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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Word count: 3760

ABSTRACT

Background: Existing analyses of the relationship between heart rate and outcomes in HFrEF patients in sinus rhythm (SR) did not adjust for natriuretic peptide concentration, the most powerful prognosticator in these patients, even though natriuretic peptide levels are higher in those with a higher heart rate. Prior studies were also too small to examine the relationship between heart rate and mode of death. These relationships are even less clear in patients with atrial fibrillation (AF) and little is known about how change in heart rate relates to outcome in either rhythm group.

Methods: We analysed patients enrolled in two large HFrEF trials. Heart rate was analysed as both a categorical (tertiles, T1-3) and a continuous variable (per 10 bpm), separately in patients in SR and AF. Outcomes were also examined using change in heart rate between baseline and one year (≤ -10 bpm, ≥ +10 bpm, < ±10 bpm). The primary endpoint was the composite of cardiovascular death or HF hospitalization. All outcomes were adjusted for other prognostic variables, including NT-proBNP.

Results: Of 13,562 patients with analysable data, 10,113 (74.6%) were in SR and 3449 (25.4%) in AF. SR patients with a higher heart rate had worse symptoms and QoL, more often had diabetes and had higher NT-proBNP concentrations. They had a higher risk of the primary endpoint (T3 vs. T1 adjusted HR 1.50; 95%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 more strongly associated with risk of death from pump failure than from sudden death: adjusted HR per 10 bpm 1.17 (95% CI 1.09-1.26; p<0.001) vs. 1.07 (1.02-1.13; p=0.011), respectively. The corresponding adjusted HR for HF hospitalisation was 1.13 (1.09-1.18; p<0.001). Heart rate was not predictive of any outcome in AF, whether analysed by tertile or as a continuous variable. In both SR and AF, an increase

in HR over time was associated with worse outcomes and a decrease in HR with better outcomes.

Conclusions: In HFrEF, an elevated heart rate was an independent predictor of both fatal and non-fatal adverse cardiovascular outcomes in patients in SR, even after adjustment for NT-proBNP. Higher heart rate had a stronger relationship with pump failure death than sudden death. There was no relationship between heart rate and outcomes in patients with HFrEF and AF.

Word count: 355

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. 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.[7] 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.[3,5,8–12] 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.[13] 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.[14] 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, randomised 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.[15–20] 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 AF). 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 hospitalisation. 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.[21] 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. 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 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).[22]

Models were adjusted for randomised 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 hospitalisation, 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.[20,23] The proportional

hazards assumption was examined using log (-log(survival)) curves and was found to valid for all models.

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 randomisation and adjusted for the same baseline characteristics as detailed above with the referent group being those with a less than 10 bpm change in ECG recorded heart rate over 12 months.

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 randomised in both trials, 1715 (11.1%) patients were reported to have a paced ECG rhythm and were excluded from this analysis. 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 Figure 1. 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 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 Supplementary Table 1. 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 (Table 2 and Figures 2 and 3). This elevated risk remained significant for all outcomes after adjustment for other prognostic variables. 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).

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 (Table 2 and Figure 2). The risk of all other outcomes was not significantly different between tertiles of heart rate (Table 2 and Figure 2 and 3). Similar

results were found in a sensitivity analysis for patients with AF at baseline using the sinus rhythm tertile heart rate ranges (Supplementary Table 2).

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 3 and Figure 4). 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 hospitalisation 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 3 and Figure 4). 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 3).

Relationship between change in heart rate at 12 months following randomisation 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 4. 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 hospitalisation) 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.

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 hospitalisation and pump failure death; a reduction in heart rate and a lower risk of all-cause mortality.

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 more strongly associated with the 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 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.[24,25] 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 hospitalisation (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.[26] The findings of our analysis of change in heart rate were also consistent with SHIFT.[2,6] 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.

In contrast to what we observed in patients in sinus rhythm, ventricular rate was of no prognostic importance 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".[27] 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. 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 hospitalisation. Of course, our findings are observational in nature and this complicated and important clinical question is yet to be addressed in an adequate randomised clinical trial. Indeed, the resultant lack of evidence is reflected in the

discrepancy between US guidance which advocates a target resting ventricular rate <80 bpm and European guidelines 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.[22,28,29]

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. 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. 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.

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Tables

Table 1: Baseline characteristics according to heart rhythm on baseline ECG and tertiles of heart rate

Table 2: Clinical outcomes according to baseline heart rhythm and heart rate tertile

Table 3: Risk of outcomes with baseline heart rate as a continuous variable (per 10bpm increase)

Table 4: Association between change in ECG recorded heart rate from baseline to 12 months and outcomes

Figures

Figure 1: Distribution of ECG recorded baseline heart rate in sinus rhythm and atrial fibrillation

Figure 2: Kaplan-Meier survival analysis according to baseline heart rate and rhythm

Figure 3: Forest plot of relationship between baseline heart rate and outcomes by baseline heart rhythm

Figure 4: Relationship between baseline heart rate modelled as a continuous variable and outcomes

Table 1: Baseline characteristics by heart rhythm on baseline ECG and tertiles of heart rate

	Sinus rhythm on baseline ECG (n=10,113)				Atrial fibrillation on baseline ECG (n=3449)			
	Tertile 1 (n=3478) ≤63 bpm	Tertile 2 (n=3678) 64-75bpm	Tertile 3 (n=2957) ≥76bpm	p value for trend	Tertile 1 (n=1220) ≤72bpm	Tertile 2 (n=1106) 73-85bpm	Tertile 3 (n=1123) ≥86bpm	p value for trend
Age, years	63.9 ± 11.0	62.1 ± 11.8	59.3 ± 12.2	<0.001	68.0 ± 9.8	67.3 ± 10.3	64.4 ± 10.7	<0.001
Female	713 (20.5%)	896 (24.4%)	726 (24.6%)	<0.001	216 (17.7%)	259 (23.4%)	237 (21.1%)	0.036
Region				<0.001				<0.001
North America	179 (5.1%)	143 (3.9%)	120 (4.1%)		34(2.8%)	23 (2.1%)	28 (2.5%)	
Latin America	721 (20.7%)	693 (18.8%)	466 (15.8%)		169 (13.9%)	136 (12.3%)	123 (11.0%)	
Western Europe	988 (28.4%)	789 (21.5%)	490 (16.6%)		387 (31.7%)	260 (23.5%)	177 (15.8%)	
Central Europe	921 (26.5%)	1031 (28.0%)	731 (24.7%)		492 (40.3%)	568 (51.4%)	636 (56.6%)	
Asia/Pacific and other	669 (19.2%)	1022 (27.8%)	1150 (38.9%)		138 (11.3%)	119 (10.8%)	159 (14.2%)	
Race				<0.001				0.15
White	2283 (65.6%)	2159 (58.7%)	1439 (48.7%)		981 (80.4%)	919 (83.1%)	871 (77.6%)	
Black	134 (3.9%)	144 (3.9%)	129 (4.4%)		17(1.4%)	14 (1.3%)	26 (2.3%)	
Asian	653 (18.8%)	989 (26.9%)	1109 (37.5%)		128 (10.5%)	111 (10.0%)	147 (13.1%)	
Other	408 (11.7%)	386 (10.5%)	280 (9.5%)		94 (7.7%)	62 (5.6%)	79 (7.0%)	
Systolic blood pressure, mmHg	123.1 ± 17.5	122.5 ± 16.8	122.3 ± 16.7	0.041	122.8 ± 16.9	124.9 ± 15.6	123.7 ± 15.5	0.15
eGFR <60ml/min/1.73 m^2	1092 (31.4%)	1048 (28.5%)	727 (24.6%)	<0.001	489 (40.1%)	344 (31.1%)	335 (29.8%)	<0.001
eGFR ml/min/1.73 m^2	70.1 ± 19.9	72.3 ± 21.6	75.7 ± 24.4	<0.001	65.4 ± 18.1	70.0 ± 29.0	70.9 ± 21.0	<0.001
Ischaemic HF aetiology	2219 (63.8%)	2298 (62.5%)	1669 (56.4%)	<0.001	632 (51.8%)	550 (49.7%)	533 (47.5%)	0.036
Ejection fraction, %	29.1 ± 5.9	28.7 ± 6.0	28.1 ± 6.1	<0.001	30.6 ± 5.5	30.8 ± 5.5	30.5 ± 5.6	0.80
BMI, kg/m^2	27.1 ± 4.9	27.30 ± 5.4	27.4 ± 5.9	0.035	28.7 ± 5.3	29.1 ± 5.6	29.7 ± 5.6	<0.001
NYHA functional class				<0.001				<0.001
I	154 (4.4%)	186 (5.1%)	111 (3.8%)		32(2.6%)	15 (1.4%)	19 (1.7%)	
II	2654 (76.4%)	2656 (72.2%)	2009 (68.0%)		799 (65.7%)	696 (63.0%)	637 (56.7%)	
III	654 (18.8%)	817 (22.2%)	797 (27.0%)		376 (30.9%)	384 (34.8%)	448 (39.9%)	
IV	13 (0.4%)	18 (0.5%)	39 (1.3%)		10(0.8%)	10 (0.9%)	19 (1.7%)	
Duration of HF				<0.001				<0.001
≤1 yr	1208 (34.7%)	1315 (35.8%)	1187 (40.1%)		303 (24.8%)	306 (27.7%)	321 (28.6%)	
1-5 yrs	1258 (36.2%)	1421 (38.7%)	1128 (38.1%)		462 (37.9%)	430 (38.9%)	487 (43.4%)	
>5yrs	1012 (29.1%)	938 (25.5%)	642 (21.7%)		455 (37.3%)	370 (33.5%)	315 (28.0%)	

Current smoker	492 (14.1%)	568 (15.4%)	479 (16.2%)	0.021	97 (8.0%)	117 (10.6%)	144 (12.8%)	<0.001
History of								
Hypertension	2273 (65.4%)	2369 (64.4%)	1822 (61.6%)	0.002	898 (73.6%)	857 (77.5%)	871 (77.6%)	0.023
Diabetes	853 (24.5%)	1209 (32.9%)	1162 (39.3%)	<0.001	352 (28.9%)	328 (29.7%)	349 (31.1%)	0.24
Myocardial infarction	1773 (51.0%)	1748 (47.5%)	1158 (39.2%)	<0.001	399 (32.7%)	293 (26.5%)	255 (22.7%)	<0.001
Valvular heart disease	95 (5.3%)	112 (5.6%)	93 (5.9%)	0.49	48 (7.3%)	62 (10.0%)	47 (7.5%)	0.83
Heart failure hospitalisation	1974 (56.8%)	2254 (61.3%)	1797 (60.8%)	0.007	746 (61.1%)	716 (64.7%)	776 (69.1%)	<0.001
Stroke	264 (7.6%)	253 (6.9%)	183 (6.2%)	0.027	128 (10.5%)	117 (10.6%)	94 (8.4%)	0.09
COPD	366 (10.5%)	402 (10.9%)	376 (12.7%)	0.007	142 (11.6%)	149 (13.5%)	164 (14.6%)	0.034
Cancer	165 (4.7%)	130 (3.5%)	74 (2.5%)	<0.001	62 (5.1%)	54 (4.9%)	24 (2.1%)	<0.001
Medications at baseline								
Beta-blocker	3266 (93.9%)	3420 (93.0%)	2632 (89.0%)	<0.001	1113 (91.2%)	1032 (93.3%)	1037 (92.3%)	0.30
MRA	1640 (47.2%)	1718 (46.7%)	1314 (44.4%)	0.033	616 (50.5%)	503 (45.5%)	540 (48.1%)	0.22
Diuretic	2549 (73.3%)	2878 (78.2%)	2417 (81.7%)	<0.001	1061 (87.0%)	908 (82.1%)	950 (84.6%)	0.10
Digoxin	707 (20.3%)	837 (22.8%)	877 (29.7%)	<0.001	604 (49.5%)	569 (51.4%)	614 (54.7%)	0.013
Amiodarone	458 (13.2%)	263 (7.2%)	137 (4.6%)	<0.001	115 (9.4%)	68 (6.1%)	71 (6.3%)	0.004
Statins	2164 (62.2%)	2078 (56.5%)	1534 (51.9%)	<0.001	571 (46.8%)	464 (42.0%)	414 (36.9%)	<0.001
Anticoagulation therapy	635 (18.3%)	531 (14.4%)	411 (13.9%)	<0.001	867 (71.1%)	759 (68.6%)	768 (68.4%)	0.16
Aspirin	2191 (63.0%)	2281 (62.0%)	1613 (54.5%)	<0.001	352 (28.9%)	311 (28.1%)	330 (29.4%)	0.79
Other antiplatelet	594 (17.1%)	632 (17.2%)	482 (16.3%)	0.42	80 (6.6%)	65 (5.9%)	61 (5.4%)	0.25
Any antiplatelet	2341 (67.3%)	2444 (66.4%)	1764 (59.7%)	<0.001	397 (32.5%)	349 (31.6%)	361 (32.1%)	0.83
ICD§	468 (13.5%)	385 (10.5%)	211 (7.1%)	<0.001	101 (8.3%)	70 (6.3%)	36 (3.2%)	<0.001
CRT	55 (1.6%)	57 (1.5%)	42 (1.4%)	0.61	13 (1.1%)	6 (0.5%)	9 (0.8%)	0.46
NT-proBNP, pg/ml ∫	1073 (640-1992)	1221 (673-2443)	1524 (769-3236)	<0.001	1885 (1102-3259)	1795 (1103-3160)	1701 (1002- 3226)	0.06
KCCQ clinical summary score‡	83.3 (68.2-93.8)	81.8 (64.6-92.7)	79.2 (60.4-91.7)	<0.001	77.1 (59.7-89.6)	75.0 (58.3-87.5)	70.3 (53.1- 86.5)	<0.001

Values are mean ± SD, n (%), or median (interquartile range). A total of 1715 patients had a paced rhythm on baseline electrocardiogram and an additional 138 had missing baseline electrocardiogram information and are not included in the table.

§ Includes both patients with implantable cardioverter defibrillator and implantable cardioverter defibrillator with cardiac resynchronisation

∫ Missing in 605 patients.

‡Missing in 1774 patients.

BMI = body mass index; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; eGFR = estimated glomerular filtration rate; HF = heart failure; ICD = implantable cardioverter defibrillator; KCCQ = Kansas City Cardiomyopathy Questionnaire; NT-proBNP = N-terminal pro–B type natriuretic peptide; NYHA = New York Heart Association.

Table 2: Clinical outcomes according to baseline heart rhythm and heart rate tertile

	Sinus rhythm (n=10,113)						Atrial fibrillation (n=3449)					
	Events (%)	Crude rate per 100 PY (95% CI)	Unadjusted HR (95% CI)	p value	Adjusted HR (95% CI)	p value	Events (%)	Crude rate per 100 PY (95% CI)	Unadjusted HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Primary Composite: CV death or HF hospitalisation												
T1	785 (22.6)	8.6 (8.0-9.2)	1.00 (Reference)		1.00 (Reference)		372 (30.5)	12.6 (11.3-13.9)	1.00 (Reference)		1.00 (Reference)	
T2	1008 (27.4)	11.4 (10.7-12.1)	1.32 (1.20-1.45)	<0.001	1.25 (1.13-1.37)	<0.001	315 (28.5)	12.2 (10.9-13.6)	0.97 (0.83-1.12)	0.653	1.03 (0.88-1.20)	0.718
T3	970 (32.8)	15.0 (14.1-16.0)	1.72 (1.57-1.90)	<0.001	1.50 (1.35-1.66)	<0.001	341(30.4)	13.0 (11.7-14.5)	1.03 (0.89-1.19)	0.684	1.07 (0.92-1.25)	0.382
HF hospitalisation												
T1	416 (12.0)	4.5 (4.1-5.0)	1.00 (Reference)		1.00 (Reference)		213 (17.5)	7.2 (6.3-8.2)	1.00 (Reference)		1.00 (Reference)	
T2	555 (15.1)	6.3 (5.8-6.8)	1.36 (1.20-1.55)	<0.001	1.30 (1.14-1.48)	<0.001	176 (15.9)	6.8 (5.9-7.9)	0.93 (0.76-1.14)	0.499	1.01 (0.83-1.24)	0.894
T3	539 (18.2)	8.3 (7.7-9.1)	1.79 (1.58-2.04)	<0.001	1.60 (1.39-1.83)	<0.001	187 (16.7)	7.1 (6.2-8.2)	0.98 (0.81-1.20)	0.862	1.04 (0.85-1.28)	0.695
CV death												
T1	513 (14.8)	5.3 (4.9-5.8)	1.00 (Reference)		1.00 (Reference)		264 (21.6)	8.2 (7.2-9.2)	1.00 (Reference)		1.00 (Reference)	
T2	654 (17.8)	6.9 (6.3-7.4)	1.29 (1.15-1.45)	<0.001	1.21 (1.07-1.36)	0.002	205 (18.5)	7.3 (6.3-8.3)	0.90 (0.75-1.08)	0.248	0.95 (0.79-1.15)	0.596
T3	650 (22.0)	9.0 (8.4-9.7)	1.70 (1.52-1.91)	<0.001	1.41 (1.24-1.59)	<0.001	222 (19.8)	7.7 (6.7-8.7)	0.94 (0.79-1.13)	0.521	1.01 (0.84-1.22)	0.882
Pump failure death												
T1	108 (3.1)	1.1 (0.9-1.4)	1.00 (Reference)		1.00 (Reference)		77 (6.3)	2.4 (1.9-3.0)	1.00 (Reference)		1.00 (Reference)	
T2	146 (4.0)	1.5 (1.3-1.8)	1.37 (1.07-1.76)	0.013	1.33 (1.03-1.72)	0.029	45 (4.1)	1.6 (1.2-2.1)	0.67 (0.47-0.97)	0.035	0.76 (0.52-1.11)	0.162
T3	158 (5.3)	2.2 (1.9-2.6)	1.98 (1.55-2.53)	<0.001	1.70 (1.30-2.22)	<0.001	46 (4.1)	1.6 (1.2-2.1)	0.67 (0.46-0.96)	0.031	0.85 (0.58-1.25)	0.398
Sudden death												
T1	228 (6.6)	2.4 (2.1-2.7)	1.00 (Reference)		1.00 (Reference)		108 (8.9)	3.3 (2.8-4.0)	1.00 (Reference)		1.00 (Reference)	
T2	306 (8.3)	3.2 (2.9-3.6)	1.34 (1.13-1.59)	0.001	1.20 (1.01 -1.43)	0.040	92 (8.3)	3.3 (2.7-4.0)	0.97 (0.74-1.29)	0.853	1.03 (0.77-1.37)	0.843
T3	290 (9.8)	4.0 (3.6-4.5)	1.67 (1.41-1.99)	<0.001	1.28 (1.06-1.54)	0.011	97 (8.6)	3.4 (2.7-4.1)	1.00 (0.76-1.32)	0.987	0.96 (0.72-1.28)	0.796
All-cause death												
T1	622 (17.9)	6.4 (6.0-7.0)	1.00 (Reference)		1.00 (Reference)		308 (25.3)	9.5 (8.5-10.6)	1.00 (Reference)		1.00 (Reference)	
T2	776 (21.1)	8.1 (7.6-8.7)	1.27 (1.14-1.41)	<0.001	1.22 (1.09-1.36)	<0.001	248 (22.4)	8.8 (7.8-9.9)	0.93 (0.79-1.10)	0.388	1.00 (0.84-1.19)	0.983
T3	750 (25.4)	10.4 (9.7-11.2)	1.63 (1.46-1.81)	<0.001	1.43 (1.27-1.60)	<0.001	276 (24.6)	9.5 (8.5-10.7)	1.01 (0.85-1.18)	0.950	1.13 (0.95-1.34)	0.166

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; PY = person-years; T1 = tertile 1; T2 = tertile 2; T3 = tertile 3. Other abbreviations as per Table 1.

Table 3: 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 hospitalisation	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 hospitalisation	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). P value for interaction calculated between sinus rhythm and atrial fibrillation. Abbreviations as per Table 1 and 2.

Table 4: Association between change in ECG recorded heart rate from baseline to 12 months and outcomes

	Sinus Rhythm (n=7756)		Atrial fibrillation/flutter (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 hospitalisation				
≤ -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
< +/-10bpm	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
< +/-10bpm	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 hospitalisation				
≤ -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
< +/-10bpm	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
< +/-10bpm	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
< +/-10bpm	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
< +/-10bpm	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

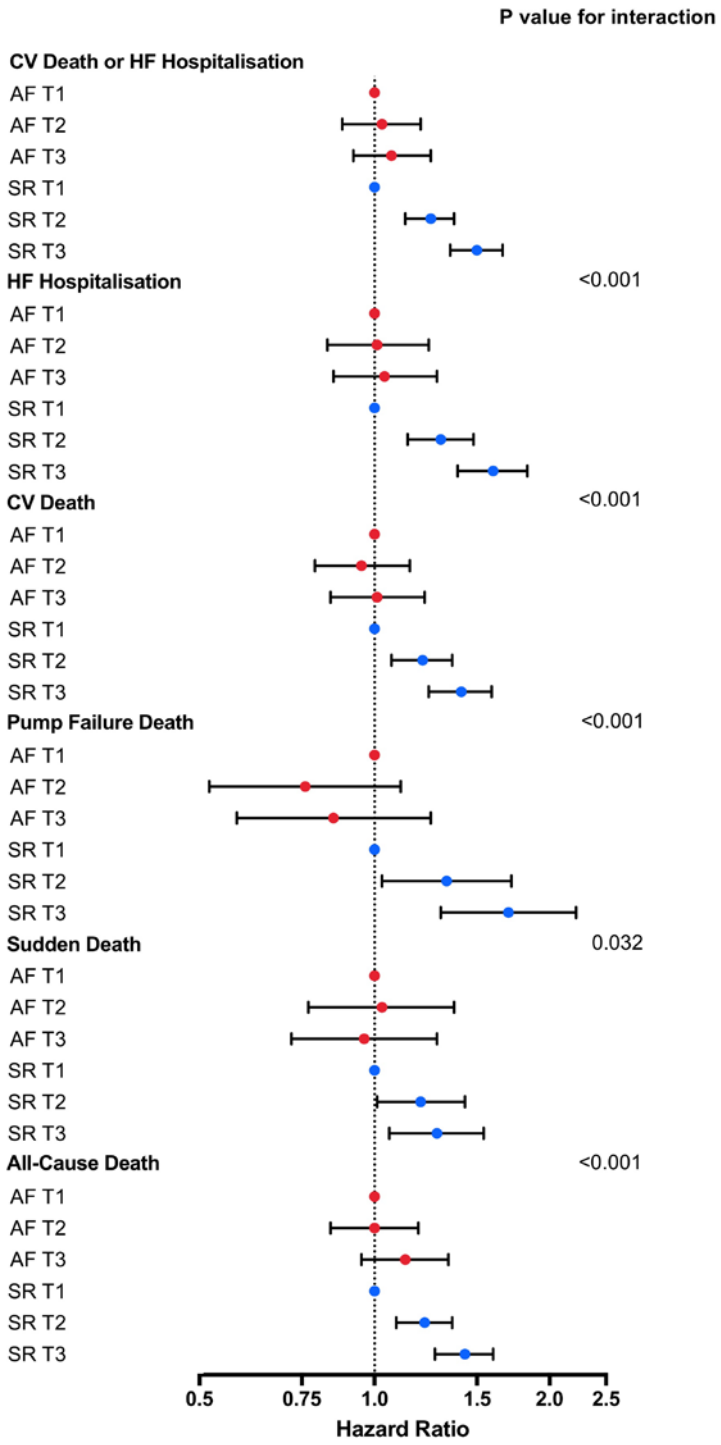
Event rates presented as per 100 patient years.
Cox model adjusted for age, sex, region, race, NYHA functional class, ejection fraction, systolic blood pressure, eGFR, diabetes, BMI, time since HF diagnosis, history of HF hospitalization, history of myocardial infarction, history of stroke, log NT-proBNP, baseline heart rate, treatment with betablocker, treatment with digoxin, treatment with amiodarone and randomized treatment (enalapril, sacubitril/valsartan, aliskiren, or combination).
Abbreviations as per Table 1 and 2.

Figure 1: Distribution of ECG recorded baseline heart rate in sinus rhythm and atrial fibrillation

Figure 2: Kaplan-Meier survival analysis according to baseline heart rate and rhythm

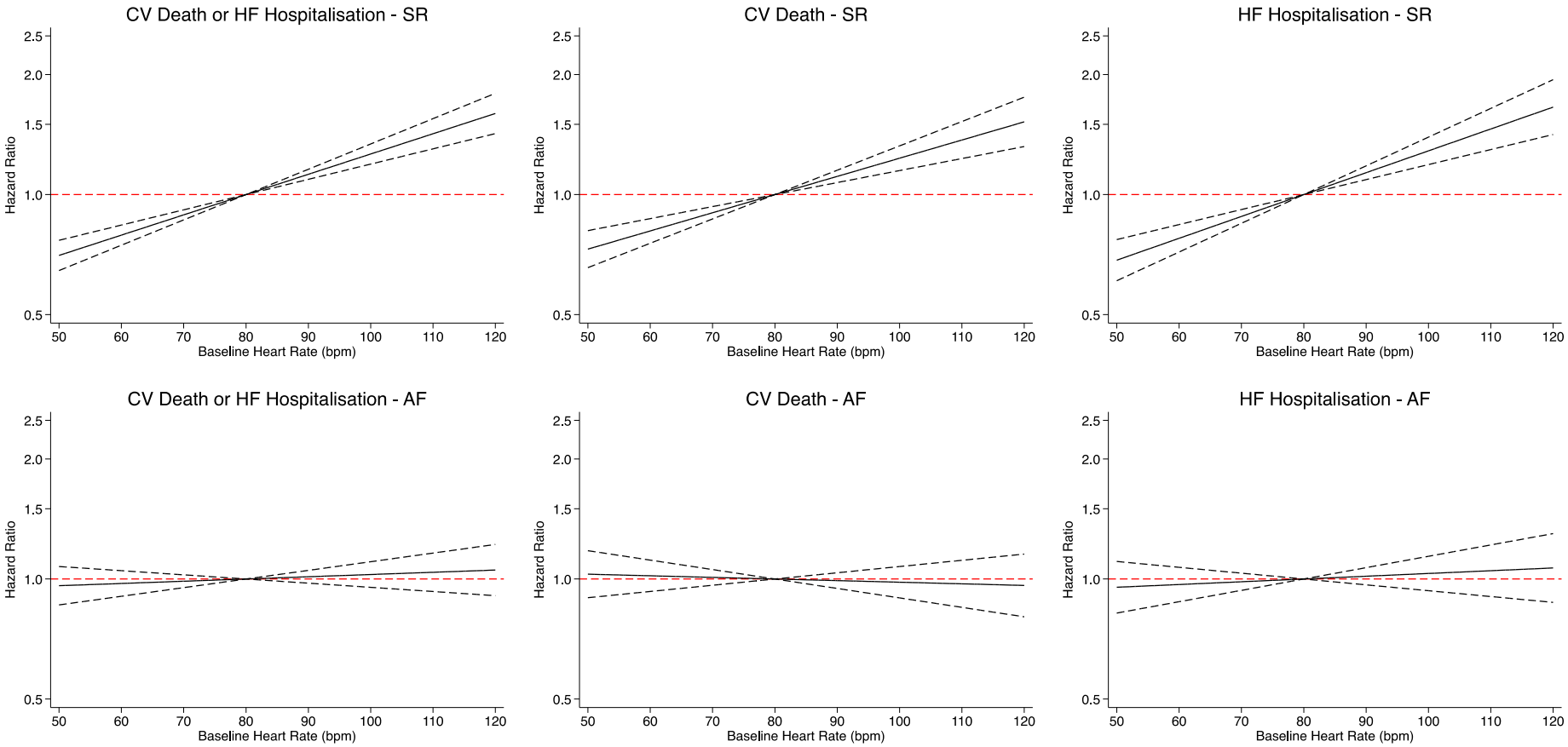
Event curves for outcomes according to baseline heart rhythm and heart rate tertiles (tertile 1 lowest/tertile 3 highest).
SR = sinus rhythm; AF = atrial fibrillation.

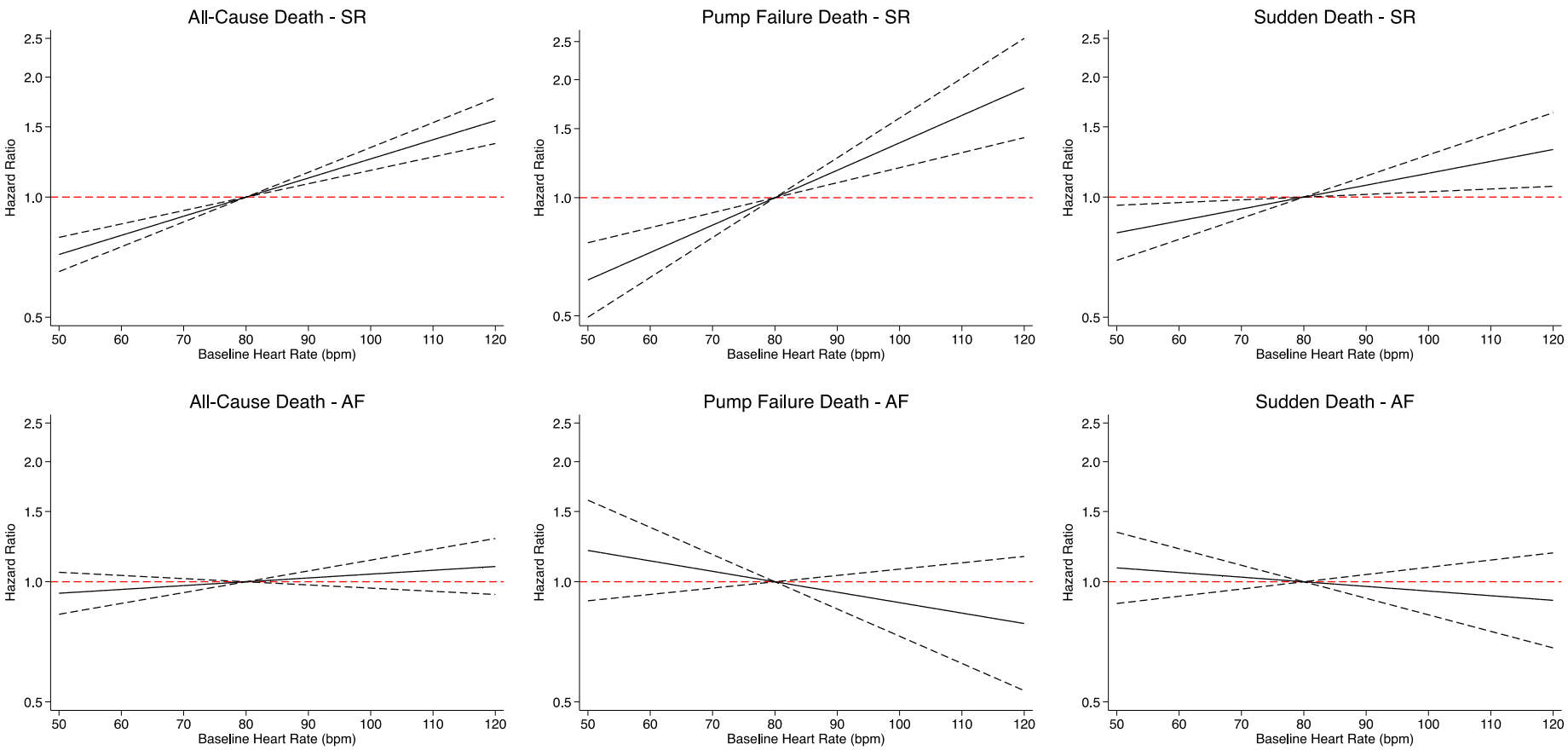
Figure 3: Forest plot of relationship between baseline heart rate and outcomes by baseline heart rhythm



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 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 beta-blocker, treatment with digoxin, treatment with amiodarone and randomized treatment (enalapril, sacubitril/valsartan, aliskiren, or combination).
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 4: 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 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).
SR = sinus rhythm; AF = atrial fibrillation.

Supplementary Material

Supplementary Table 1: Baseline characteristics according to heart rhythm on baseline ECG

Supplementary Table 2: Sensitivity analysis – AF analysed in sinus rhythm heart rate tertiles

Supplementary Table 1: Baseline characteristics according to heart rhythm on baseline ECG

	Sinus rhythm (n=10,113)	Atrial fibrillation (n=3449)	p-value
Age, years	61.9 ± 11.8	66.6 ± 10.4	<0.001
Female sex	2335 (23.1%)	712 (20.6%)	0.003
Region			<0.001
North America	442 (4.4%)	85 (2.5%)	
Latin America	1880 (18.6%)	428 (12.4%)	
Western Europe	2267 (22.4%)	824 (23.9%)	
Central Europe	2683 (26.5%)	1696 (49.2%)	
Asia/Pacific and other	2841 (28.1%)	416 (12.1%)	
Race			<0.001
White	5881 (58.2%)	2771 (80.3%)	
Black	407 (4.0%)	57 (1.7%)	
Asian	2751 (27.2%)	386 (11.2%)	
Other	1074 (10.6%)	235 (6.8%)	
SBP, mmHg	122.6 ± 17.0	123.8 ± 16.1	<0.001
Heart rate, beats/minute	70.10 ± 13.1	79.86 ± 17.2	<0.001
eGFR <60ml/min/1.73 m^2	2867 (28.3%)	1168 (33.9%)	<0.001
eGFR ml/min/1.73 m^2	72.5 ± 22.0	68.7 ± 23.1	<0.001
Ischaemic HF aetiology	6186 (61.2%)	1715 (49.7%)	<0.001
Ejection fraction, %	28.66 ± 6.0	30.62 ± 5.5	<0.001
BMI, kg/m2	27.3 ± 5.4	29.2 ± 5.5	<0.001
NYHA functional class			<0.001
I	451 (4.5%)	66 (1.9%)	
II	7319 (72.4%)	2132 (61.9%)	
III	2268 (22.4%)	1208 (35.1%)	
IV	70 (0.7%)	39 (1.1%)	
Duration of HF			<0.001
≤1 yr	3710 (36.7%)	930 (27.0%)	
1-5 yrs	3807 (37.7%)	1379 (40.0%)	
>5yrs	2592 (25.6%)	1140 (33.1%)	
Current smoker	1539 (15.2%)	358 (10.4%)	<0.001
History of			
Hypertension	6464 (63.9%)	2626 (76.1%)	<0.001
Diabetes	3224 (31.9%)	1029 (29.8%)	0.025
Myocardial infarction	4679 (46.3%)	947 (27.5%)	<0.001
Valvular heart disease	300 (5.6%)	157 (8.2%)	<0.001
Heart failure hospitalisation	6025 (59.6%)	2238 (64.9%)	<0.001
Stroke	700 (6.9%)	339 (9.8%)	<0.001
COPD	1144 (11.3%)	455 (13.2%)	0.003
Cancer	369 (3.6%)	140 (4.1%)	0.27
Medications at baseline			
Beta-blocker	9318 (92.1%)	3182 (92.3%)	0.82
MRA	4672 (46.2%)	1659 (48.1%)	0.05
Diuretic	7844 (77.6%)	2919 (84.6%)	<0.001
Digoxin	2421 (23.9%)	1787 (51.8%)	<0.001
Amiodarone	858 (8.5%)	254 (7.4%)	0.039
Statins	5776 (57.1%)	1449 (42.0%)	<0.001
Anticoagulation therapy	1577 (15.6%)	2394 (69.4%)	<0.001
Aspirin	6085 (60.2%)	993 (28.8%)	<0.001
Other antiplatelet	1708 (16.9%)	206 (6.0%)	<0.001
Any antiplatelet	6549 (64.8%)	1107 (32.1%)	<0.001
ICD§	1064 (10.5%)	207 (6.0%)	<0.001

CRT	154 (1.5%)	28 (0.8%)	0.002
NT-proBNP, pg/ml ∫	1230.5 (681.5 - 2477.5)	1794.0 (1070.0 - 3229.0)	<0.001
KCCQ clinical summary score‡	81.3 (64.6 - 92.7)	74.0 (56.8 - 87.5)	<0.001

Values are mean ± SD, n (%), or median (interquartile range). A total of 1715 patients had a paced rhythm on baseline electrocardiogram and an additional 138 had missing baseline electrocardiogram information and are not included in the table. § Includes both patients with implantable cardioverter defibrillator and implantable cardioverter defibrillator with cardiac resynchronisation ∫ Missing in 605 patients. ‡Missing in 1,774 patients. BMI = body mass index; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; eGFR = estimated glomerular filtration rate; HF = heart failure; ICD = implantable cardioverter defibrillator; KCCQ = Kansas City Cardiomyopathy Questionnaire; NT-proBNP = N-terminal pro–B type natriuretic peptide; NYHA = New York Heart Association.

Supplementary table 2: Sensitivity analysis – AF analysed in sinus rhythm heart rate tertiles

	Sinus rhythm (n=10,113)						Atrial fibrillation (n=3449)					
	Events (%)	Crude rate per 100 PY (95% CI)	Unadjusted HR (95% CI)	p value	Adjusted HR (95% CI)	p value	Events (%)	Crude rate per 100 PY (95% CI)	Unadjusted HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Primary Composite: CV death or HF hospitalisation												
T1	785 (22.6)	8.6 (8.0-9.2)	1.00 (Reference)		1.00 (Reference)		167 (31.4)	13.1 (11.2-15.2)	1.00 (Reference)		1.00 (Reference)	
T2	1008 (27.4)	11.4 (10.7-12.1)	1.32 (1.20-1.45)	<0.001	1.25 (1.13-1.37)	<0.001	295 (31.9)	12.9 (11.5-14.5)	0.99 (0.82-1.20)	0.926	1.10 (0.91-1.34)	0.314
T3	970 (32.8)	15.0 (14.1-16.0)	1.72 (1.57-1.90)	<0.001	1.50 (1.35-1.66)	<0.001	566 (28.9)	12.3 (11.3-13.3)	0.94 (0.79-1.12)	0.470	1.02 (0.85-1.22)	0.826
HF hospitalisation												
T1	416 (12.0)	4.5 (4.1-5.0)	1.00 (Reference)		1.00 (Reference)		94 (17.7)	7.3 (6.0-9.0)	1.00 (Reference)		1.00 (Reference)	
T2	555 (15.1)	6.3 (5.8-6.8)	1.36 (1.20-1.55)	<0.001	1.30 (1.14-1.48)	<0.001	166 (17.4)	7.3 (6.3-8.5)	0.99 (0.77-1.27)	0.922	1.11 (0.86-1.43)	0.423
T3	539 (18.2)	8.3 (7.7-9.1)	1.79 (1.58-2.04)	<0.001	1.60 (1.39-1.83)	<0.001	316 (16.1)	6.9 (6.1-7.7)	0.93 (0.73-1.16)	0.508	1.03 (0.81-1.30)	0.822
CV death												
T1	513 (14.8)	5.3 (4.9-5.8)	1.00 (Reference)		1.00 (Reference)		122 (22.9)	8.8 (7.3-10.5)	1.00 (Reference)		1.00 (Reference)	
T2	654 (17.8)	6.9 (6.3-7.4)	1.29 (1.15-1.45)	<0.001	1.21 (1.07-1.36)	0.002	207 (21.7)	8.3 (7.2-9.5)	0.95 (0.76-1.18)	0.632	1.04 (0.83-1.30)	0.765
T3	650 (22.0)	9.0 (8.4-9.7)	1.70 (1.52-1.91)	<0.001	1.41 (1.24-1.59)	<0.001	362 (18.5)	7.2 (6.5-7.9)	0.82 (0.67-1.01)	0.061	0.91 (0.73-1.12)	0.373
Pump failure death												
T1	108 (3.1)	1.1 (0.9-1.4)	1.00 (Reference)		1.00 (Reference)		37 (7.0)	2.7 (1.9-3.7)	1.00 (Reference)		1.00 (Reference)	
T2	146 (4.0)	1.5 (1.3-1.8)	1.37 (1.07-1.76)	0.013	1.33 (1.03-1.72)	0.029	54 (5.7)	2.2 (1.6-2.8)	0.81 (0.54-1.24)	0.334	0.95 (0.62-1.46)	0.827
T3	158 (5.3)	2.2 (1.9-2.6)	1.98 (1.55-2.53)	<0.001	1.70 (1.30-2.22)	<0.001	77 (3.9)	1.5 (1.2-1.9)	0.57 (0.39-0.85)	0.006	0.74 (0.49-1.12)	0.155
Sudden death												
T1	228 (6.6)	2.4 (2.1-2.7)	1.00 (Reference)		1.00 (Reference)		56 (10.5)	4.0 (3.1-5.2)	1.00 (Reference)		1.00 (Reference)	
T2	306 (8.3)	3.2 (2.9-3.6)	1.34 (1.13-1.59)	0.001	1.20 (1.01 -1.43)	0.040	77 (8.1)	3.1 (2.5-3.8)	0.76 (0.54-1.08)	0.126	0.83 (0.58-1.18)	0.293
T3	290 (9.8)	4.0 (3.6-4.5)	1.67 (1.41-1.99)	<0.001	1.28 (1.06-1.54)	0.011	164 (8.4)	3.2 (2.8-3.8)	0.81 (0.59-1.09)	0.163	0.83 (0.60-1.13)	0.237
All-cause death												
T1	622 (17.9)	6.4 (6.0-7.0)	1.00 (Reference)		1.00 (Reference)		146 (27.4)	10.5 (8.9-12.3)	1.00 (Reference)		1.00 (Reference)	
T2	776 (21.1)	8.1 (7.6-8.7)	1.27 (1.14-1.41)	<0.001	1.22 (1.09-1.36)	<0.001	234 (24.5)	9.3 (0.8-10.6)	0.89 (0.73-1.10)	0.278	0.98 (0.79-1.20)	0.824
T3	750 (25.4)	10.4 (9.7-11.2)	1.63 (1.46-1.81)	<0.001	1.43 (1.27-1.60)	<0.001	452 (23.0)	8.9 (8.2-9.8)	0.86 (0.71-1.03)	0.103	0.98 (0.81-0.19)	0.816

Tertile distribution for AF patients: T1 ≤63 bpm [n=532], T2 64-75 bpm [n=955], T3 ≥76 bpm [n=1962). 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; PY = person-years; T1 = tertile 1; T2 = tertile 2; T3 = tertile 3. Other abbreviations as per Supplementary Table 1.