Title: Relationship between heart rate and outcomes in patients in sinus rhythm or atrial fibrillation with heart failure and reduced ejection fraction.

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ABSTRACT

Aims: To investigate the relationship between heart rate and outcomes in heart failure and reduced ejection fraction (HFrEF) patients in sinus rhythm (SR) and atrial fibrillation (AF) adjusting for natriuretic peptide concentration, a powerful prognosticator.

Methods and Results: Of 13,562 patients from two large HFrEF trials, 10,113 (74.6%) were in SR and 3449 (25.4%) in AF. The primary endpoint was the composite of cardiovascular death or HF hospitalization. Heart rate was analysed as a categorical (tertiles, T1-3) and continuous variable (per 10-beats per minute [bpm]), separately in patients in SR and AF. Outcomes were adjusted for prognostic variables, including N-terminal prohormone of B-type natriuretic peptide (NT-proBNP), and also examined using change from baseline heart rate to one year (≤-10-bpm, ≥+10-bpm, <±10-bpm).

SR patients with a higher heart rate had worse symptoms and quality of life, more often had diabetes and higher NT-proBNP concentrations. They had higher risk of the primary endpoint (T3 vs. T1 adjusted-hazard ratio [HR] 1.50; 95% confidence interval [CI] 1.35–1.66; p<0.001; per 10-bpm 1.12, 1.09-1.16; p<0.001). In SR, heart rate was associated with a relatively higher risk of pump failure than sudden death: adjusted-HR per 10-bpm 1.17 (1.09-1.26; p<0.001) vs. 1.07 (1.02-1.13; p=0.011), respectively. Heart rate was not predictive of any outcome in AF.

Conclusions: In HFrEF, an elevated heart rate was an independent predictor of adverse cardiovascular outcomes in patients in SR, even after adjustment for NT-proBNP. There was no relationship between heart rate and outcomes in AF.

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INTRODUCTION

In heart failure with reduced ejection fraction (HFrEF) elevated resting heart rate is associated with higher morbidity and mortality in patients in sinus rhythm.[1–5] Furthermore, in these patients, heart rate has been demonstrated to be a modifiable risk factor using ivabradine, an inhibitor of the sinus node I_f current which has the sole pharmacological effect of lowering heart rate.[6] However, some questions remain regarding the relationship between heart rate and outcomes in HFrEF patients in sinus rhythm. Existing analyses did not adjust for natriuretic peptide concentration, which is the single most powerful predictor of outcome in HF and natriuretic peptide levels are higher in patients with a higher heart rate.[7] The prior studies were also too small to examine the relationship between heart rate and the major modes of death in HFrEF i.e. sudden death and death due to worsening HF. Finally, little is known about how *change* in heart rate relates to outcomes.

The relationship between heart rate and outcomes for HFrEF patients in atrial fibrillation (AF) is not as well studied or as clear-cut. AF is frequent in HFrEF and becomes more common as HF severity worsens.[8] Although several *post-hoc* analyses of trial and observational cohorts have reported no relationship between heart rate and outcomes in HFrEF and AF, these studies have a number of limitations.[3,5,9–13] For example, not all differentiated between history of AF and AF documented on an ECG at time of enrolment. This is relevant for a number of reasons, including the recent finding that only paroxysmal and new-onset AF, but not permanent or persistent AF, are associated with worse outcomes in patients with HFrEF.[14] More importantly, none of these prior studies included routine measurement of natriuretic peptides, which are elevated further in patients with AF, compared to those in sinus rhythm.[15] Existing studies cannot, therefore, reliably tell whether resting ventricular rate is an independent predictor of adverse cardiovascular outcomes in

patients with HFrEF and AF. Neither can these studies provide a like-with-like comparison of the relationship between ventricular rate and outcomes in patients in AF and sinus rhythm, which needs to take account of differing levels of natriuretic peptides in these two groups. As in patients in sinus rhythm, little is known about how change in heart rate relates to outcomes.

We therefore examined the association between baseline resting ventricular rate (hereafter referred to as "heart rate") and outcomes in two large, international, multicentre, contemporary, randomized clinical trials in patients with HFrEF using rhythm determined by a baseline ECG and adjusting for N-terminal prohormone of B-type natriuretic peptide (NT-pro BNP) concentration.

METHODS

Study population and procedures

The design, baseline characteristics and results of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) and Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure (ATMOSPHERE) trials have been published in detail previously.[16–21] Both trials were approved by the ethics committee at each study centre and all patients provided written informed consent.

The inclusion criteria for PARADIGM-HF and ATMOSPHERE were broadly similar. In brief, patients were eligible for inclusion if they were ≥18 years of age, were New York Heart Association (NYHA) functional class II to IV, had a left ventricular ejection fraction (LVEF) ≤35% (changed from ≤40% initially in the PARADIGM-HF trial by amendment) and had elevated natriuretic peptide levels (cut-off was independent of the presence or not of atrial fibrillation). Prior to screening, treatment with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker at a dose equivalent to enalapril 10 mg daily for at least 4 weeks was mandatory, along with a beta-blocker (unless contraindicated or not tolerated) and a mineralocorticoid receptor antagonist, if indicated. Exclusion criteria at screening included symptomatic hypotension or systolic blood pressure <95 mm Hg (<90 mm Hg in the ATMOSPHERE trial), estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2 (<35 ml/min/1.73 m^2 in the ATMOSPHERE trial), and potassium >5.4 mmol/l (>5.2 mmol/l in the ATMOSPHERE trial).

Both trials involved a sequential run-in period where baseline therapy with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker was stopped and patients first

received enalapril followed by sacubitril/valsartan in the PARADIGM-HF trial and enalapril followed by the combination of enalapril plus aliskiren in the ATMOSPHERE trial. Patients who tolerated the target doses of the drugs were then randomly assigned to double-blind therapy with sacubitril/valsartan 97/103mg BID or enalapril 10mg BID in a 1:1 ratio in the PARADIGM-HF trial or enalapril 10mg BID, aliskiren 150mg OD (increased to 300mg OD after two weeks if tolerated), or both drugs in a 1:1:1 ratio in the ATMOSPHERE trial.

In the two trials, investigators were asked to report on the heart rhythm from the baseline electrocardiograph (ECG) along with the ECG recorded heart rate. For the purposes of this analysis, the small number of patients with atrial flutter are included along with those patients with AF on their baseline ECG. Patients who were recorded as having a paced rhythm on their baseline ECG were excluded from this analysis.

Outcomes

The primary outcome of both trials was a composite of time to first occurrence of cardiovascular (CV) death or HF hospitalization. In this analysis, we investigated the association between baseline heart rate and the risk of the primary outcome, each of its components, sudden death, pump failure death and death from any cause. We performed these analyses separately in those patients with sinus rhythm and those with AF on baseline ECG. All endpoints were adjudicated by the same clinical endpoint committee according to prespecified criteria.

Statistical analysis

Baseline characteristics are presented by groups defined by heart rate tertile (calculated separately for AF and sinus rhythm), with mean ± standard deviation or median (interquartile

range) for continuous variables and frequency and percentage for categorical variables. Differences in baseline characteristics according to heart rate tertile from baseline ECG recorded heart rate distribution were assessed with a test for trend by means of variance weighted least square regression for continuous variables and with a nonparametric test for trend for categorical variables.[22] Differences in baseline characteristics according to baseline heart rhythm were assessed using the chi-square test for categorical variables and analysis of variance (ANOVA) or Kruskal–Wallis test for continuous variables.

Incidence rates for the outcomes are presented per 100 person-years. Time to event curves are presented by tertiles of baseline ECG recorded heart rate, estimated using the Kaplan-Meier method and compared using the log-rank test. Cumulative incidence functions for the endpoints of interest were calculated accounting for the competing risks of all-cause death and non-CV death. No significant differences were observed, therefore Kaplan-Meier estimates are presented. Hazard ratios (HRs) with 95% confidence intervals (CIs) of outcomes according to heart rate tertiles were calculated using Cox proportional hazard models using tertile 1 as the referent. A sensitivity analysis was performed using the calculated sinus rhythm heart rate tertiles in those patients in AF on baseline ECG.
Heart rate was also modelled as a continuous variable with hazard ratios and 95% CIs presented for 10 beats per minute (bpm) increments. This relationship is presented graphically in a linear model with the hazard ratios relative to a baseline heart rate of 80bpm (chosen on the basis of the Rate Control Efficacy in Permanent Atrial Fibrillation: a Comparison between Lenient versus Strict Rate Control II [RACE II] trial).[23] The presence of any interaction between heart rate and rhythm on outcomes was tested.

Models were adjusted for randomized treatment (enalapril, sacubitril/valsartan, aliskiren, or combination of enalapril and aliskiren), and the following baseline characteristics: age, sex, race, geographical region, NYHA functional class, LVEF, systolic blood pressure, body mass index, eGFR, duration of HF, history of HF hospitalization, history of myocardial infarction, history of diabetes, history of stroke, treatment with digoxin, treatment with beta-blockers, treatment with amiodarone and log NT pro-BNP. Data for NT-proBNP at baseline was missing in 12 and 593 patients in the analysis from PARADIGM-HF and ATMOSPHERE respectively. For the 593 patients in ATMOSPHERE, imputed values were used as calculated for the original primary trial analysis and detailed in the trial protocol.[21,24] The proportional hazards assumption was examined using log (-log(survival)) curves and was found to valid for all models. A sensitivity analysis was performed for the primary composite outcome and the outcome of sudden cardiac death with the addition of covariates indicating treatment with mineralocorticoid receptor antagonists and the use of implantable cardioverter defibrillators and/or cardiac resynchronisation therapy to the adjusted Cox models. The addition of these covariates did not significantly alter the results presented (data not shown). A further sensitivity analysis including patients with a paced rhythm on baseline ECG who had a cardiac resynchronisation therapy device did also not significantly influence the results (data not shown).

The association between change in heart rate over time and outcomes was explored for patients who had ECGs at both baseline and 12-months and who remained in the same rhythm as their baseline ECG. Three groups were identified; those whose heart rate increased by 10 bpm or more, those whose heart rate decreased by 10 bpm or more and those whose heart rate increased or decreased by less than 10 bpm. Outcomes were analysed using Cox proportional hazard models for events occurring at least 12 months following randomization

and adjusted for the same baseline characteristics as detailed above and baseline heart rate, with the referent group being those with a less than 10 bpm change in ECG recorded heart rate over 12 months. The proportion of patients reporting a clinically meaningful change in KCCQ clinical summary score (5 or more points) and mean difference in NT-pro BNP (only available for patients enrolled in ATMOSPHERE) at 12 months were calculated and compared between the three groups using the same statistical methods as for baseline characteristics detailed above.

All P-values are two-sided and a P-value of <0.05 was considered significant. Analyses were performed using Stata version 15.1 (StataCorp, College Station, Texas, United States of America).

RESULTS

Of the 15,145 patients randomized in both trials, 1715 (11.1%) patients were reported to have a paced ECG rhythm and were excluded from this analysis (Supplemental Figure 1). An additional 138 (0.9%) had either no baseline ECG recorded or missing heart rate data. 13,562 patients remained, of which 3449 (25.4%) and 10,113 (74.6%) were reported as having a baseline ECG rhythm of AF and sinus rhythm, respectively.

Baseline characteristics

The distribution of ECG recorded baseline heart rate for patients in sinus rhythm and those in AF is displayed in Supplemental Figure 2. The mean heart rate was higher in patients with AF (79.9 bpm ± 17.2) compared to those in sinus rhythm (70.1 bpm ± 13.1; $p<0.001$). Tertiles for baseline heart in AF were calculated as follows: tertile 1 (T1) ≤72 bpm, tertile 2 (T2) 73-85 bpm, and tertile 3 (T3) ≥86 bpm. The corresponding rates for patients in sinus rhythm were: ≤63 bpm, 64-75 bpm and ≥76 bpm.

Baseline characteristics are summarised in Supplemental Table 1 according to heart rate tertiles and baseline ECG heart rhythm. The differences between those with sinus rhythm or AF at baseline are summarised in Supplemental Table 2. Irrespective of heart rhythm, patients with a lower heart rate were more commonly male, older, had a lower eGFR, reported less severe NYHA functional class symptoms, had a longer duration of HF, were less likely to have been hospitalised for HF and more often had an ischaemic aetiology. Treatment with digoxin was less common in the lowest tertile of heart rate but amiodarone was used more commonly, and these patients were more likely to have an implantable cardioverter defibrillator (ICD). The use of diuretics was more common in the highest tertile of heart rate in patients with sinus rhythm whereas no significant difference between tertiles

was seen in AF. In sinus rhythm but not AF, beta-blocker use was highest in the lowest heart rate tertile (T1 vs. T3 93.9% vs 89.0%, p<0.001). Lower baseline heart rate was associated with a higher LVEF in sinus rhythm but not in AF.

N-terminal prohormone of B-type natriuretic peptide

NT-proBNP concentration increased from the lowest to highest tertile of heart rate in patients with sinus rhythm (p<0.001), whereas in AF there was a trend to *lower* levels of NT-proBNP with a *higher* heart rate, but this did not reach statistical significance (p=0.06).

Kansas City Cardiomyopathy Questionnaire

In both AF and sinus rhythm, a lower heart rate was associated with a higher (better) Kansas City Cardiomyopathy Questionnaire (KCCQ) score (p<0.001 in both).

Clinical outcomes according to heart rate tertile

Sinus rhythm

The risk of all outcomes was significantly higher in patients with a higher heart rate on their baseline ECG (Figure 1 and Supplemental table 3). This elevated risk remained significant for all outcomes after adjustment for other prognostic variables (Figure 2 and Supplemental table 3). The greatest relative risk was observed for pump failure death where there was a 70% greater risk of this mode of death in those in the highest heart rate tertile compared to the lowest (adjusted hazard ratio [HR] 1.70; 95% confidence interval [CI] 1.30-2.22; p<0.001). The corresponding adjusted HR for sudden death was 1.28; 95%CI 1.06-1.54; p=0.011.

Atrial fibrillation

In patients with AF on their baseline ECG, only the risk of pump failure death differed according to heart rate, with a *lower* risk in the upper two heart rate tertiles compared to the lowest tertile (T2 unadjusted HR 0.67; 95% CI 0.47-0.97; p=0.035 and T3 unadjusted HR 0.67; 95% CI 0.46-0.96; p=0.031). However, this risk was not significant after adjustment for prognostic variables (Figure 2 and Supplemental table 3). The risk of all other outcomes was not significantly different between tertiles of heart rate (Figures 1, 2 and Supplemental table 3). Similar results were found in a sensitivity analysis for patients with AF at baseline using the sinus rhythm tertile heart rate ranges (Supplemental Table 4).

Clinical outcomes using heart rate as a continuous variable

Sinus rhythm

When modelled as a continuous variable, a 10 bpm increase in baseline heart rate was associated with a significantly higher risk of all outcomes for patients in sinus rhythm, even after adjustment for other prognostic variables (Table 1). This ranged from a 7% higher risk of sudden death (adjusted HR 1.07; 95% CI 1.02-1.13; p=0.011) to a 17% higher risk of pump failure death (adjusted HR 1.17; 95% CI 1.09-1.26; p<0.001). The risk of HF hospitalization was 13% higher per 10 bpm increase in heart rate (adjusted HR 1.13; 95% CI 1.09-1.18; p<0.001). The risk of each of cardiovascular and all-cause mortality was also significantly higher per 10 bpm increase - by 11% and 12%, respectively, after adjustment for prognostic variables.

Atrial fibrillation

In AF, there was no association between a 10 bpm increase in baseline heart rate and any of the outcomes of interest after adjustment for other prognostic variables (Table 1). There was

a significant interaction for all outcomes between baseline heart rhythm (sinus rhythm or AF) and baseline heart rate as a continuous variable (Table 1).

Relationship between change in heart rate at 12 months following randomization and outcomes

Data on heart rate and rhythm recorded on ECG at 12 months were available for 10260 patients (75.7%) who remained in the same rhythm as on baseline ECG. Of these, 7756 (75.6%) were in sinus rhythm and 2504 (24.4%) in AF.

Sinus rhythm

Mean heart rate at twelve months in patients in sinus rhythm was 0.7 bpm higher than at baseline (70.0 bpm vs. 69.3 bpm, $p<0.001$). For most patients in sinus rhythm (4943 [63.7%]), heart rate differed by less than 10 bpm from baseline. Heart rate was lower than baseline by at least 10 bpm in 1274 patients (16.4%) and higher by 10 bpm or more in 1539 (19.8%).

The associations between change in heart rate and outcomes occurring after 12 months of follow-up are reported in Table 2. In sinus rhythm, the risk of all outcomes examined, except sudden cardiac death, was significantly higher in those with an increase in heart rate of 10 bpm or more, compared to those whose rate increased by less than 10 bpm or decreased. A lower risk of the primary composite endpoint (and HF hospitalization) was observed in those with a HR decrease of at least 10 bpm by 12 months of follow-up. All other endpoints showed similar trends, but these were not statistically significant.

An increase in heart rate of 10bpm or more at 12 months in patients in sinus rhythm was associated with a mean increase of NT-pro BNP of 424 pg/ml (SD 2754), whereas a decrease in heart rate of 10bpm or more was associated with a fall of 414 pg/ml (SD 2271), p for trend <0.001 (Table 3). A greater proportion of patients with a reduction in heart rate of at least 10 bpm reported a clinically meaningful increase in the KCCQ clinical summary score at twelve months. Conversely, a greater proportion of patients with an increase in heart rate of 10 bpm or more reported a reduction in the KCCQ clinical summary score of at least 5 points (p for trend <0.001).

Atrial fibrillation

In patients with AF, baseline heart rate was 79.9 bpm and 80.5 bpm at 12 months (p=0.05). In patients with AF at 12 months, 1217 (48.6%) had a difference of less than 10 bpm, 611 (24.4%) had a lower heart rate (at least 10 bpm lower) and 676 (27.0%) had an increase of at least 10 bpm. Similar trends were seen for a higher risk in those experiencing an increase in heart rate and a lower risk associated with a reduction in heart rate, although only some of these were statistically significant: an increase in heart rate was associated with a higher risk of the composite primary endpoint, HF hospitalization and pump failure death; a reduction in heart rate and a lower risk of all-cause mortality.

The changes in NT-pro BNP levels and KCCQ clinical summary score associated with changes in heart at 12 months seen in patients with AF were similar to those described above in patients in sinus rhythm (Table 3).

DISCUSSION

This analysis from the PARADIGM-HF and ATMOSPHERE trials is to our knowledge, the first to describe the relationship between baseline heart rate and cardiovascular outcomes in patients with chronic, ambulatory, HFrEF in both sinus rhythm and AF, where risk was adjusted for natriuretic peptide levels. Additional unique features of our study are that we had an assessment of health-related quality of life in all participants at baseline and that our dataset was large enough to examine both major modes of death in patients with HFrEF i.e. sudden death and death due to pump failure.

Although many adverse prognostic findings were more common at baseline in patients in sinus rhythm with higher heart rates, heart rate remained a predictor of outcome after adjustment for these differences. We also observed that higher heart rate was associated with higher natriuretic peptide concentration in these individuals. However, the prognostic importance of an elevated heart rate persisted even after additional adjustment for natriuretic peptide levels, confirming that heart rate is a robust, independent, marker of adverse outcomes in HFrEF patients in sinus rhythm.

Another important finding was that, in patients in sinus rhythm, an elevated heart rate was associated with a relatively higher risk of death from progressive pump failure than with sudden death, although the risk of both modes of death was higher in patients with a higher heart rate (adjusted hazard ratio per 10 bpm increase in heart rate: 1.17 [95% CI 1.09-1.26] vs. 1.07 [1.02-1.13]). This relatively stronger association between heart rate and pump failure, compared with sudden death was also seen in our analysis of change in heart rate. It is of interest, therefore, that in the Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial (SHIFT), pump failure death was reduced significantly by ivabradine (HR

0·74; 95% CI 0·58–0·94, p=0·014) whereas sudden death was not (HR 1.05; 95% CI 0·87–1.26, p=0·63).[6] Collectively, these findings suggest that the purported beneficial effects of a lower heart rate, including myocardial energy conservation, improved coronary blood flow secondary to diastolic prolongation, as well as an improvement in the positive force–frequency relationship (Bowditch effect), have more impact on worsening pump function.[25,26] These findings also point to an additional effect of beta-blockers beyond heart rate lowering, as beta-blockers also lead to a substantial reduction in sudden death. This suggests that increased adrenergic activity increases the risk of ventricular arrhythmias independently of increasing heart rate and that reduction in sudden death is a non-heart rate-related benefit from beta-blockade.

Our findings related to heart failure hospitalization (lower risk in patients with a lower heart rate) and quality of life (better KCCQ clinical summary score in patients with a lower heart rate) are also consistent with the benefits of heart rate reduction in HFrEF patients in sinus rhythm demonstrated in SHIFT.[27] The findings of our analysis of change in heart rate were also consistent with SHIFT and a post-hoc analysis of the CHARM (candesartan in heart failure: assessment of reduction in mortality and morbidity) program.[2,6,28] Specifically, in SHIFT, a mean overall placebo-corrected reduction in heart rate of 9.1 bpm with ivabradine at 1 year was associated with a 18% reduction in risk of the primary composite endpoint; in our analysis a decrease in HR of 10 bpm at 1 year was associated with a 26% lower risk of the same outcome. In the placebo group in SHIFT, a 5 bpm increase in heart rate was associated with a 16% higher risk of the primary composite outcome and in our study a 10 bpm increase was associated with a 52% higher risk.[2] Furthermore, our observation that a reduction in heart rate was associated with a greater proportion of patients reporting improvements in quality of life, as measured by KCCQ clinical summary score, is similar to

that observed in SHIFT.[27] Additionally, we report that a decrease in heart rate was accompanied by a reduction in NT-pro BNP levels.

In contrast to what we observed in patients in sinus rhythm, ventricular rate was of no prognostic import in those with AF on their baseline ECG. It has been suggested that this discrepancy may be explained by any benefit of heart rate reduction in AF being offset by an increase in risk related to the use of heart rate lowering drugs in these patients. The two principal concerns are that such treatments may aggravate atrioventricular conduction disease and worsen haemodynamic status in patients reliant on a higher ventricular rate to maintain cardiac output in the face of loss of the "atrial-kick".[29] On the other hand, we found that quality of life (as measured by the KCCQ clinical summary score) was better in patients with a lower ventricular rate and this finding was supported by examination of NYHA functional class. Moreover, we found that an increase in ventricular rate over time in patients with AF was associated with worse outcomes as previously reported in an analysis of the CHARM programme.[28] An increase in ventricular rate was accompanied by an increase in NT-pro BNP level and a deterioration in quality of life. This suggests that the relationship between ventricular rate and health status in HFrEF patients with AF is more complex than perhaps previously appreciated. It is even possible that achieving the optimum ventricular rate in HFrEF patients with AF may involve a trade-off between symptom control and risk of death and hospitalization. Of course, our findings are observational in nature and this complicated and important clinical question is yet to be addressed in an adequate randomized clinical trial of rate control targets in patients with HFrEF and AF. Indeed, the resultant lack of evidence is reflected in the discrepancy between US guidance which advocates a target resting ventricular rate <80 bpm ,the European guidelines for AF which suggest a target of <110 bpm based on the RACE-II trial, although the few patients in that trial with HF

predominantly had HFpEF, and the European guidelines for HF which suggest that a target of 60-100bpm in patients with AF and HF may be preferable.[23,30–32]

STRENGTHS AND LIMITATIONS

The main strength of this study is its size, global nature and high levels of contemporary therapy, allowing generalisation of the results to a large proportion of HFrEF patients similar to those included in these trials. All study outcomes in both trials were adjudicated by the same clinical endpoint committee. The use of ECG reported heart rate negates issues with reliability in the manual recording of ventricular rate in AF. Additionally, the number of patients with missing data for NT-proBNP was small allowing for multivariable-adjusted models in almost the entire cohort after imputation for the 593 patients with missing data from the ATMOSPHERE trial (no imputation was performed for the 12 patients with missing NT-proBNP data from PARADIGM-HF). Our study also has limitations. It is a retrospective analysis and we have only accounted for heart rate and the presence or not of AF at baseline ECG recording. Our analysis does not account for the development of, or paroxysms of AF during the study. The analysis examining the associations between temporal changes in heart rate and outcomes do not account for changes in rate-limiting drug use or dose which may affect heart rate. The number of patients with very high or very low heart-rates were small. We have made efforts to adjust for differences in baseline characteristics between patients with AF and sinus rhythm and across heart rate tertiles. Despite this, as is inherent in any analysis of this nature, the risk of residual confounding remains high and our findings should be interpreted in context of this.[33,34] Our results do not extend to those patients who were not eligible for inclusion in the clinical trials, for example, those with HFpEF or severe renal impairment.

CONCLUSION

In patients with HFrEF, an elevated heart rate in sinus rhythm was an independent predictor of both fatal and non-fatal adverse cardiovascular outcomes, even after adjustment for natriuretic peptide levels. Higher heart rate had a stronger relationship with death from pump failure than for sudden death. There was no relationship between heart rate and outcomes in patients with HFrEF and atrial fibrillation.

REFERENCES

1. Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R, BEAUTIFUL investigators. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomised controlled trial. *Lancet* 2008;**372**:817–821.
2. Böhm M, Swedberg K, Komajda M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L. Heart rate as a risk factor in chronic heart failure (SHIFT): The association between heart rate and outcomes in a randomised placebo-controlled trial. *Lancet* 2010;**376**:886–894.
3. Castagno D, Skali H, Takeuchi M, Swedberg K, Yusuf S, Granger CB, Michelson EL, Pfeffer MA, McMurray JJ V, Solomon SD. Association of heart rate and outcomes in a broad spectrum of patients with chronic heart failure: Results from the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity) program. *J Am Coll Cardiol* 2012;**59**:1785–1795.
4. Simpson J, Castagno D, Doughty RN, Poppe KK, Earle N, Squire I, Richards M, Andersson B, Ezekowitz JA, Komajda M, Petrie MC, McAlister FA, Gamble GD, Whalley GA, McMurray JJV. Is heart rate a risk marker in patients with chronic heart failure and concomitant atrial fibrillation? Results from the MAGGIC meta-analysis. *Eur J Heart Fail* 2015;**17**:1182–1191.
5. Kotecha D, Flather MD, Altman DG, Holmes J, Rosano G, Wikstrand J, Packer M, Coats AJS, Manzano L, Böhm M, Veldhuisen DJ van, Andersson B, Wedel H, Lueder TG von, Rigby AS, Hjalmarson Å, Kjekshus J, Cleland JGF. Heart Rate and Rhythm and the Benefit of Beta-Blockers in Patients With Heart Failure. *J Am Coll Cardiol* 2017;**69**:2885–2896.
6. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G,

Tavazzi L. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010;**376**:875–885.

7. Zile MR, Claggett BL, Prescott MF, McMurray JJV, Packer M, Rouleau JL, Swedberg K, Desai AS, Gong J, Shi VC, Solomon SD. Prognostic Implications of Changes in N-Terminal Pro-B-Type Natriuretic Peptide in Patients With Heart Failure. *J Am Coll Cardiol* 2016;**68**:2425–2436.

8. Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: Epidemiology, pathophysiology, and rationale for therapy. *Am J Cardiol* 2003;**91**:2–8.

9. Rienstra M, Gelder IC Van, Berg MP Van Den, Boomsma F, Hillege HL, Veldhuisen DJ Van. A comparison of low versus high heart rate in patients with atrial fibrillation and advanced chronic heart failure: Effects on clinical profile, neurohormones and survival. *Int J Cardiol* 2006;**109**:95–100.

10. Laskey WK, Alomari I, Cox M, Schulte PJ, Zhao X, Hernandez AF, Heidenreich PA, Eapen ZJ, Yancy C, Bhatt DL, Fonarow GC. Heart rate at hospital discharge in patients with heart failure is associated with mortality and rehospitalization. *J Am Heart Assoc* 2015;**4**:e001626.

11. Cullington D, Goode KM, Zhang J, Cleland JGF, Clark AL. Is heart rate important for patients with heart failure in atrial fibrillation? *JACC Hear Fail* 2014;**2**:213–220.

12. Mulder BA, Veldhuisen DJ Van, Crijns HJGM, Tijssen JGP, Hillege HL, Alings M, Rienstra M, Groenveld HF, Berg MP Van Den, Gelder IC Van. Lenient vs. strict rate control in patientswith atrial fibrillation and heart failure: A post-hoc analysis of the RACE 2 study. *Eur J Heart Fail* 2013;**15**:1311–1318.

13. Li SJ, Sartipy U, Lund LH, Dahlstrom U, Adiels M, Petzold M, Fu M. Prognostic Significance of Resting Heart Rate and Use of β-Blockers in Atrial Fibrillation and Sinus Rhythm in Patients with Heart Failure and Reduced Ejection Fraction : Findings

from the Swedish Heart Failure Registry. *Circ Hear Fail* 2015;**8**:871–879.

14. Mogensen UM, Jhund PS, Abraham WT, Desai AS, Dickstein K, Packer M, Rouleau JL, Solomon SD, Swedberg K, Zile MR, Køber L, McMurray JJV, on behalf of the PARADIGM-HF and ATMOSPHERE Investigators and Committees. Type of Atrial Fibrillation and Outcomes in Patients With Heart Failure and Reduced Ejection Fraction. *J Am Coll Cardiol* 2017;**70**:2490–2500.

15. Kristensen SL, Jhund PS, Mogensen UM, Rørth R, Abraham WT, Desai A, Dickstein K, Rouleau JL, Zile MR, Swedberg K, Packer M, Solomon SD, Køber L, McMurray JJV. Prognostic Value of N-Terminal Pro-B-Type Natriuretic Peptide Levels in Heart Failure Patients With and Without Atrial Fibrillation. *Circ Heart Fail* 2017;**10**:1–10.

16. McMurray JJ V, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau J, Shi VC, Solomon SD, Swedberg K, Zile MR. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: Rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact. *Eur J Heart Fail* 2013;**15**:1062–1073.

17. McMurray JJ V, Packer M, Desai AS, Gong J, Lefkowitz M, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR. Baseline characteristics and treatment of patients in Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in heart failure trial (PARADIGM-HF). *Eur J Heart Fail* 2014;**16**:817–825.

18. McMurray JJV V, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, PARADIGM-HF Investigators and Committees. Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure. *N Engl J Med* 2014;**371**:993–1004.

19. Krum H, Massie B, Abraham WT, Dickstein K, Kober L, McMurray JJV, Desai A, Gimpelewicz C, Kandra A, Reimund B, Rattunde H, Armbrecht J, ATMOSPHERE Investigators. Direct renin inhibition in addition to or as an alternative to angiotensin converting enzyme inhibition in patients with chronic systolic heart failure: rationale and design of the Aliskiren Trial to Minimize OutcomeS in Patients with HEart failuRE (ATMOSPHERE) study. *Eur J Heart Fail* 2011;**13**:107–114.

20. Krum H, McMurray JJV, Abraham WT, Dickstein K, Køber L, Desai AS, Solomon SD, Chiang Y, Gimpelewicz C, Reimund B, Ali MA, Tarnesby G, Massie BM, ATMOSPHERE Committees and Investigators. The Aliskiren Trial to Minimize OutcomeS in Patients with HEart failure trial (ATMOSPHERE): revised statistical analysis plan and baseline characteristics. *Eur J Heart Fail* 2015;**17**:1075–1083.

21. McMurray JJV V, Krum H, Abraham WT, Dickstein K, Køber L V., Desai AS, Solomon SD, Greenlaw N, Ali MA, Chiang Y, Shao Q, Tarnesby G, Massie BM, ATMOSPHERE Committees Investigators. Aliskiren, Enalapril, or Aliskiren and Enalapril in Heart Failure. *N Engl J Med* 2016;**374**:1521–1532.

22. Cuzick J. A wilcoxon-type test for trend. *Stat Med* 1985;**4**:87–90.

23. Gelder IC Van, Groenveld HF, Crijns HJGM, Tuininga YS, Tijssen JGP, Alings AM, Hillege HL, Bergsma-Kadijk JA, Cornel JH, Kamp O, Tukkie R, Bosker HA, Veldhuisen DJ Van, Berg MP Van den. Lenient versus Strict Rate Control in Patients with Atrial Fibrillation. *N Engl J Med* 2010;**362**:1363–1373.

24. Protocol for: McMurray JJV, Krum H, Abraham WT, Dickstein K, Køber L V., Desai AS, Solomon SD, Greenlaw N, Ali MA, Chiang Y, Shao Q, Tarnesby G, Massie BM, ATMOSPHERE Committees Investigators. Aliskiren, enalapril, or aliskiren and enalapril in heart failure. N Engl J Med 2016;374:1521-32. DOI: 10.1056/NEJMoa1514859.

http://www.nejm.org/doi/suppl/10.1056/NEJMoa1514859/suppl_file/nejmoa1514859_protocol.pdf (16 March 2018)

25. Mulder P, Barbier S, Chagraoui A, Richard V, Henry JP, Lallemand F, Renet S, Lerebours G, Mahlberg-Gaudin F, Thuillez C. Long-Term Heart Rate Reduction Induced by the Selective IfCurrent Inhibitor Ivabradine Improves Left Ventricular Function and Intrinsic Myocardial Structure in Congestive Heart Failure. *Circulation* 2004;**109**:1674–1679.

26. Mulieri LA, Hasenfuss G, Leavitt B, Allen PD, Alpert NR. Altered myocardial force-frequency relation in human heart failure. *Circulation* 1992;**85**:1743–1750.

27. Ekman I, Chassany O, Komajda M, Böhm M, Borer JS, Ford I, Tavazzi L, Swedberg K. Heart rate reduction with ivabradine and health related quality of life in patients with chronic heart failure: results from the SHIFT study. *Eur Heart J* 2011;**32**:2395–2404.

28. Vazir A, Claggett B, Jhund P, Castagno D, Skali H, Yusuf S, Swedberg K, Granger CB, McMurray JJ V, Pfeffer MA, Solomon SD. Prognostic importance of temporal changes in resting heart rate in heart failure patients: An analysis of the CHARM program. *Eur Heart J* 2015;**36**:669–675.

29. Daoud EG, Weiss R, Bahu M, Knight BP, Bogun F, Goyal R, Harvey M, Strickberger SA, Man KC, Morady F. Effect of an irregular ventricular rhythm on cardiac output. *Am J Cardiol* 1996;**78**:1433–1436.

30. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener H-C, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Putte B Van, Vardas P. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;**37**:2893–2962.

31. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Conti JB,

Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW, ACC/AHA Task Force Members, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Creager MA, Curtis LH, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Yancy CW. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: Executive summary: A report of the American College of cardiology/American heart association task force on practice guidelines and the heart rhythm society. *Circulation* 2014;**130**:2071–2104.

32. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). *Eur Heart J* 2016;**37**:2129–2200.

33. Rush CJ, Campbell RT, Jhund PS, Petrie MC, McMurray JJV. Association is not causation: treatment effects cannot be estimated from observational data in heart failure. *Eur Heart J* 2018;**39**:3417–3438.

34. Aguirre Dávila L, Weber K, Bavendiek U, Bauersachs J, Wittes J, Yusuf S, Koch A. Digoxin–mortality: randomized vs. observational comparison in the DIG trial. *Eur Heart J* 2019; doi.org/10.1093/eurheartj/ehz395

TABLES

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FIGURES

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Figure 2: Forest plot of relationship between baseline heart rate and outcomes by baseline heart rhythm

Legend: Hazard ratios (HRs) of outcomes according to heart rhythm (AF or sinus rhythm) using each groups tertile 1 as reference. HRs with 95% confidence intervals were calculated using Cox models adjusted for same variables as detailed in Table 1. The p values are for interaction between AF and sinus rhythm with heart rate considered as a continuous variable. Abbreviations as per figure 2

Figure 3: Relationship between baseline heart rate modelled as a continuous variable and outcomes

Legend: Hazard ratio for the effect of baseline heart rate on outcomes relative to a baseline heart rate of 80 beats per minute. Solid line represents the point estimates with dashed lines representing the 95% confidence intervals. Cox model adjusted for same variables as detailed in Table 2. SR = sinus rhythm; AF = atrial fibrillation.

Table 1: Risk of outcomes with baseline heart rate as a continuous variable (per 10bpm increase)

	Sinus rhythm (n=10,113)				Atrial fibrillation (n=3449)				
	Unadjusted HR (95% CI)	**p value**	**Adjusted HR (95% CI)**	**p value**	**Unadjusted HR (95% CI)**	**p value**	**Adjusted HR (95% CI)**	**p value**	**p value for interaction**
CV death or HF hospitalization	1.18 (1.15-1.21)	<0.001	1.12 (1.09-1.16)	<0.001	1.00 (0.97-1.04)	0.950	1.01 (0.98-1.05)	0.493	<0.001
HF hospitalization	1.18 (1.14-1.22)	<0.001	1.13 (1.09-1.18)	<0.001	1.00 (0.95-1.05)	0.949	1.02 (0.97-1.07)	0.530	<0.001
CV death	1.19 (1.15-1.23)	<0.001	1.11 (1.07-1.15)	<0.001	0.97 (0.93-1.02)	0.213	0.99 (0.95-1.04)	0.688	<0.001
Pump failure death	1.25 (1.17-1.33)	<0.001	1.17 (1.09-1.26)	<0.001	0.89 (0.81-0.98)	0.014	0.94 (0.85-1.04)	0.222	<0.001
Sudden death	1.18 (1.12-1.24)	<0.001	1.07 (1.02-1.13)	0.011	0.98 (0.92-1.05)	0.545	0.97 (0.91-1.04)	0.444	0.032
All-cause death	1.17 (1.14-1.21)	<0.001	1.12 (1.08-1.15)	<0.001	1.00 (0.96-1.04)	0.832	1.02 (0.98-1.06)	0.284	<0.001

Cox model adjusted for age, sex, region, race, NYHA functional class, ejection fraction, systolic blood pressure, eGFR, diabetes, BMI, time since HF diagnosis, history of HF hospitalization, history of myocardial infarction, history of stroke, log NT-proBNP, treatment with betablocker, treatment with digoxin, treatment with amiodarone and randomized treatment (enalapril, sacubitril/valsartan, aliskiren, or combination).
CI=confidence interval; CV=cardiovascular; HR=hazard ratio; HF=heart failure. P value for interaction calculated between sinus rhythm and atrial fibrillation.

Table 2: Association between change in ECG recorded heart rate from baseline to 12 months and outcomes

	Sinus Rhythm (n=7756)		Atrial fibrillation (n=2504)	
	Event rate (95% C.I.)	**Adjusted HR (95% C.I.)**	**Event rate (95% C.I.)**	**Adjusted HR (95% C.I.)**
CV death or HF hospitalization				
≤ -10 bpm	10.0 (8.7-11.4)	0.74 (0.63-0.87); p<0.001	10.9 (9.1-13.1)	0.83 (0.65-1.07); p=0.147
< +/-10 bpm	9.9 (9.2-10.5)	1.00 (Referent)	11.8 (10.4-13.4)	1.00 (Referent)
≥ +10 bpm	14.5 (13.1-16.0)	1.52 (1.34-1.72); p<0.001	14.5 (12.4-16.9)	1.31 (1.07-1.61); p=0.010
CV death				
≤ -10 bpm	6.4 (5.4-7.5)	0.82 (0.67-1.01); p=0.060	6.8 (5.4-8.5)	0.81 (0.60-1.10); p=0.173
< +/-10 bpm	5.7 (5.3-6.2)	1.00 (Referent)	7.6 (6.5-8.8)	1.00 (Referent)
≥ +10 bpm	8.6 (7.6-9.8)	1.53 (1.31-1.80); p=<0.001	8.7 (7.2-10.5)	1.23 (0.96-1.58); p=0.103
HF hospitalization				
≤ -10 bpm	5.2 (4.3-6.3)	0.69 (0.55-0.87); p=0.001	6.3 (4.9-8.0)	1.01 (0.73-1.39); p=0.972
< +/-10 bpm	5.6 (5.1-6.1)	1.00 (Referent)	6.3 (5.4-7.5)	1.00 (Referent)
≥ +10 bpm	8.4 (7.4-9.7)	1.60 (1.36-1.90); p<0.001	9.1 (7.5-11.1)	1.55 (1.18-2.02); p=0.001
Pump failure death				
≤ -10 bpm	1.4 (1.0-2.0)	0.73 (0.48-1.13); p=0.163	1.0 (0.6-1.8)	0.55 (0.27-1.18); p=0.110
< +/-10 bpm	1.4 (1.2-1.7)	1.00 (Referent)	1.9 (1.4-2.5)	1.00 (Referent)

≥ +10 bpm	1.9 (1.5-2.5)	1.51 (1.08-2.10); p=0.015	3.5 (2.6-4.8)	2.26 (1.46-3.52); p<0.001
Sudden cardiac death				
≤ -10 bpm	2.9 (2.3-3.7)	0.82 (0.61-1.12); p=0.218	3.1 (2.2-4.3)	0.91 (0.57-1.45); p=0.681
< +/-10 bpm	2.5 (2.2-2.9)	1.00 (Referent)	2.9 (2.3-3.7)	1.00 (Referent)
≥ +10 bpm	3.2 (2.6-3.9)	1.20 (0.94-1.55); p=0.150	3.0 (2.1-4.1)	1.01 (0.66-1.54); p=0.969
All-cause death				
≤ -10 bpm	7.7 (6.6-8.9)	0.83 (0.69-1.00); p=0.050	7.8 (6.3-9.6)	0.75 (0.56-0.99); p=0.040
< +/-10 bpm	6.9 (6.4-7.5)	1.00 (Referent)	9.1 (8.0-10.5)	1.00 (Referent)
≥ +10 bpm	10.0 (8.8-11.2)	1.51 (1.31-1.75); p<0.001	10.2 (8.6-12.2)	1.21 (0.96-1.52); p=0.099

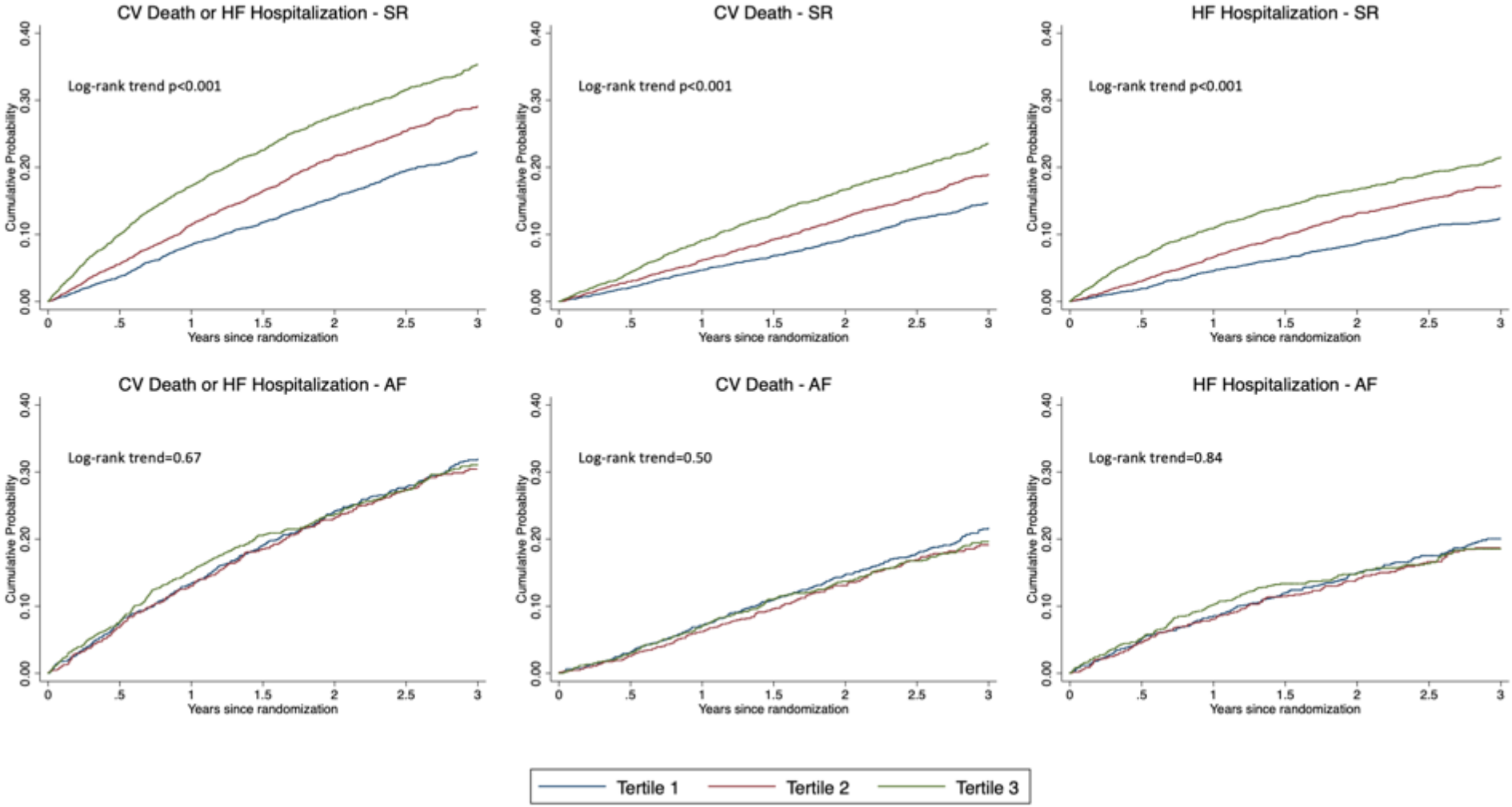
Event rates presented as per 100 patient years.
Cox model adjusted for same variables as detailed in Table 1 and baseline heart rate.
Abbreviations as per Table 1.

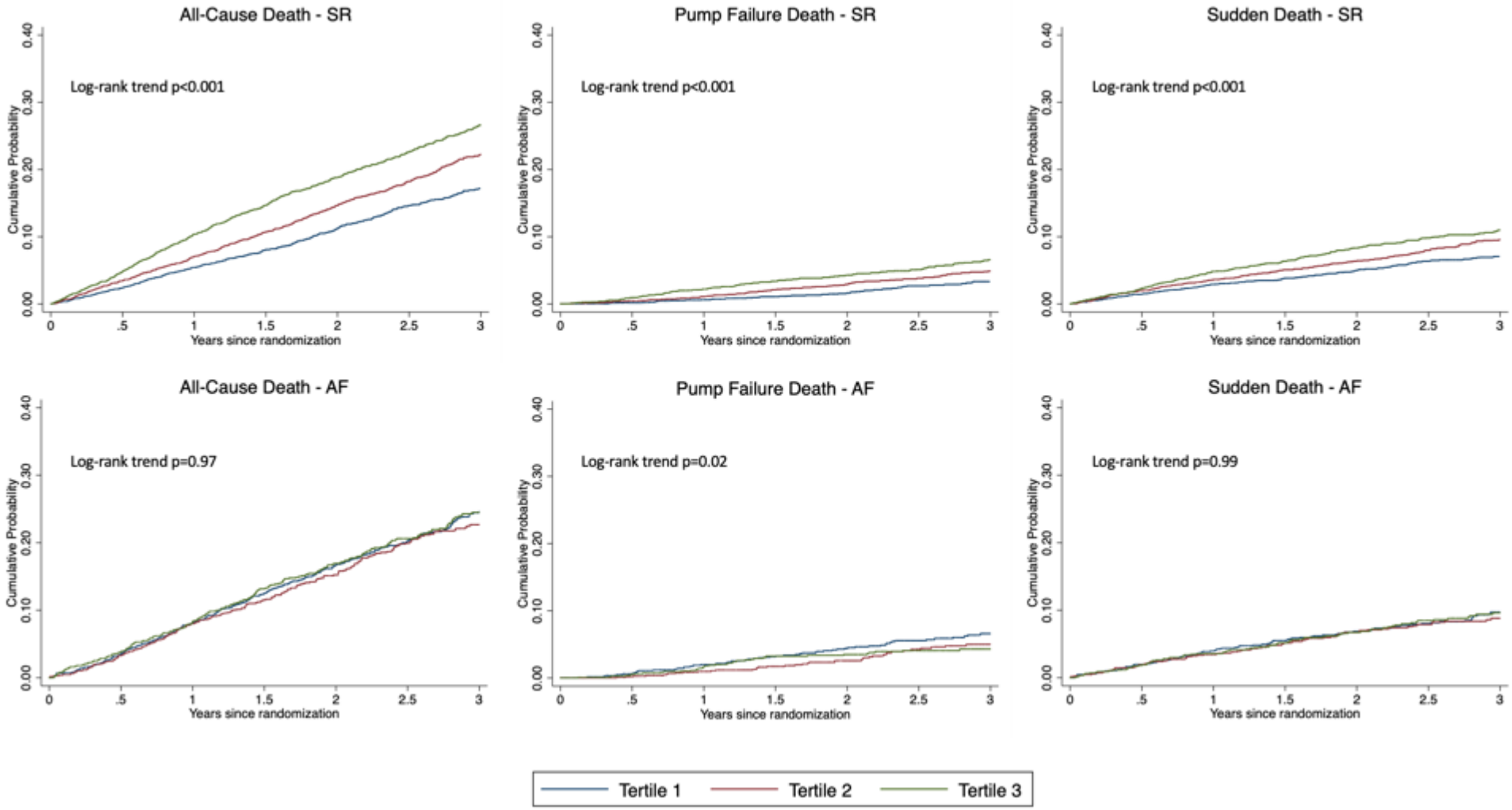
Table 3: Association between change in heart rate at 12 months and change in KCCQ and NT-proBNP

Change in heart rate	Sinus Rhythm				Atrial Fibrillation			
	≤ -10 bpm (n=1274)	< +/-10 bpm (n=4943)	≥ +10 bpm (n=1539)	p for trend	≤ -10 bpm (n=611)	< +/-10 bpm (n=1217)	≥ +10 bpm (n=676)	p for trend
Increase in KCCQ at 12 months ≥ 5 points	423 (33.2%)	1399 (28.3%)	369 (24.0%)	p<0.001	214 (35.0%)	384 (31.6%)	201 (29.7%)	p=0.044
Decrease in KCCQ at 12 months ≥ 5 points	272 (21.4%)	1139 (23.0%)	421 (27.4%)	p<0.001	153 (25.0%)	332 (27.3%)	206 (30.5%)	p=0.029
Mean (±SD) change in NT-proBNP at 12 months (pg/ml)*	-414±2271	+59±2294	+424±2754	p<0.001	-121±2279	-40±1412	259±2327	p=0.034

*Data available for 3835 (84%) patients from ATMOSPHERE only

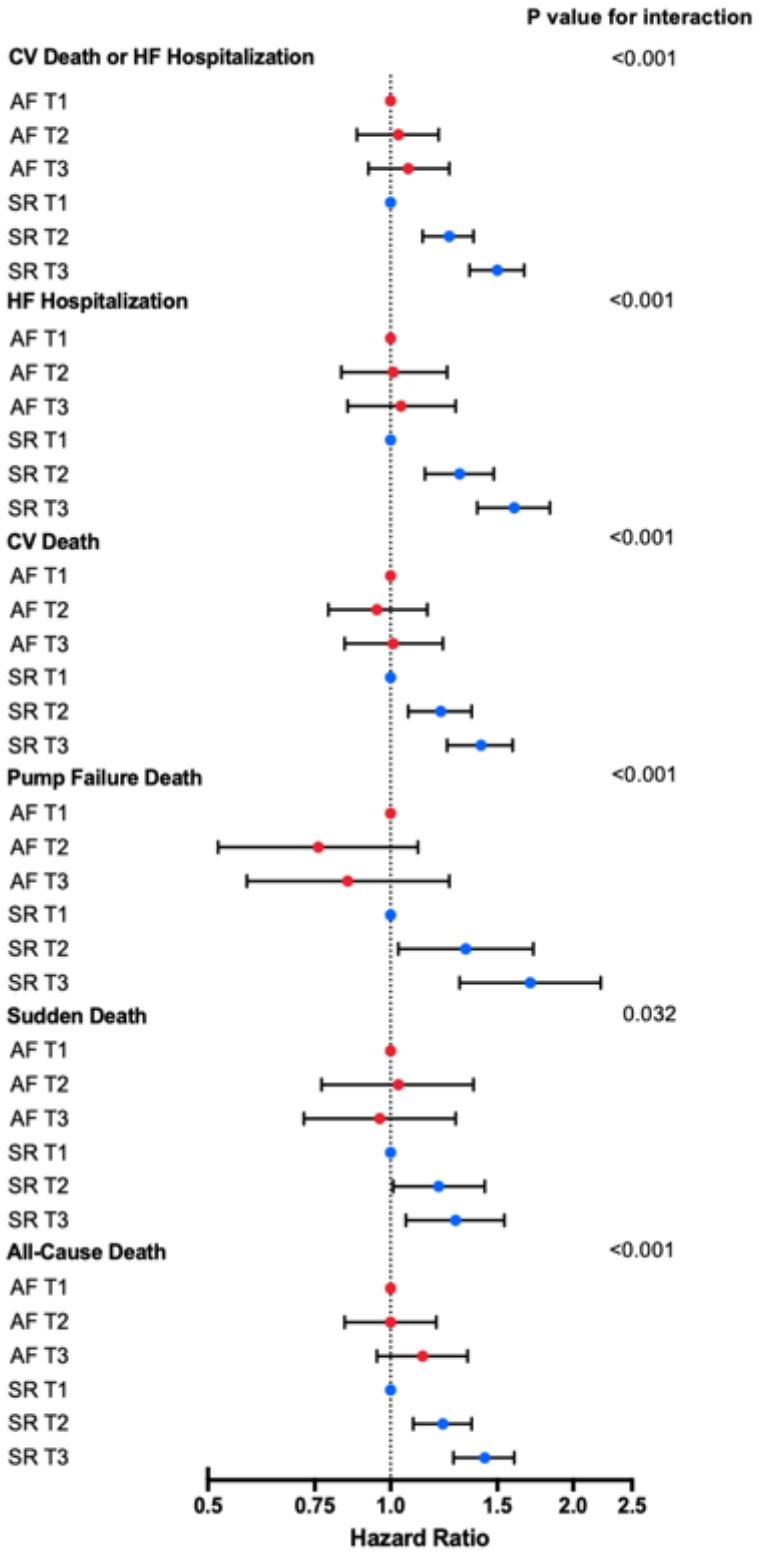
Figure 1: Kaplan-Meier survival analysis according to baseline heart rate and rhythm





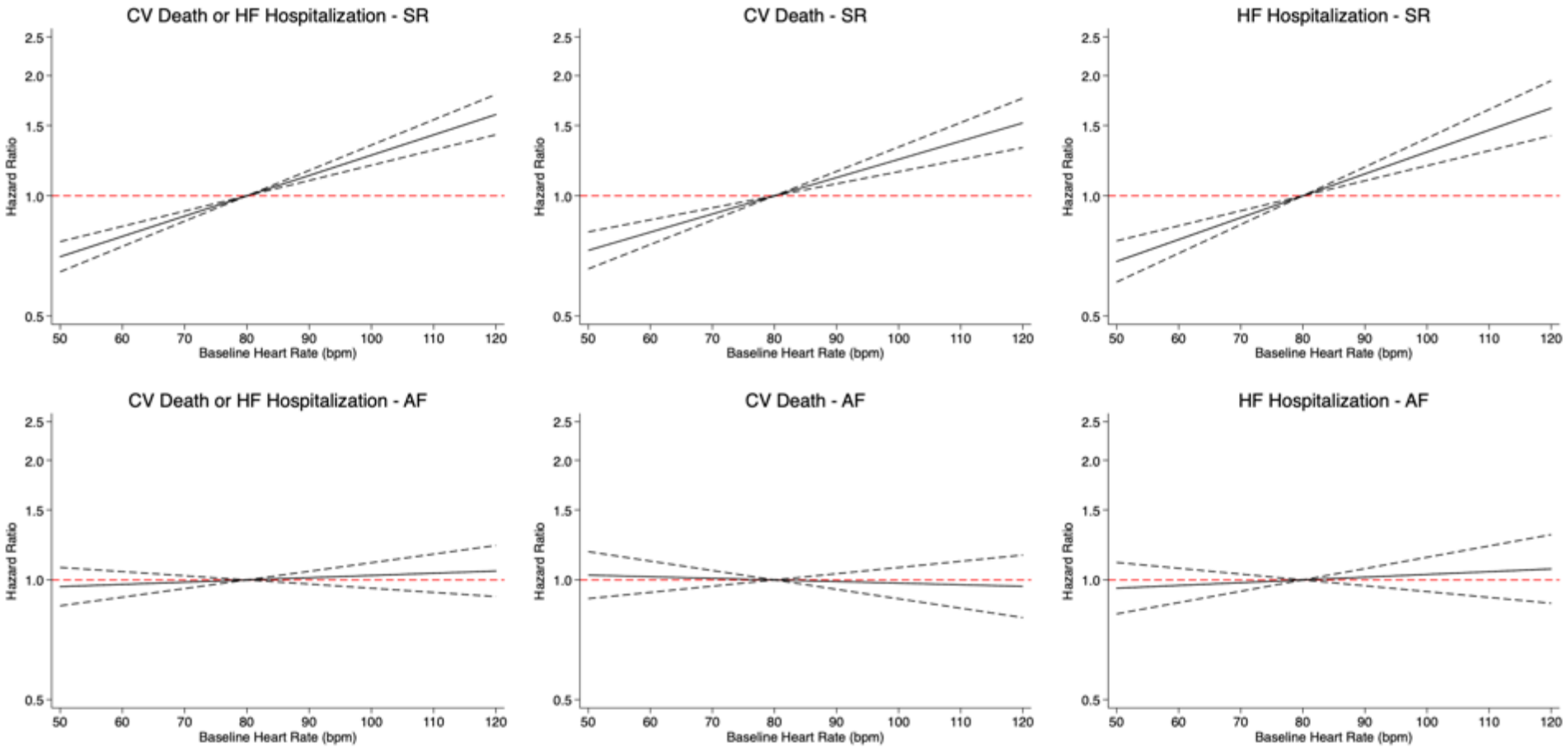
Event curves for outcomes according to baseline heart rhythm and heart rate tertiles (tertile 1 lowest/tertile 3 highest). SR = sinus rhythm; AF = atrial fibrillation.

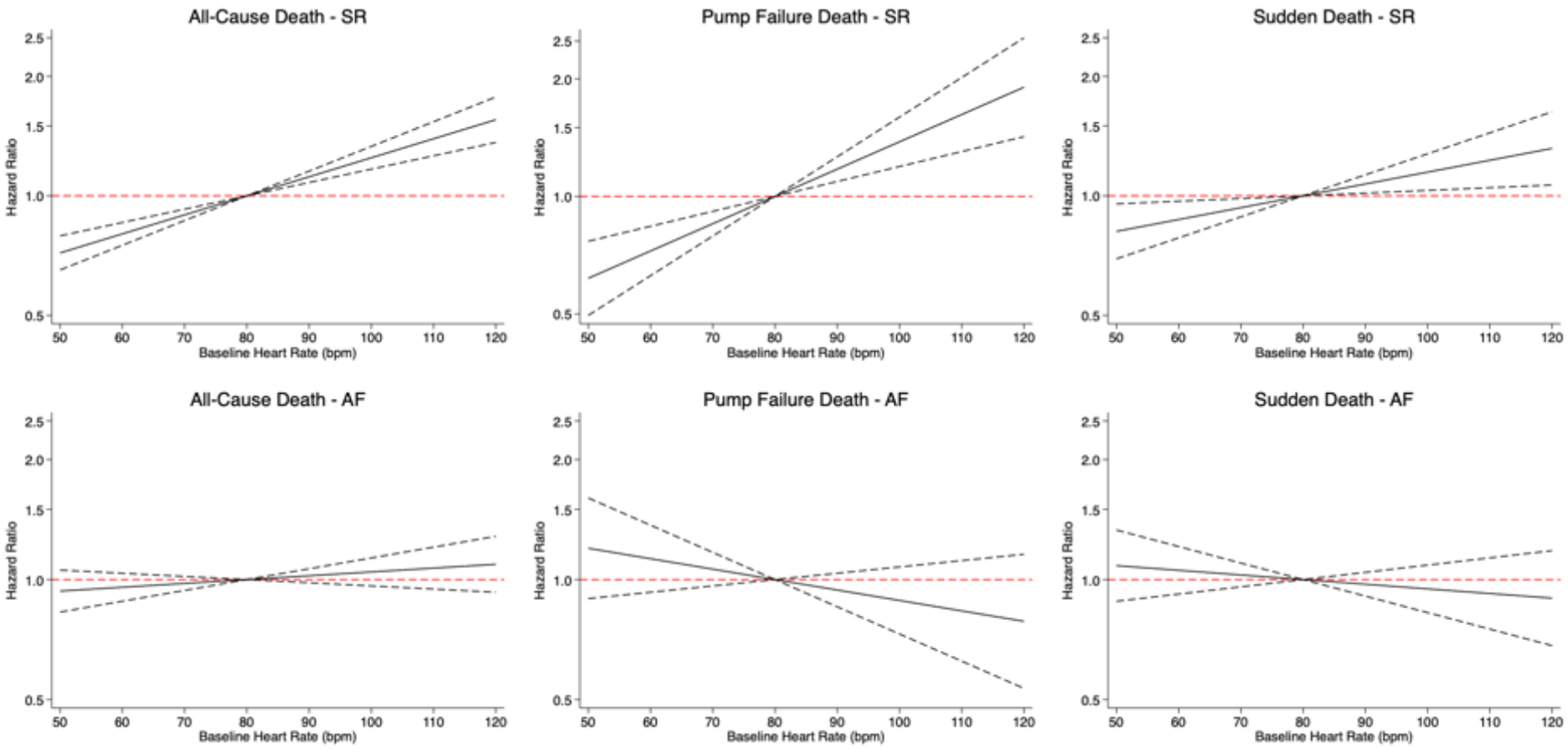
Figure 2: Forest plot of relationship between baseline heart rate and outcomes by baseline heart rhythm



Hazard ratios (HRs) of outcomes according to heart rhythm (AF or sinus rhythm) using each groups tertile 1 as reference. HRs with 95% confidence intervals were calculated using Cox models adjusted for same variables as detailed in Table 1. The p values are for interaction between AF and sinus rhythm with heart rate considered as a continuous variable. Abbreviations as per figure 2.

Figure 3: Relationship between baseline heart rate modelled as a continuous variable and outcomes





Hazard ratio for the effect of baseline heart rate on outcomes relative to a baseline heart rate of 80 beats per minute. Solid line represents the point estimates with dashed lines representing the 95% confidence intervals. Cox model adjusted for same variables as detailed in Table 1
SR = sinus rhythm; AF = atrial fibrillation.