N with data | Value |
|--|-------------|------------------|
| Age (years) | 6505 | 60.9 \pm 11.4 |
| Male | 6505 | 4970 (76.4%) |
| Body mass index (kg/m ²) | 6504 | 25.8 \pm 2.4 |
| <i>Cardiac parameters</i> | | |
| Heart rate (bpm) | 6501 | 79.9 \pm 9.6 |
| Systolic blood pressure (mm Hg) | 6505 | 121.7 \pm 16.0 |
| Diastolic blood pressure (mm Hg) | 6505 | 75.7 \pm 9.5 |
| Left ventricular ejection fraction (%) | 6505 | 29.0 \pm 5.2 |
| <i>Laboratory parameters</i> | | |
| eGFR (mL/min per 1.73 m ²) | 6485 | 74.6 \pm 22.9 |
| Serum creatinine (μ mol/L) | 6485 | 96.7 \pm 26.4 |
| Anaemia (Hb ≤ 120 g/L) | 6483 | 550 (8.5%) |
| ALT (U/L) | 6470 | 25.4 \pm 14.9 |
| Total cholesterol ≤ 3.4 mmol/L | 6505 | 637 (9.8%) |
| Total cholesterol 3.41 to < 4.8 mmol/L | 6505 | 2032 (31.2%) |
| Total cholesterol ≥ 4.9 mmol/L | 6505 | 3836 (59.0%) |
| Potassium < 4.2 mmol/L | 6435 | 1394 (21.7%) |
| Potassium 4.2 to 4.4 mmol/L | 6435 | 1460 (22.7%) |
| Potassium 4.5 to 4.8 mmol/L | 6435 | 1969 (30.6%) |
| Potassium ≥ 4.9 mmol/L | 6435 | 1612 (25.1%) |
| Sodium (mmol/L) | 6455 | 140.5 \pm 3.6 |
| <i>Medical history</i> | | |
| NYHA class III/IV vs class II | 6503 | 3334 (51.3%) |
| Heart failure duration (years) | 6505 | 41.9 \pm 50.4 |
| Ischaemic heart failure | 6505 | 4418 (67.9%) |
| History of myocardial infarction | 6505 | 3666 (56.4%) |
| History of hypertension | 6505 | 4314 (66.3%) |
| History of diabetes | 6505 | 1979 (30.4%) |
| History of stroke | 6505 | 523 (8.0%) |
| Atrial fibrillation/flutter | 6505 | 522 (8.0%) |
| Prior coronary surgery | 6505 | 886 (13.6%) |
| History of hyperlipidaemia/dyslipidaemia | 6505 | 1890 (29.1%) |
| History of chronic obstructive pulmonary disease | 6505 | 730 (11.2%) |
| History of left bundle branch block | 6505 | 912 (14.0%) |
| <i>Treatments</i> | | |
| Beta-blocker | 6505 | 5820 (89.5%) |
| Angiotensin-converting enzyme inhibitor | 6505 | 5116 (78.6%) |
| Cardiac glycosides | 6505 | 1416 (21.8%) |
| Angiotensin II receptor blocker | 6505 | 927 (14.3%) |
| Diuretic | 6505 | 5414 (83.2%) |
| Antiarrhythmic agent | 6505 | 197 (3.0%) |
| Mineralocorticoid receptor antagonist | 6505 | 3922 (60.3%) |
| Vitamin K antagonist | 6505 | 1082 (16.6%) |
| Lipid-lowering medication | 6505 | 3794 (58.3%) |
| CRT device | 6505 | 72 (1.1%) |
| ICD device | 6505 | 207 (3.2%) |
| Ivabradine treatment | 6505 | 3241 (49.8%) |

Values are means \pm SD or numbers (%). NYHA = New York Heart Association. eGFR = estimated glomerular filtration rate (modification in diet in renal disease formula). CRT = cardiac resynchronisation therapy. ICD = implantable cardioverter defibrillator.

hazard models. We first reviewed all continuous risk factors univariately to assess whether or not there was evidence of a non-linear relationship with risk of each outcome. Variables were then included in the analysis as continuous variables or were categorised by tertiles or quartiles of their distribution as appropriate. As was done in the models fitted for the CHARM trials [5], all patients under the age of 60 years were assigned the same risk and a linear continuous relationship was assumed above the age of 60 years. A similar approach was adopted for body mass index (BMI) where the same risk was assumed for all BMI > 27.5 kg/m², with a continuous relationship below 27.5 kg/m².

Two strategies for risk modelling were used (Appendix A). In the first approach, we selected the top 10 best predictors for each outcome, in addition to randomised treatment allocation in the case of cardiovascular death or hospitalisation for HF. We excluded randomised treatment for other outcomes as there was no significant association of randomised treatment with mortality outcomes. On the basis of the univariate Cox models, all variables with $p < 0.05$ for association for a

particular outcome were entered into forward stepwise Cox regression model analysis with $p < 0.05$ to enter the model, with the exception that randomised allocation to ivabradine or placebo was forced into the models for cardiovascular death or hospitalisation for HF and hospitalisation for heart failure. We fitted models both including and excluding baseline therapies (drugs and devices). This provided two models for each outcome.

In the second approach, we adopted a similar strategy, but allowed all variables to potentially enter the models without a limit on the number of variables in the model. This provided a further two models for each outcome. Results for the best 10 predictors are provided in the main manuscript (first approach) and for the larger models in Appendix B (second approach).

To assess the ability of the models to discriminate between patients who do and do not have events, we calculated c-statistics. To measure goodness of fit of our models, we first calculated outcome-specific risk scores for each subject and used these to assign the patients to 10 categories based on deciles of their risk scores. The categorical variables associated with the 10 subgroups were then added to each fitted risk model and a Wald test for the added terms was computed as a lack-of-fit test. The observed and predicted numbers of events in the ten subgroups were compared graphically using bar charts (results only for the models including baseline therapies are presented in the paper).

Finally, for the primary outcome, a risk model was developed excluding randomised treatment group. All patients were then assigned to five subgroups on the basis of quintiles of their estimated baseline risk scores. The effect of ivabradine treatment compared to placebo was then evaluated within each subgroup and then compared across subgroups in a Cox regression model to test for evidence of an interaction between treatment and underlying risk using a trend test. A description of the calculations involved in deriving risk probabilities is given in Appendix A.

Statistical analyses were performed by the Robertson Centre for Biostatistics (Glasgow, UK) using SAS (version 9.2).

3. Results

Baseline characteristics for potential risk factors are given in Table 1. Univariable associations of each potential risk factor with each of the four outcomes studied are given in Table 2. The patterns of associations are almost identical for all-cause and cardiovascular mortality, with all factors being associated with outcome, with the exception of device use, ACE inhibitor, and vitamin K antagonist use, and a history of diabetes; there were only weak associations for ARB use, prior coronary surgery, and ischaemic HF. Associations with the primary outcome and HF hospitalisation were broadly similar. However for these outcomes, there was no association with gender, no or weaker associations with history of ischaemic HF or myocardial infarction, hypertension, and hyperlipidaemia/dyslipidaemia, and stronger associations with ACE inhibitor use, vitamin K antagonist use, and use of devices.

The top 10 predictors of outcomes in the models excluding baseline therapies are given in Table 3. Increased heart rate, low LVEF, raised creatinine, being in NYHA class III/IV, longer duration of HF, increased age (with the exception of cardiovascular mortality), history of left bundle branch block and low systolic blood pressure were strong predictors for all four outcomes. Additional predictors of outcome were low BMI for all-cause and cardiovascular mortality, male gender for all-cause mortality, ischaemic HF for cardiovascular mortality, lower levels of cholesterol for the primary outcome and HF hospitalisation, a history of atrial fibrillation/flutter for primary outcome, and diabetes or lack of history of hyperlipidaemia/dyslipidaemia for HF hospitalisation. The c-statistics for the four outcomes in Table 3 ranged from 67.6% to 69.5%. There was no evidence for lack of fit for the primary outcome, cardiovascular mortality, or HF hospitalisation ($p = 0.10$, $p = 0.54$, and $p = 0.07$, respectively). However there was some evidence for lack of fit for the model predicting all-cause mortality ($p = 0.017$).

The top 10 predictors of outcomes in the model including baseline therapies are given in Table 4. For the primary outcome and HF hospitalisation, compared to the model excluding baseline therapies, systolic blood pressure and atrial fibrillation/flutter dropped out of the model to be replaced by treatment with cardiac glycosides and MRAs. For all-cause mortality, history of left bundle branch block and male gender dropped out to be replaced by history of ischaemic HF and treatment with cardiac glycosides. For cardiovascular mortality, systolic blood pressure and history of left bundle branch block dropped out to be replaced by treatment with cardiac glycosides, MRAs, and not being treated with lipid-lowering agents. The c-statistics increased slightly ranging from 68.2% to 70.2% (Table 4). For these models, there was no evidence of lack of fit for the all-cause and cardiovascular mortality models ($p = 0.11$ and $p = 0.47$, respectively), while there was evidence of lack of fit for the primary outcome and HF hospitalisation ($p = 0.005$ and $p < 0.0001$, respectively).

Similar results were found in the approach using all variables to the approach including the top 10 predictors, with the exception that inclusion of additional predictors resulted in no evidence of lack of fit for the models incorporating baseline therapies. The corresponding results are presented Appendix B.

Comparisons of the predicted numbers of events (percentage event rate) with the actual numbers of events observed in the SHIFT trial are illustrated for the four outcomes in the model including baseline therapies in Fig. 1. Fig. 2 shows Kaplan–Meier time to primary outcome plots for the estimated treatment effects of ivabradine or placebo for the study participants split into fifths of baseline risk. There is no evidence of an interaction between benefit and risk with clear evidence of benefit in both the lowest and highest fifths of the distribution of risk (Fig. 3).

4. Discussion

Our SHIFT Risk Model was constructed from an analysis in patients with systolic HF in sinus rhythm with high levels of the use of current evidence-based medical therapy (79% ACE inhibitors, 14% ARBs, 90% beta-blockers, and 60% mineralocorticoid receptor antagonists) [10]. The parameters in the model are all easy to obtain in routine clinical practice or with simple laboratory tests, and the result is a model that is reasonably good at predicting mortality and morbidity outcomes over 2 years (c-statistic, 67.6% to 69.5%). The best predictors of poor prognosis were resting heart rate, LVEF, creatinine, BMI, NYHA class, duration of HF, age, SBP, history of left bundle branch block, male sex, ischaemic HF, total cholesterol, and history of atrial fibrillation/flutter.

The role of elevated resting heart rate in predicting morbidity and mortality outcomes in patients with systolic HF is well established, and there is a progressive rise in risk as resting heart rate rises above 70 bpm [11,12]. In the SHIFT population, which, by definition, already had a resting heart rate ≥ 70 bpm, every 10-bpm increase in resting heart rate was associated with a 31% increase in the primary composite endpoint, a 26% increase in all-cause mortality, a 27% increase in cardiovascular mortality, and a 32% increase in HF hospitalisation. As an important component of risk, therefore, resting heart rate was also an important parameter in the risk model.

Our analysis also confirms the importance of conventional HF risk factors. Poor outcomes are expected to be more likely in the very elderly and, accordingly, we found that a 10-year increase over the age of 60 years increased the risk for primary composite endpoint by 24%, all-cause mortality by 29%, and HF hospitalisation by 25%. Whether this increase in risk with age is due to greater severity, increasing number of unmeasured comorbidities, or discrepancies in care of elderly HF patients remains unclear [13]. In this context, we also found that patients with long-standing disease were at 7% to 9% higher risk for all four outcomes for each 2 years they have lived with HF. Measures of severity of congestive HF also came out as strong predictors in the SHIFT Risk Model. NYHA class constitutes a clinical measure of symptomatic severity and is known to be a strong predictor of survival in

Table 2
Univariable associations of baseline factors with risk for primary endpoint, all-cause mortality, cardiovascular mortality, and heart failure (HF) hospitalisation.

| Baseline characteristic | Primary outcome | | All-cause mortality | | Cardiovascular mortality | | HF hospitalisation | |
|---|------------------|---------|---------------------|---------|--------------------------|---------|--------------------|---------|
| | HR (95% CI) | p value | HR (95% CI) | p value | HR (95% CI) | p value | HR (95% CI) | p value |
| Age (10 years over 60 years) | 1.32 (1.24–1.41) | <0.001 | 1.34 (1.23–1.45) | <0.001 | 1.30 (1.19–1.42) | <0.001 | 1.33 (1.23–1.44) | <0.001 |
| Male | 1.11 (0.99–1.24) | 0.085 | 1.37 (1.18–1.61) | <0.001 | 1.34 (1.14–1.58) | <0.001 | 0.99 (0.86–1.13) | 0.84 |
| Body mass index (1 kg/m ² below 27.5 kg/m ²) | 1.07 (1.05–1.09) | <0.001 | 1.10 (1.07–1.12) | <0.001 | 1.10 (1.07–1.13) | <0.001 | 1.05 (1.03–1.08) | <0.001 |
| <i>Cardiac parameters</i> | | | | | | | | |
| Heart rate (10-bpm increase) | 1.32 (1.27–1.38) | <0.001 | 1.29 (1.22–1.36) | <0.001 | 1.29 (1.22–1.37) | <0.001 | 1.35 (1.28–1.42) | <0.001 |
| SBP (10-mm Hg decrease) | 1.14 (1.10–1.17) | <0.001 | 1.18 (1.13–1.23) | <0.001 | 1.19 (1.14–1.24) | <0.001 | 1.15 (1.11–1.20) | <0.001 |
| DBP (10-mm Hg decrease) | 1.19 (1.13–1.25) | <0.001 | 1.24 (1.17–1.33) | <0.001 | 1.24 (1.16–1.33) | <0.001 | 1.22 (1.15–1.30) | <0.001 |
| LVEF (5% decrease) | 1.30 (1.25–1.36) | <0.001 | 1.31 (1.24–1.38) | <0.001 | 1.32 (1.25–1.40) | <0.001 | 1.35 (1.28–1.42) | <0.001 |
| <i>Laboratory parameters</i> | | | | | | | | |
| eGFR (10-unit decrease) | 1.11 (1.08–1.13) | <0.001 | 1.10 (1.07–1.13) | <0.001 | 1.10 (1.07–1.13) | <0.001 | 1.13 (1.10–1.16) | <0.001 |
| Creatinine (10-unit increase) | 1.09 (1.07–1.11) | <0.001 | 1.10 (1.08–1.12) | <0.001 | 1.10 (1.08–1.12) | <0.001 | 1.09 (1.07–1.11) | <0.001 |
| Anaemic (Hb ≤120 g/L) | 1.58 (1.37–1.84) | <0.001 | 1.60 (1.33–1.92) | <0.001 | 1.51 (1.24–1.85) | <0.001 | 1.73 (1.45–2.05) | <0.001 |
| ALT (per 10 unit decrease) | 1.08 (1.05–1.12) | <0.001 | 1.09 (1.04–1.15) | <0.001 | 1.10 (1.04–1.15) | <0.001 | 1.08 (1.04–1.13) | <0.001 |
| Total cholesterol: ≤3.4 vs ≥4.5 mmol/L | 1.51 (1.30–1.75) | <0.001 | 1.42 (1.17–1.72) | 0.001 | 1.39 (1.14–1.71) | 0.005 | 1.73 (1.46–2.06) | <0.001 |
| Total cholesterol: 3.41–4.49 vs ≥4.5 mmol/L | 1.14 (1.02–1.26) | | 1.11 (0.97–1.27) | | 1.11 (0.97–1.28) | | 1.23 (1.09–1.40) | |
| Potassium <4.2 vs ≥4.9 mmol/L | 1.04 (0.91–1.19) | <0.001 | 0.99 (0.83–1.18) | 0.006 | 1.01 (0.84–1.21) | 0.002 | 1.03 (0.88–1.21) | 0.003 |
| Potassium 4.2–4.4 vs ≥4.9 mmol/L | 0.73 (0.63–0.84) | | 0.74 (0.62–0.89) | | 0.72 (0.59–0.87) | | 0.75 (0.63–0.90) | |
| Potassium 4.5–4.8 vs ≥4.9 mmol/L | 0.91 (0.80–1.03) | | 0.89 (0.76–1.04) | | 0.87 (0.74–1.03) | | 0.93 (0.80–1.08) | |
| Sodium (per 1 unit decrease) | 1.04 (1.02–1.05) | <0.001 | 1.05 (1.03–1.06) | <0.001 | 1.04 (1.03–1.06) | <0.001 | 1.05 (1.03–1.06) | <0.001 |
| <i>Medical history</i> | | | | | | | | |
| NYHA class III/IV vs II | 1.68 (1.52–1.85) | <0.001 | 1.63 (1.44–1.85) | <0.001 | 1.71 (1.50–1.96) | <0.001 | 1.71 (1.52–1.92) | <0.001 |
| HF duration (2 years increase) | 1.09 (1.07–1.11) | <0.001 | 1.08 (1.06–1.11) | <0.001 | 1.09 (1.07–1.12) | <0.001 | 1.09 (1.07–1.12) | <0.001 |
| Ischaemic heart failure | 1.09 (0.98–1.21) | 0.11 | 1.16 (1.01–1.32) | 0.032 | 1.19 (1.03–1.37) | 0.017 | 1.01 (0.89–1.14) | 0.91 |
| Myocardial infarction | 1.12 (1.02–1.24) | 0.019 | 1.18 (1.04–1.33) | 0.009 | 1.24 (1.08–1.41) | 0.002 | 1.03 (0.92–1.15) | 0.63 |
| Hypertension | 0.91 (0.82–1.00) | 0.051 | 0.86 (0.76–0.97) | 0.016 | 0.82 (0.72–0.93) | 0.003 | 0.90 (0.80–1.01) | 0.080 |
| Diabetes | 1.23 (1.11–1.35) | <0.001 | 1.12 (0.99–1.28) | 0.073 | 1.07 (0.94–1.23) | 0.31 | 1.32 (1.17–1.48) | <0.001 |
| Stroke | 1.43 (1.23–1.67) | <0.001 | 1.48 (1.23–1.79) | <0.001 | 1.42 (1.16–1.74) | <0.001 | 1.42 (1.18–1.71) | <0.001 |
| Atrial fibrillation/flutter | 1.40 (1.20–1.63) | <0.001 | 1.30 (1.07–1.58) | 0.009 | 1.24 (1.00–1.54) | 0.046 | 1.47 (1.23–1.76) | <0.001 |
| Prior coronary surgery | 1.03 (0.90–1.18) | 0.71 | 1.14 (0.99–1.32) | 0.063 | 1.17 (1.01–1.36) | 0.042 | 1.17 (1.00–1.37) | 0.047 |
| History of hyperlipidaemia/dyslipidaemia | 0.87 (0.78–0.96) | 0.009 | 0.73 (0.64–0.85) | <0.001 | 0.74 (0.64–0.86) | 0.001 | 0.93 (0.82–1.05) | 0.25 |
| Chronic obstructive pulmonary disease | 1.55 (1.36–1.77) | <0.001 | 1.38 (1.16–1.63) | <0.001 | 1.31 (1.09–1.57) | 0.004 | 1.71 (1.46–1.99) | <0.001 |
| History of LBBB | 1.65 (1.47–1.86) | <0.001 | 1.49 (1.28–1.74) | <0.001 | 1.49 (1.26–1.75) | <0.001 | 1.86 (1.63–2.14) | <0.001 |
| <i>Treatments</i> | | | | | | | | |
| Beta-blocker | 0.69 (0.60–0.79) | <0.001 | 0.61 (0.51–0.72) | <0.001 | 0.62 (0.52–0.74) | <0.001 | 0.69 (0.58–0.81) | <0.001 |
| Angiotensin-converting enzyme inhibitor | 0.86 (0.77–0.97) | 0.011 | 0.97 (0.83–1.12) | 0.64 | 0.99 (0.84–1.16) | 0.87 | 0.80 (0.70–0.92) | 0.001 |
| Cardiac glycosides | 1.77 (1.60–1.97) | <0.001 | 1.72 (1.51–1.97) | <0.001 | 1.79 (1.56–2.06) | <0.001 | 1.91 (1.69–2.16) | <0.001 |
| Angiotensin II receptor blocker | 1.06 (0.92–1.21) | 0.42 | 0.82 (0.68–0.99) | 0.043 | 0.80 (0.65–0.98) | 0.029 | 1.17 (1.00–1.37) | 0.045 |
| Diuretic | 1.75 (1.51–2.04) | <0.001 | 1.38 (1.15–1.65) | <0.001 | 1.45 (1.19–1.76) | <0.001 | 2.15 (1.76–2.62) | <0.001 |
| Antiarrhythmic medication | 1.66 (1.33–2.08) | <0.001 | 1.69 (1.28–2.22) | <0.001 | 1.65 (1.23–2.21) | <0.001 | 1.68 (1.28–2.19) | <0.001 |
| Mineralocorticoid receptor antagonist | 1.55 (1.40–1.72) | <0.001 | 1.49 (1.30–1.69) | <0.001 | 1.58 (1.38–1.82) | <0.001 | 1.61 (1.42–1.82) | <0.001 |
| Vitamin K antagonist | 1.32 (1.18–1.49) | <0.001 | 1.11 (0.95–1.29) | 0.21 | 1.13 (0.96–1.33) | 0.14 | 1.39 (1.21–1.60) | <0.001 |
| Lipid-lowering medication | 0.76 (0.69–0.83) | <0.001 | 0.70 (0.62–0.79) | <0.001 | 0.68 (0.60–0.78) | <0.001 | 0.76 (0.67–0.85) | <0.001 |
| CRT | 1.95 (1.37–2.79) | <0.001 | 0.73 (0.37–1.47) | 0.38 | 0.62 (0.28–1.38) | 0.24 | 2.75 (1.92–3.96) | <0.001 |
| ICD | 1.57 (1.24–1.98) | <0.001 | 0.85 (0.58–1.25) | 0.42 | 0.85 (0.57–1.27) | 0.43 | 2.22 (1.75–2.83) | <0.001 |
| Ivabradine treatment | 0.82 (0.75–0.90) | <0.001 | 0.91 (0.80–1.02) | 0.11 | 0.91 (0.80–1.03) | 0.15 | 0.75 (0.66–0.84) | <0.001 |

HR = hazard ratio. CI = confidence interval. SBP = systolic blood pressure. DBP = diastolic blood pressure. LVEF = left ventricular ejection fraction. NYHA = New York Heart Association. eGFR = estimated glomerular filtration rate. CRT = cardiac resynchronisation therapy. ICD = Implantable cardioverter defibrillator.

HF [3]. Indeed, in our study, being in NYHA class III/IV, i.e. having moderate to severe symptoms, was associated with a 43% increase in risk for the SHIFT primary composite endpoint versus those who were only mildly symptomatic (NYHA class II). Worsening myocardial function, as recorded by decreased LVEF, is known to predict morbidity and mortality endpoints [14]. In line with this, we found that a reduction of LVEF by 5% led to a 20% increase in risk for the primary composite endpoint.

The inverse relationship between BMI and prognosis in HF is well known, and the so-called “obesity paradox,” by which decreased BMI is associated with poorer outcomes in HF in contrast to the situation in CAD, has been widely discussed in the literature [15–17]. Similar paradoxical relationships are observed for blood pressure and total cholesterol [17–19], insofar as low SBP and/or serum lipoprotein levels are associated with substantially greater risk in HF. Our results are totally in line with this.

Meta-analyses have indicated that renal dysfunction confers a substantially higher risk of mortality than those with normal renal function [20,21]. An increase in creatinine by 10 units was found to be predictive of primary endpoint (6% increase in risk) in the SHIFT Risk Model. Left

bundle branch block and history of atrial fibrillation are also known to affect prognosis in patients with HF [22,23]. Accordingly, we found that the presence of one of these conditions in the SHIFT population was an important contributor of increased risk for the primary outcome. This is in line with the findings from the CHARM database, in which atrial fibrillation was a predictor of outcome, particularly for HF with preserved ejection fraction [24].

In our study, ischaemic aetiology was predictive of mortality outcomes, but not for HF hospitalisation. By contrast, diabetes was predictive only for HF hospitalisation, but not mortality outcomes, and being on ACE inhibitor was univariately associated with lower risk of HF hospitalisation but not mortality; this association was lost in multivariate analysis. Possible explanations for differences when compared to other studies include the more homogeneous cohort recruited in SHIFT, notably since the patients had a relatively high heart rate and higher rates of usage of guideline-recommended cardiovascular medications than patients recruited in other trials.

A number of risk models have been developed in HF [5–7,16,25–27]. Although all the models are helpful, their performance is inconsistent

Table 3

Top 10 multivariable predictors of each of primary composite outcome, all-cause mortality, cardiovascular mortality, and heart failure (HF) hospitalisation (approach excluding baseline therapies).

| Baseline characteristic | Primary outcome | | All-cause mortality | | Cardiovascular mortality | | HF hospitalisation | |
|--|------------------|---------|---------------------|---------|--------------------------|---------|--------------------|---------|
| | HR (95% CI) | p value | HR (95% CI) | p value | HR (95% CI) | p value | HR (95% CI) | p value |
| Randomised treatment | 0.83 (0.75–0.91) | <0.001 | – | – | – | – | 0.74 (0.66–0.83) | <0.001 |
| Heart rate (10-bpm increase) | 1.31 (1.25–1.36) | <0.001 | 1.26 (1.20–1.34) | <0.001 | 1.25 (1.18–1.33) | <0.001 | 1.32 (1.26–1.40) | <0.001 |
| LVEF (5% decrease) | 1.20 (1.15–1.26) | <0.001 | 1.19 (1.13–1.26) | <0.001 | 1.22 (1.15–1.30) | <0.001 | 1.23 (1.17–1.29) | <0.001 |
| Creatinine (10-unit increase) | 1.06 (1.04–1.08) | <0.001 | 1.07 (1.05–1.10) | <0.001 | 1.09 (1.07–1.12) | <0.001 | 1.06 (1.04–1.08) | <0.001 |
| BMI (1-kg/m ² decrease below 27.5 kg/m ²) | – | – | 1.06 (1.04–1.09) | <0.001 | 1.07 (1.04–1.10) | <0.001 | – | – |
| NYHA class III/IV vs II | 1.43 (1.30–1.59) | <0.001 | 1.40 (1.23–1.59) | <0.001 | 1.44 (1.25–1.65) | <0.001 | 1.42 (1.26–1.61) | <0.001 |
| Duration of heart failure (2-year increase) | 1.07 (1.05–1.09) | <0.001 | 1.07 (1.04–1.09) | <0.001 | 1.09 (1.06–1.11) | <0.001 | 1.08 (1.05–1.10) | <0.001 |
| Age (10-year increase over age 60) | 1.24 (1.15–1.33) | <0.001 | 1.29 (1.17–1.41) | <0.001 | – | – | 1.25 (1.15–1.37) | <0.001 |
| SBP (10-mm Hg decrease) | 1.10 (1.06–1.13) | <0.001 | 1.12 (1.08–1.17) | <0.001 | 1.13 (1.08–1.18) | <0.001 | 1.11 (1.07–1.15) | <0.001 |
| History of left bundle branch block | 1.43 (1.27–1.62) | <0.001 | 1.28 (1.10–1.50) | 0.002 | 1.29 (1.09, 1.52) | 0.003 | 1.63 (1.42–1.88) | <0.001 |
| Male | – | – | 1.43 (1.21–1.68) | <0.001 | – | – | – | – |
| Ischaemic heart failure | – | – | – | – | 1.39 (1.20–1.62) | <0.001 | – | – |
| Total cholesterol ≤3.4 vs ≥4.5 mmol/L | 1.42 (1.22–1.66) | <0.001 | – | – | – | – | 1.57 (1.31–1.88) | <0.001 |
| Total cholesterol 3.41–4.49 vs ≥4.5 mmol/L | 1.11 (1.00–1.23) | – | – | – | – | – | 1.20 (1.05–1.36) | – |
| Atrial fibrillation/flutter | 1.35 (1.15–1.57) | <0.001 | – | – | – | – | – | – |
| Diabetes | – | – | – | – | – | – | 1.26 (1.12–1.43) | <0.001 |
| History of hyperlipidaemia/dyslipidaemia | – | – | – | – | 0.77 (0.66–0.90) | <0.001 | – | – |
| c-Statistic | 67.6% | – | 67.7% | – | 68.3% | – | 69.5% | – |
| p (lack of fit) | 0.10 | – | 0.017 | – | 0.54 | – | 0.07 | – |

Dashes (–) reflect variables not included in the model. HR = hazard ratio. CI = confidence interval. BMI = body mass index. LVEF = left ventricular ejection fraction. SBP = systolic blood pressure. NYHA = New York Heart Association.

[26] and many are overly complex for routine clinical practice. Moreover, insofar as the use of contemporary therapies may affect the utility of the models, there is a need for models constructed in contemporary environments using parameters that are easily measured at the bedside [28]. The SHIFT Risk Score constitutes a simple solution for patient with higher heart rates, and is now accessible on the internet (www.shift-study.com), with full details of the computation of risk probabilities so that these can readily be programmed into local clinical systems. Our findings can therefore be used in routine clinical practice to provide a measure of the mortality risk for the individual patient.

The main limitation to our study is that it is restricted by the profile of the patients included in the SHIFT trial, i.e. patients with chronic HF in

sinus rhythm and with a resting heart rate ≥70 bpm. The model can predict outcomes over 2 years, i.e. the duration of the SHIFT follow-up, extrapolation beyond the SHIFT-type patient and longer follow-up may be unreliable. A number of potentially important variables are missing from the model, such as N-terminal pro-brain natriuretic peptide, since the data were not available. Incorporation of such information is likely to improve the goodness of fit of the models for the primary outcome and hospitalisation for HF. However, we note that the goodness of fit for predicting these outcomes was significantly improved in the more complex models presented in Appendix B. We have not yet tested the risk model outside the realms of the SHIFT population. Prospective validation in other populations would provide important additional information.

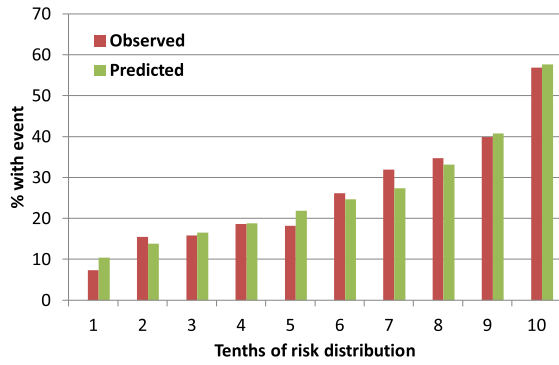
Table 4

Top 10 multivariable predictors of the primary outcome, all-cause mortality, cardiovascular mortality, and heart failure (HF) hospitalisation (approach including baseline therapies).

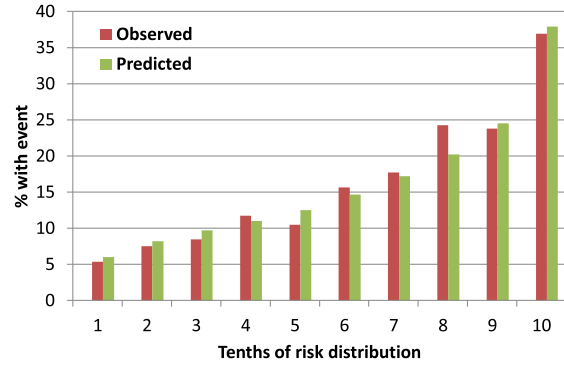
| Baseline characteristic | Primary outcome | | All-cause mortality | | Cardiovascular mortality | | HF hospitalisation | |
|--|------------------|---------|---------------------|---------|--------------------------|---------|--------------------|---------|
| | HR (95% CI) | p value | HR (95% CI) | p value | HR (95% CI) | p value | HR (95% CI) | p value |
| Randomised treatment | 0.81 (0.74–0.89) | <0.001 | – | – | – | – | 0.73 (0.65–0.82) | <0.001 |
| Heart rate (10-bpm increase) | 1.29 (1.24–1.35) | <0.001 | 1.26 (1.19–1.34) | <0.001 | 1.24 (1.17–1.31) | <0.001 | 1.31 (1.24–1.38) | <0.001 |
| Ejection fraction (5% decrease) | 1.19 (1.14–1.24) | <0.001 | 1.21 (1.14–1.28) | <0.001 | 1.23 (1.16–1.30) | <0.001 | 1.21 (1.15–1.27) | <0.001 |
| Creatinine (10-unit increase) | 1.07 (1.05–1.09) | <0.001 | 1.08 (1.06–1.11) | <0.001 | 1.10 (1.08–1.13) | <0.001 | 1.07 (1.05–1.09) | <0.001 |
| BMI (1-kg/m ² decrease below 27.5 kg/m ²) | – | – | 1.06 (1.03–1.09) | <0.001 | 1.08 (1.05–1.10) | <0.001 | – | – |
| NYHA class III/IV vs II | 1.40 (1.27–1.55) | <0.001 | 1.34 (1.18–1.53) | <0.001 | 1.36 (1.19–1.56) | <0.001 | 1.40 (1.24–1.58) | <0.001 |
| Duration of heart failure (2-year increase) | 1.07 (1.05–1.09) | <0.001 | 1.07 (1.04–1.09) | <0.001 | 1.09 (1.06–1.11) | <0.001 | 1.08 (1.05–1.10) | <0.001 |
| Age (10-year increase over age 60) | 1.28 (1.19–1.37) | <0.001 | 1.24 (1.13–1.36) | <0.001 | – | – | 1.28 (1.18–1.40) | <0.001 |
| SBP (10-mm Hg decrease) | – | – | 1.12 (1.07–1.17) | <0.001 | – | – | – | – |
| History of left bundle branch block | 1.38 (1.22–1.56) | <0.001 | – | – | – | – | 1.55 (1.35–1.79) | <0.001 |
| Male | – | – | – | – | – | – | – | – |
| Ischaemic heart failure | – | – | 1.36 (1.17–1.57) | <0.001 | 1.64 (1.40–1.93) | <0.001 | – | – |
| Total cholesterol ≤3.4 vs ≥4.5 mmol/L | 1.46 (1.26–1.70) | <0.001 | – | – | – | – | 1.69 (1.41–2.01) | <0.001 |
| Total cholesterol 3.41–4.49 vs ≥4.5 mmol/L | 1.14 (1.03–1.27) | – | – | – | – | – | 1.25 (1.10–1.42) | – |
| Atrial fibrillation/flutter | – | – | – | – | – | – | – | – |
| Cardiac glycosides | 1.45 (1.30–1.62) | <0.001 | 1.51 (1.31–1.73) | <0.001 | 1.47 (1.27–1.70) | <0.001 | 1.52 (1.34–1.73) | <0.001 |
| Mineralocorticoid receptor antagonist | 1.41 (1.27–1.57) | <0.001 | – | – | 1.42 (1.23–1.64) | <0.001 | 1.44 (1.27–1.64) | <0.001 |
| Lipid-lowering medication | – | – | – | – | 0.71 (0.62–0.82) | <0.001 | – | – |
| c-Statistic | 68.3% | – | 68.2% | – | 69.0% | – | 70.2% | – |
| P (lack of fit) | 0.005 | – | 0.11 | – | 0.47 | – | <0.001 | – |

Dashes (–) reflect variables not included in the model. HR = hazard ratio. CI = confidence interval. BMI = body mass index. LVEF = left ventricular ejection fraction. SBP = systolic blood pressure. NYHA = New York Heart Association.

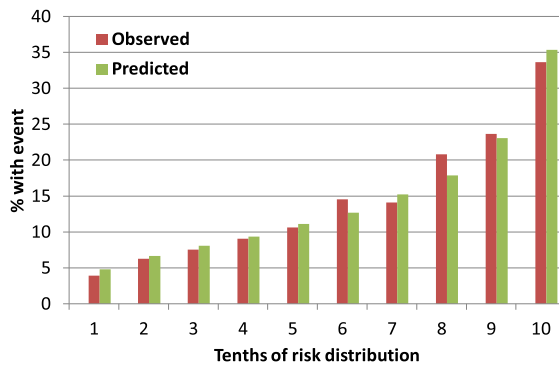
A: Primary Outcome



B: All-Cause Mortality



C: Cardiovascular Mortality



D: HF Hospitalisation

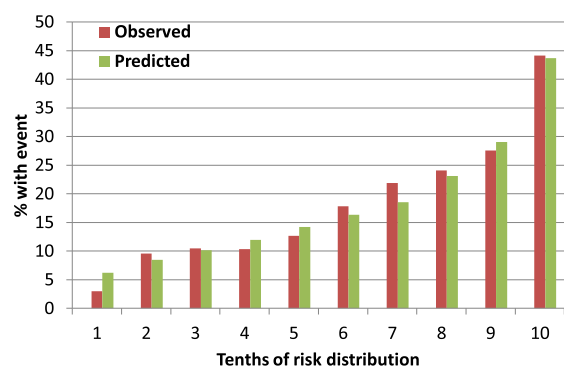


Fig. 1. Observed and predicted risk for primary outcome (A), all-cause mortality (B), cardiovascular mortality (C), and heart failure (HF) hospitalisation (D) by tenths of the distribution of predicted risk (approach excluding baseline therapies).

In conclusion, a risk model using simple, readily obtainable clinical characteristics can provide important prognostic information in patients with chronic HF and systolic dysfunction. The SHIFT Risk Models provide valuable information for clinical decision-making and can support the delivery of appropriate therapy to the patients for whom the benefits are likely to be the greatest.

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Conflict of interest

Ian Ford has received research grants and honoraria for appearing on a steering committee from Servier. Michele Robertson reports no relationships that could be construed as a conflict of interest. Michel Komajda has been on the Speaker's Bureau for Servier and Menarini and the executive committee of SHIFT. Michael Böhm has been on the Speaker's Bureau for AstraZeneca, AWD Dresden, Bayer, Boehringer Ingelheim, Berlin-Chemie, Daiichi-Sankyo, MSD, Novartis, Sanofi-Aventis, and Servier; and on Advisory Boards for AstraZeneca, Bayer AG, Boehringer Ingelheim, Daiichi-Sankyo, MSD, Novartis, Pfizer-

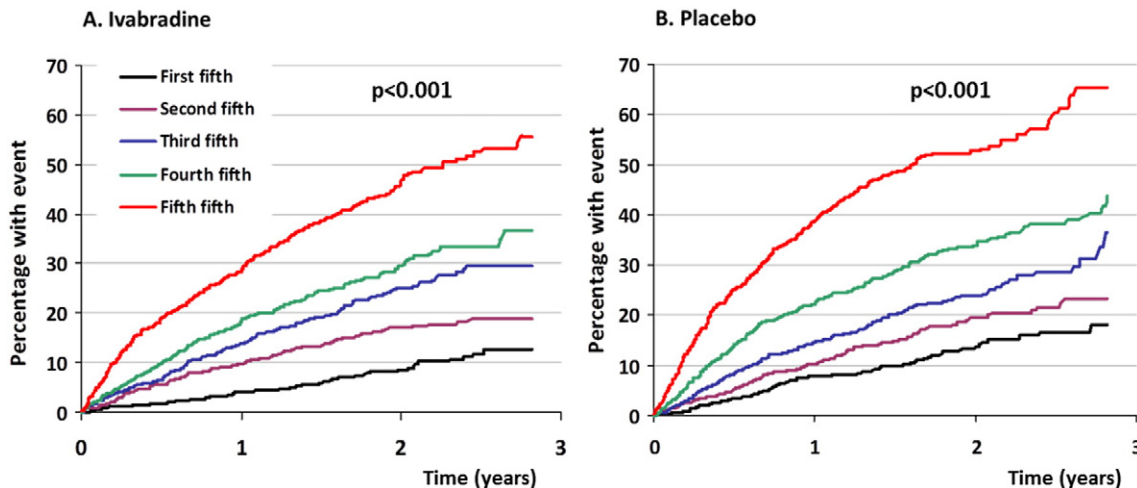


Fig. 2. Kaplan–Meier time to primary endpoint plots for patients split by fifths of the distribution of risk separately in the ivabradine and placebo groups (patients in the highest fifth are at highest baseline risk) for the model including therapies.

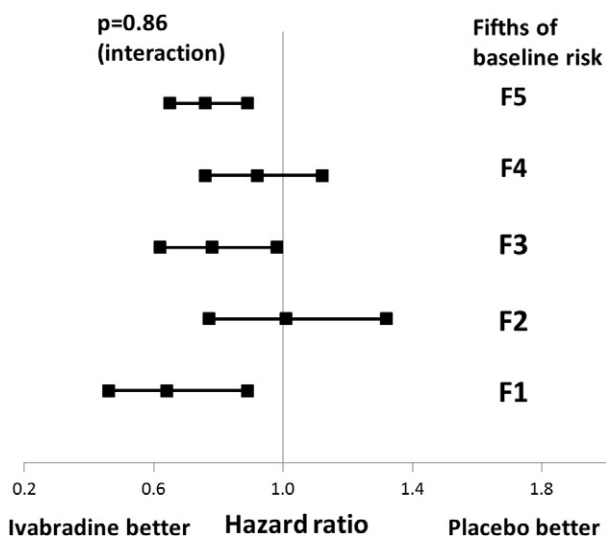


Fig. 3. Hazard ratios and 95% confidence intervals for the effect of ivabradine versus placebo on the primary endpoint by fifths of the distribution of baseline risk (denoted by F1 to F5, with F5 being the highest risk), based on the best 10 models including baseline therapies.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ijcard.2015.02.001>.

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