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Short title: Heart Rate, Rhythm, Beta-Blockers, and Heart Failure

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Abstract

Background: The relationship between mortality and heart rate remains unclear for patients with heart failure and reduced ejection fraction (HFrEF) in either sinus rhythm or atrial fibrillation (AF).

Objective: To investigate the prognostic importance of heart rate in HFrEF in randomized controlled trials (RCTs) comparing beta-blockers and placebo.

Methods: The Beta-blockers in Heart Failure Collaborative Group performed a meta-analysis of harmonized individual-patient data from eleven double-blind RCTs. The primary outcome was all-cause mortality, analysed with Cox proportional hazard ratios (HR) modelling heart rate measured at baseline and approximately six-months post-randomization.

Results: A higher heart rate at baseline was associated with greater all-cause mortality in patients with sinus rhythm (n=14,166; adjusted HR 1.11 per 10 beats/minute; 95% CI 1.07-1.15, p<0.0001), but not in AF (n=3,034; HR 1.03 per 10 beats/minute; 0.97-1.08, p=0.38). Beta-blockers reduced ventricular rate by 12 beats/minute in both sinus rhythm and AF. Mortality was lower for patients in sinus rhythm randomised to beta-blockers (HR 0.73 versus placebo, 95% CI 0.67-0.79; p<0.001), regardless of baseline heart rate (interaction p=0.35). Beta-blockers had no effect on mortality in patients with AF (HR 0.96, 95% CI 0.81-1.12; p=0.58) at any heart rate (interaction p=0.48). A lower achieved resting heart rate, irrespective of treatment, was associated with better prognosis only for patients in sinus rhythm (HR 1.16 per 10 beats/minute increase, 95% CI 1.11-1.22; p<0.0001).

Conclusions: Regardless of pre-treatment heart rate, beta-blockers reduce mortality in patients with HFrEF in sinus rhythm. Achieving a lower heart rate is associated with better prognosis, but only for those in sinus rhythm.

Key Words: Heart failure; Heart rate; Beta-blockers; Atrial fibrillation; Individual-Patient-Data-Meta-Analysis

Condensed Abstract (100 words)

Meta-analysis of individual-patient data from eleven double-blind randomized trials found that higher baseline heart rate was associated with greater all-cause mortality for those in sinus rhythm, but not for those in AF. Mortality was lower for patients in sinus rhythm assigned beta-blockers (HR 0.73, 95% CI 0.67-0.79; p<0.001), regardless of baseline heart rate. Beta-blockers had no effect on mortality in patients with AF (HR 0.96, 95% CI 0.81-1.12; p=0.58) at any heart rate. A lower achieved resting heart rate was associated with better prognosis only for patients in sinus rhythm (HR 1.16 per 10 beats/minute increase, 95% CI 1.11-1.22; p<0.0001).

Abbreviations

AF	atrial fibrillation
CI	confidence intervals
ECG	electrocardiogram
GFR	glomerular filtration rate
HFrEF	heart failure and reduced left ventricular ejection fraction
HR	hazard ratios
IPD	individual patient data
IQR	interquartile range
LVEF	left ventricular ejection fraction

RCT	randomized controlled trial
SD	standard deviation

Introduction

Beta-blockers reduce morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (HFrEF) in sinus rhythm (1,2). It is not clear whether the key mechanism underpinning their benefits is protection of adrenergic receptors from heightened sympathetic activity or reduction in heart rate. It is also uncertain whether the efficacy of beta-blockers is related to dose, reduction in heart rate or achieved heart rate.(3-10) These questions are conceptually important for how clinicians manage and follow-up patients with HFrEF. Furthermore, there may be a clinically important interaction with heart rhythm.(11) Although beta-blockers reduce the incidence of new-onset atrial fibrillation (AF) in HFrEF(1,12), they do not appear to reduce mortality for patients with established HFrEF and concomitant AF.(1)

The Beta-blockers in Heart Failure Collaborative Group pooled individual patient-data (IPD) from major randomized controlled trials (RCTs) comparing beta-blockers to placebo in patients with heart failure in order to investigate further their efficacy and safety.(13) With almost all the available IPD, this analysis permits a robust assessment of the associations between heart rate, heart rhythm and mortality. Our aims were to answer three questions for patients with HFrEF according to their heart rhythm: 1) does baseline heart rate predict mortality?; 2) does the effect of beta-blockers on mortality differ according to baseline heart rate?; and 3) what is the association between achieved heart rate, achieved dose and mortality?

Methods

The Beta-blockers in Heart Failure Collaborative Group (BB-meta-HF) includes leading investigators from relevant landmark trials, with the support of the pharmaceutical companies that conducted them (AstraZeneca, GlaxoSmithKline, Merck Serono and Menarini). This report was prepared according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) IPD guidance(14) and prospectively registered with Clinicaltrials.gov

(NCT0083244) and the PROSPERO database of systematic reviews (CRD42014010012).(15) Detailed rationale and methods have previously been published (1,2,13). Each trial required appropriate ethical approval.

Eligibility & search strategy

A systematic search was performed of Medline and Current Contents, scrutiny of reference lists of trials, trials registries, meeting abstracts, review articles as well as discussion with group members and pharmaceutical manufacturers (1,2,13). We included RCTs that reported mortality as a primary or part of a composite outcome comparing beta-blockers versus placebo with recruitment of >300 patients and planned follow-up of >6 months. Eleven studies were included that account for 95.7% of eligible participants recruited in RCTs based on a systematic literature review: the Australia/New Zealand Heart Failure Study (ANZ)(16), the Beta-Blocker Evaluation Survival Trial (BEST)(17), the Carvedilol Post-Infarct Survival Control in LV Dysfunction Study (CAPRICORN)(18), the Carvedilol Hibernating Reversible Ischaemia Trial: Marker of Success Study (CHRISTMAS)(19), the Cardiac Insufficiency Bisoprolol Study (CIBIS I)(20), the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II)(21), the Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS)(22), the Metoprolol in Idiopathic Dilated Cardiomyopathy Study (MDC)(23), the Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF)(24), the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS) (25) and the U.S. Carvedilol Heart Failure Study (US-HF).(26) All included studies had low risk of bias (27).

Data collection & IPD integrity

Data were extracted from original source files provided by the pharmaceutical companies and lead investigators.(13) All trials provided IPD and databases were harmonized according to a standardized data request form to match patient characteristics and outcomes across all trials. Discrepancies, inconsistencies and incomplete data were checked against original case report forms, trial documentation and published reports to ensure IPD integrity. The clinically-derived resting heart rate was used in analysis, as this was consistently recorded in all trials at each major study visit. Due to the small amount of missing data, imputation was not performed.

Participants

We included all patients with a baseline electrocardiogram (ECG) that showed either sinus rhythm or AF/atrial flutter. For the purposes of this report, reference to AF therefore includes atrial flutter.(1) Patients with a missing baseline ECG or a paced rhythm were excluded. We also excluded all patients with documented heart block, as 2nd/3rd degree heart block was an exclusion criterion in some of the trials.

Outcomes & effect measures

The outcome for this analysis was all-cause mortality, including additional deaths on follow-up available from seven studies (19-21, 25, 26, 28, 29). Our analysis used heart rate as a continuous variable and also categorized into pre-specified clinical groups (<70, 70-90 and >90 beats/minute). All trials excluded patients with lower heart rates, as defined in **Figure 1**.

Statistical analysis

A statistical analysis plan was generated and finalized by the Collaborative Group in advance of data analysis. Summary results are presented as percentages, or median and interquartile range (IQR; displayed as 25^{th} to 75^{th} quartiles). Estimated glomerular filtration rate

(GFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula, normalized to a body surface area of 1.73 m^2.

All analyses followed the principle of intention to treat. Baseline heart rhythm groups (sinus rhythm or AF) were analysed separately. Outcomes were analysed using a Cox proportional hazards regression model(28), stratified by study. This is a one-stage fixed effects approach and assumes that all trials are estimating a common treatment effect with baseline hazards that vary across studies. The independent variable was continuously-distributed heart rate. We assessed the relationship between continuous heart rate and mortality using fractional polynomials to find the best transformation(29), however a linear association was the best fit (with note taken of the scarce data below a heart rate of 60 beats/minute due to trial exclusion criteria). Hazard ratios (HR) and 95% confidence intervals (CI) are presented, along with corresponding p-values. We pre-specified adjustment in Cox models for age, gender, left-ventricular ejection fraction, systolic blood pressure, prior myocardial infarction, and baseline use of angiotensin converting enzyme inhibitors/angiotensin receptor blockers and diuretic therapy. Treatment allocation and heart rate were also adjusted for, where appropriate. The goodness-of-fit C-statistic for the main stratified Cox model was 0.66 for sinus rhythm and 0.64 for AF at 20 months. Kaplan-Meier plots were used to graph the pooled trial data. Few patients were followed for more than three years and therefore data were censored at 1200 days (3.3 years) from randomization. Heterogeneity was assessed using the chi-squared test and I^2 statistic, with the estimate of heterogeneity taken from the inverse-variance fixed-effects two-stage model.(30) Predefined sensitivity analyses were alternative censor points (1 year and 2 year), alternative methodology (two-stage meta-analysis and fixed versus random effects(31)) and restriction to a heart rate between 60 and 140 beats/minute at baseline.

Analyses at the interim study time-point (mean of 184 days from randomization) excluded those who had died, withdrawn consent or were lost to follow-up. Not all patients attended an interim visit or had a heart rate recorded at this time; however, the number of patients without interim data was similar across treatment groups for both sinus rhythm and AF. Furthermore, there was no significant difference in baseline heart rate compared to those with interim data, or any difference in the observed hazards for either heart rate or beta-blocker efficacy. We performed two post-hoc analyses not detailed in our pre-specified analysis plan: (i) assessment of mortality in patients on beta-blockers who attained a heart rate <60 beats/minute; and (ii) assessment of mortality according to beta-blocker dose achieved at the interim visit. There were missing data on dosage in all studies, and two studies provided no information.(17,19) For consistency across the different beta-blockers and trials, dose achieved was expressed as the percentage of maximum target dose according to the particular beta-blocker and specific trial design.

There was no evidence of violation of the proportional hazards assumption in any multivariate model as determined by Schoenfeld residuals.(32) Effect modification was assessed using p-values from interaction terms fitted in the multivariate models.(29,33) A two-tailed p-value of 0.05 was considered statistically significant. Analyses were performed on Stata Version 14.1 (StataCorp LP, Texas) and R Version 3.2.1 (R Core Team, Vienna).

Results

Individual patient-data were obtained for 18,637 patients. Patients were excluded due to a missing baseline electrocardiogram (n=118), heart block (n=510) or paced rhythm (n=616). A further 15 participants had missing baseline heart rate. The final cohort included 14,313 patients

in sinus rhythm and 3,065 in AF (**Figure 1**). Three patients (one in sinus rhythm and two in AF) had missing event dates and were excluded from outcome analyses.

Median age was 65 years (IQR 55-72), 24% were women, and median left ventricular ejection fraction (LVEF) at baseline was 0.27 (IQR 0.21-0.33). Median baseline heart rate was 80 beats/minute for those in sinus rhythm (IQR 72-88) and 81 beats/minute for those in AF (IQR 72-92). Characteristics according to baseline heart rhythm are presented in **Table 1**. Regardless of heart rhythm, patients with higher heart rate were younger and more likely to be women, have non-ischemic cardiomyopathy and have lower LVEF and more severe symptoms. There were no differences in patient characteristics according to randomized treatment for either sinus rhythm (**Online Table 1**) or AF (**Online Table 2**) in any heart rate group.

Heart rate at baseline and mortality for patients in sinus rhythm or AF

For patients in sinus rhythm, there were 2,141 deaths in 14,166 patients (15.1%) over a mean follow-up of 1.5 years (SD 1.1). Baseline heart rate was associated with all-cause mortality, with a HR of 1.11 per 10 beats/minute (95% CI 1.07-1.15, p<0.0001), adjusted for baseline variables and treatment allocation. From the Kaplan Meier analysis (**Figure 2-A**), higher baseline heart rates were associated with higher mortality in patients assigned to either placebo or beta-blockers.

For patients in AF at baseline, there were 609 deaths in 3,034 patients (20.1%), but there was no association between baseline heart rate and mortality (adjusted HR 1.03, 95% CI 0.97-1.08, p=0.38; **Figure 2-B**).

The **Central Illustration** displays the modelling of heart rate as a continuous variable and the hazard ratio of death, according to baseline heart rhythm. Contrary to results in sinus rhythm, there was no relationship between baseline heart rate and mortality for those in AF

(p=0.003 for interaction). Sensitivity analyses showed similar results to the main findings (**Online Table 3**).

Efficacy of beta-blockers according to baseline heart rate

Beta-blockers reduced heart rate by 11 to 12 beats/minute in both sinus rhythm and AF (**Online Table 4** and **Figure 1**). The overall HR for mortality comparing beta-blockers with placebo for patients in sinus rhythm was 0.73 (95% CI 0.67-0.79; p<0.0001) with similar benefit for all three strata of baseline heart rate (**Table 2** and **Figure 3).** There was no interaction with baseline heart rate as a continuous variable (p=0.35).In contrast, beta-blockers did not reduce mortality for patients in AF, either overall (HR 0.96, 95% CI 0.81-1.12; p=0.58) or for any baseline heart rate stratum (interaction p=0.48; **Table 2**). Similar results were seen in sensitivity analyses (**Online Table 3**).

Achieved versus change in post-randomization heart rate and mortality

A landmark analysis was performed, starting at an interim visit after expected dose-titration for each surviving participant (mean of 184 ± 144 days from randomization)with a recorded interim heart rate (n=12,441 in sinus rhythm and n=2,566 in AF). Mean heart rate was similar at the interim and final visits for surviving patients in sinus rhythm or AF, suggesting stable beta-blockade had been reached (**Online Figure 1**).

For patients in sinus rhythm, the heart rate achieved at the interim visit was more strongly associated with mortality than the change in heart rate from baseline (HR per 10 beats/minute 1.16, 95% CI 1.11-1.22; **Online Table 5**). The lowest mortality in sinus rhythm was observed in patients who attained lower heart rates after beta-blocker therapy **(Figure 4-A)**. Conversely, in patients with AF, neither attained nor change in heart rate were associated with survival **(Figure 4-B and Online Table 5)**.

Analysis of post-randomization beta-blocker dosage in sinus rhythm

Separately-fitted models in patients with sinus rhythm for those assigned to placebo or beta-blockers showed consistent findings for the association of interim heart rate and mortality. In patients randomized to beta-blockers (n=6,327), the adjusted HR was 1.12 per 10 beats/minute (95% CI 1.05-1.19). In patients randomized to placebo, where dose does not affect heart rate (n=6,114), the adjusted HR was 1.13 per 10 beats/minute (95% CI 1.08-1.19).

Analysis of dose achieved (**Online Table 6**) was complicated by susceptibility to bias due to non-random missing data. Achieving a higher dose was associated with lower mortality in both the placebo and beta-blocker arms (**Online Figure 2**).

Discussion

Our analysis confirms a reduction in mortality with beta-blockers for patients with HFrEF in sinus rhythm, irrespective of pre-treatment heart rate within the studied range. Resting heart rate is an important prognostic indicator, both before and after initiation of beta-blockers; a lower achieved heart rate is associated with lower subsequent mortality and is more likely to occur in patients initiated on a beta-blocker. In patients with concomitant AF, heart rate was not associated with mortality and beta-blockers did not reduce mortality at any observed heart rate.

Insights on the mechanism of action of beta-blockers

Whether reduction in morbidity and mortality in patients with HFrEF in sinus rhythm is related to myocardial protection from heightened sympathetic activity or due to reductions in heart rate is uncertain. Chronic adrenergic over-stimulation is thought to provoke myocyte dysfunction and arrhythmias(34), providing a theoretical rationale for prescribing beta-blockers for HFrEF. However, a large trial of moxonidine, which inhibits sympathetic activation, was stopped prematurely for harm, which casts doubt on this hypothesis.(35) Heart rate reduction

may also improve cardiac myocyte metabolism by conserving energy, improving calcium recycling, increasing diastolic blood flow and protecting against ischemia. Our finding that beta-blockers reduce mortality regardless of pre-treatment heart rate within the studied range, suggests that the mechanism of action of beta-blockers is not simply due to lowering heart rate. Moreover, ivabradine, which decreases heart rate by I_f-channel blockade rather than by sympathetic inhibition, did not reduce mortality overall when added to beta-blockers, although it did reduce the composite of cardiovascular death or hospital admission for worsening heart failure (36).

Divergent responses in patients with atrial fibrillation

Numerous observational studies suggest a relationship between resting heart rate and prognosis in patients with AF(37) and those with HFrEF in sinus rhythm (5,38). However, ventricular rate appears to be a poor predictor of outcomes for patients with concomitant HFrEF and AF. Lower ventricular rates in AF may even be associated with adverse prognosis(39), but why the relationship between heart rate and prognosis should differ by heart rhythm is uncertain. Perhaps, heart rate is a good reflection of sympathetic activation only for patients in sinus rhythm. A major determinant of heart rate is also vagal activity, which may be increased by beta-blockade and potentially more important for patients in sinus rhythm compared to AF.(40) Alternatively, the relationship could be confounded by an increase in risk associated with variable R-R intervals in AF or ventricular pauses.(41) The Rate Control Efficacy in Permanent Atrial Fibrillation (RACE-II) study, an RCT of strict compared to lenient heart rate control of AF, failed to show a difference in outcome between these strategies, even amongst those patients with concomitant heart failure (42).

We previously identified a highly significant interaction between the effects of beta-blockers on mortality and heart rhythm (p=0.002) (1), but why beta-blockers do not reduce mortality in HFrEF patients with AF remains unclear.(43,44) If their benefits are mediated by blocking adrenergic-receptors on cardiac myocytes, then heart rhythm should be irrelevant. Similarly, if their benefits are mediated by reducing ventricular rate then these should also be similar regardless of heart rhythm. Further work is clearly warranted to identify patterns of autonomic function and the effects of autonomic modulation in patients with heart failure and AF.

Target heart rate versus target dose

Whether clinicians should strive to achieve a target heart rate or a target does of beta-blocker remains unanswered and the authors of this paper were unable to reach a consensus. In this analysis, beta-blockers reduced mortality regardless of baseline heart rates for patients with HFrEF in sinus rhythm. All trial protocols, which form the basis for current international guidelines, requested titration to a target dose of beta-blocker, provided they were tolerated and did not cause excessive bradycardia. A dose-dependent improvement in LVEF and survival was observed in the Multicenter Oral Carvedilol Heart Failure Assessment (MOCHA) trial(45), although this trial only included 345 patients. No large trial has randomized patients to higher versus lower doses, although post-hoc analyses suggest greater benefit from higher doses.(3,9,46) A trial-level meta-analysis of seven dose-ranging studies of beta-blockers provided inconclusive evidence of a dose relationship with mortality (47); further prospective trials are required to clarify this issue.

Conversely, for those that believe that lowering heart rate is the key mediator of beta-blocker benefit for patients with HFrEF in sinus rhythm, our analysis supports the notion that

achieving a lower rate (~60 beats/minute) is beneficial, perhaps because it is a physiological marker indicating that adequate beta-receptor blockade has been achieved. The advantage of an approach that titrates to a target heart rate is clinical simplicity that, serendipitously, may lead to increased use of the guideline-recommended target doses of beta-blockers, as well as being a measure of patient adherence to therapy.

Ultimately, heart rate and prescribed beta-blocker dose are intimately related; one is a surrogate for the other although the relationship may be complicated by other factors such as genetic variations in beta-blocker response and drug metabolism. Our observation of dose-related differences in mortality in patients assigned to placebo clearly demonstrates that it is unsafe to make strong inference from any analysis of a post-randomization variable such as dose. Dose achieved is itself an outcome(48), affected by confounding patient factors, adherence, physician preferences and bias, including the perceived risk of adverse outcomes.

Limitations

This was a retrospective analysis and background therapy, including devices, will have changed since these trials were conducted. Heart rate was not measured in a standardized fashion across trials, and may have been less accurate in patients with AF. Although by using IPD we were able to adjust for many known confounders with sufficient power for statistical analysis, unmeasured variables may have affected heart rate or dose of beta-blocker. The trials had different patient populations and used different beta-blockers; we have previously demonstrated that excluding individual trials had no impact on results(1), and the diversity of trial participants could be considered a strength. Our analysis plan specified that only mortality would be analysed as an outcome. Although data on hospitalization were available, this outcome may be biased as heart rate can influence the likelihood of a physician admitting a patient. The

power to explore effects in the subgroup with AF is limited by its modest size (albeit large in comparison to many other reports) and includes a small number of patients with atrial flutter. Few patients with a resting heart rate <65 beats/minute were enrolled in these RCTs, and hence we are unable to comment on patients with slower heart rates prior to receiving a beta-blocker. There is uncertainty at where the nadir of risk in the relationship between heart rate and risk lies, but there will be a rate below which mortality rises.

Conclusions

Beta-blockers reduce mortality at all studied heart rates in patients with HFrEF in sinus rhythm, and those who achieved lower resting heart rates in dose-titrated randomized controlled trials had lower mortality. This does not hold true for patients with concomitant AF, for whom there was no mortality benefit from beta-blockade, nor a relationship between heart rate and mortality.

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FIGURE LEGENDS

CENTRAL ILLUSTRATION: Modeling of heart rate at baseline and the hazard of death. Hazard ratio for the effect of baseline heart rate on mortality relative to a patient with a heart rate of 80 beats/minute, showing a strong positive correlation in [A] sinus rhythm, but not in [B] atrial fibrillation. Note that all trials excluded patients with bradycardia at enrollment (**Figure 1**). HFrEF = heart failure with reduced ejection fraction.

Figure 1: Study flowchart. Population assessed, including numbers of participants from individual trials and exclusion criteria pertaining to heart rate in beats/minute (bpm). *The CHRISTMAS study excluded patients with atrial fibrillation.

Figure 2: Baseline heart rate and all-cause mortality. Kaplan Meier survival curves for [A] sinus rhythm and [B] atrial fibrillation in patients randomized to placebo or beta-blockers. Higher baseline heart rate is associated with higher risk of mortality in sinus rhythm but not in atrial fibrillation, with similar results in patients randomized to placebo or beta-blockers. bpm, beats/minute.

Figure 3: Mortality in patients randomly assigned to placebo or beta-blockers according to baseline heart rate in sinus rhythm. Beta-blockers versus placebo in patients with sinus rhythm, showing similar efficacy regardless of baseline heart rate group. For hazard ratios, see **Table 3**. ARR, absolute risk reduction; bpm, beats/minute; NNT, number needed to treat; RRR, relative risk reduction.

Figure 4: Heart rate measured at the interim visit and all-cause mortality for patients assigned to placebo or beta-blocker. Kaplan Meier survival curves censored from time of the interim visit (mean of 184 days from randomization), showing clear relationship between achieved heart rate and mortality for both placebo and beta-blocker patients in [A] sinus rhythm,

but not in [B] atrial fibrillation. Includes a post-hoc grouping of heart rate that separates patients <60 beats/minute (bpm) in the beta-blocker arm.

Table 1: Baseline characteristics

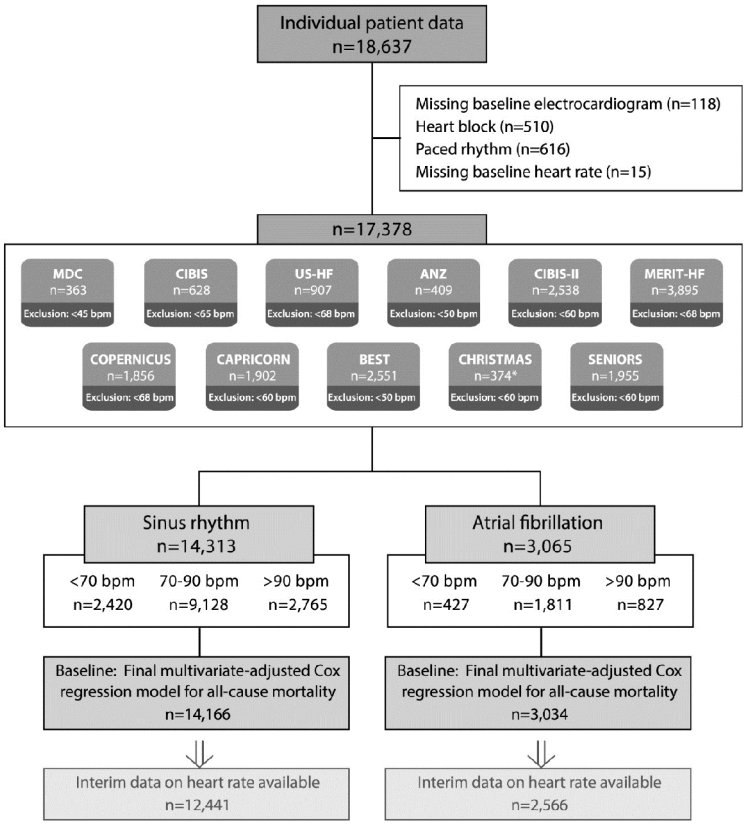
Characteristic	Sinus rhythm*			Atrial fibrillation†		
	Heart rate <70 bpm n=2,420	Heart rate 70-90 bpm n=9,128	Heart rate >90 bpm n=2,765	Heart rate <70 bpm n=427	Heart rate 70-90 bpm n=1,811	Heart rate >90 bpm n=827
Heart rate, median bpm (IQR)	65 (62 - 68)	80 (74 - 84)	98 (94 - 103)	65 (62 - 68)	80 (74 - 85)	100 (95 - 110)
Age, median years (IQR)	67 (58 - 73)	64 (55 - 71)	60 (50 - 69)	70 (62 - 76)	70 (61 - 75)	66 (59 - 73)
Women, %	507 (21.0%)	2303 (25.2%)	731 (26.4%)	74 (17.3%)	323 (17.8%)	197 (23.8%)
Years with HF diagnosis, median (IQR)	2 (1 - 5)	3 (1 - 6)	2 (1 - 5)	4 (2 - 7)	4 (2 - 7)	3 (1 - 7)
Ischemic HF etiology, %	1873 (77.4%)	6465 (70.8%)	1499 (54.2%)	258 (60.4%)	1023 (56.5%)	400 (48.4%)
Prior myocardial infarction, %	1649 (68.3%)	5463 (60.0%)	1197 (43.4%)	209 (49.3%)	747 (41.4%)	243 (29.5%)
Diabetes Mellitus, %	410 (18.0%)	2114 (24.5%)	778 (30.5%)	90 (22.2%)	407 (23.6%)	177 (22.6%)
NYHA class III/IV, %	1275 (56.8%)	4853 (64.5%)	1755 (76.2%)	280 (73.1%)	1059 (73.6%)	562 (82.8%)
LVEF, median % (IQR)	0.30 (0.24 - 0.35)	0.27 (0.21 - 0.33)	0.24 (0.19 - 0.30)	0.28 (0.22 - 0.33)	0.27 (0.22 - 0.33)	0.26 (0.20 - 0.33)
Systolic BP, median mmHg (IQR)	124 (112 - 140)	124 (111 - 140)	120 (110 - 135)	124 (110 - 140)	127 (114 - 140)	130 (115 - 145)
Diastolic BP, median mmHg (IQR)	75 (69 - 80)	78 (70 - 82)	78 (70 - 85)	74 (66 - 80)	80 (70 - 83)	80 (70 - 90)
Body mass index, median kg/m2 (IQR)	27 (24 - 30)	27 (24 - 31)	28 (24 - 33)	28 (25 - 32)	27 (25 - 31)	27 (25 - 31)
Estimated GFR, median mL/min (IQR)	65 (52 - 78)	64 (51 - 78)	65 (52 - 79)	59 (47 - 71)	60 (48 - 73)	63 (50 - 77)
Any diuretic therapy, %	1892 (78.2%)	7752 (84.9%)	2534 (91.6%)	391 (91.6%)	1682 (92.9%)	792 (95.8%)
ACEi or ARB, %	2278 (94.1%)	8633 (94.6%)	2615 (94.6%)	403 (94.4%)	1712 (94.5%)	782 (94.6%)
Aldosterone antagonists, %	154 (6.9%)	667 (7.8%)	272 (10.5%)	64 (15.3%)	285 (16.1%)	151 (18.9%)
Digoxin, %	934 (40.2%)	4669 (52.5%)	1772 (65.2%)	349 (81.7%)	1506 (83.2%)	704 (85.1%)

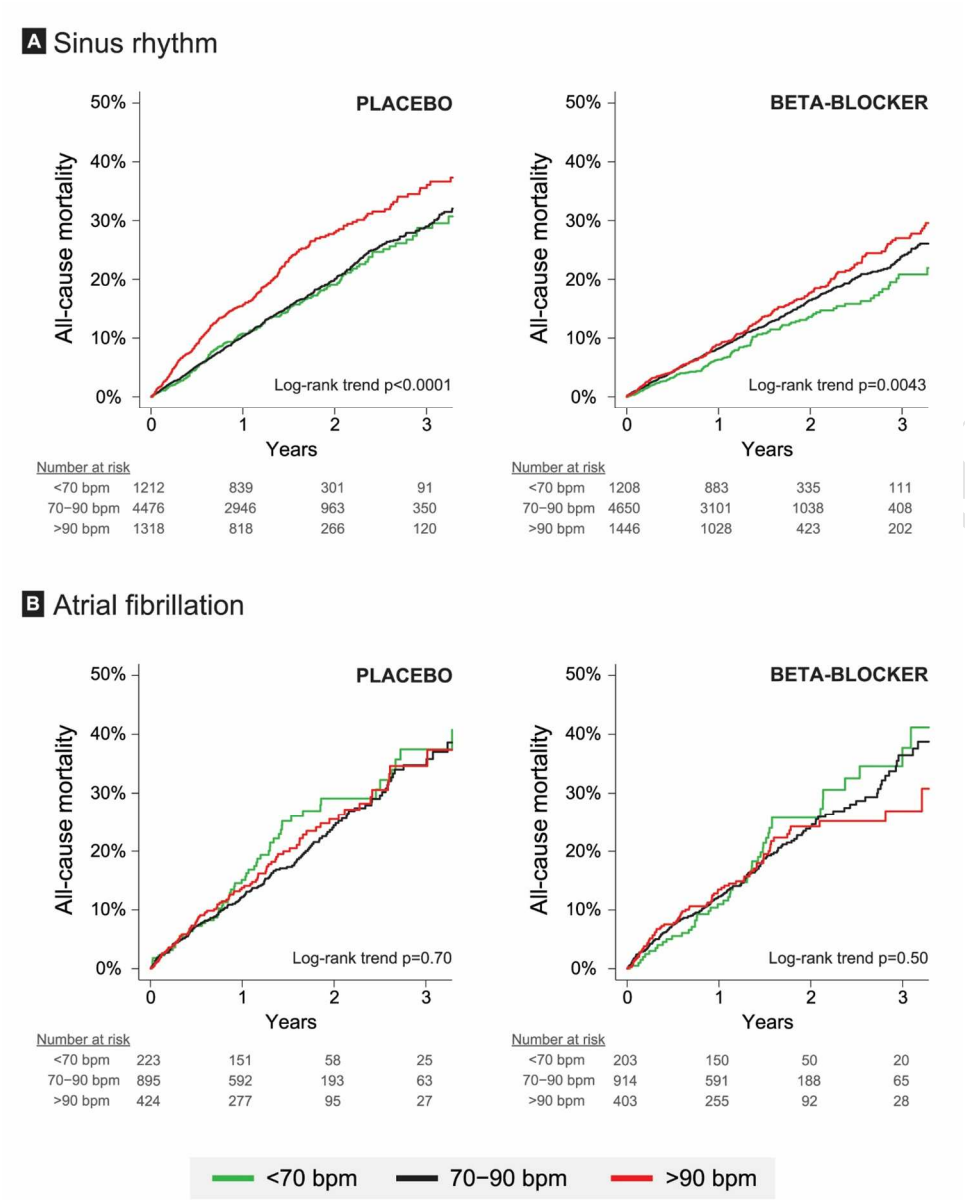
ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; bpm, beats/minute; GFR, glomerular filtration rate; HF, heart failure; IQR, interquartile range; LVEF, left-ventricular ejection fraction; NYHA, New York Heart Association. *See Online Table A for missing data report. †See Online Table B for missing data report.

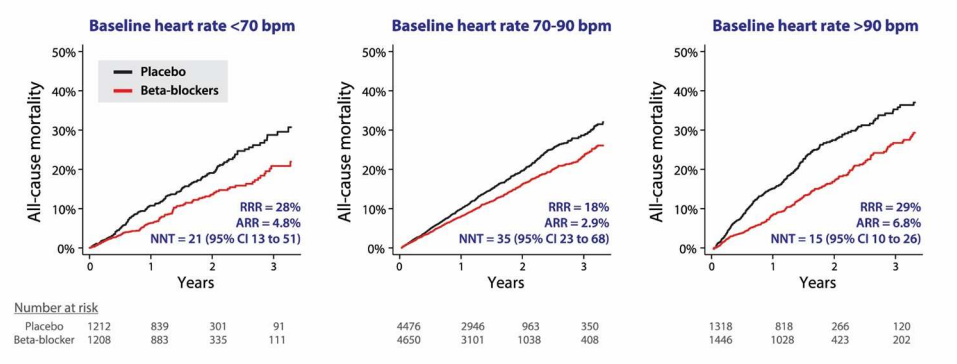
Table 2: Beta-blockers versus placebo and all-cause mortality according to baseline heart rate and rhythm at randomization

Beta-blockers versus placebo	**Heart rate <70 bpm**		**Heart rate 70-90 bpm**		**Heart rate >90 bpm**		**Interaction p-value for heart rate as a continuous variable**
	N (events /patients	HR, 95% CI, p-value	N (events /patients	HR, 95% CI, p-value	N (events /patients	HR, 95% CI, p-value	
Sinus rhythm	328 / 2,386	0.64, 0.51-0.80, p<0.0001	1,293 / 9,042	0.79, 0.71-0.89, p<0.0001	520 / 2,738	0.62, 0.52-0.74, p<0.0001	0.35
Atrial fibrillation	104 / 423	0.76, 0.51-1.13, p=0.18	345 / 1,791	1.07, 0.87-1.33, p=0.51	160 / 820	0.87, 0.63-1.19, p=0.38	0.48

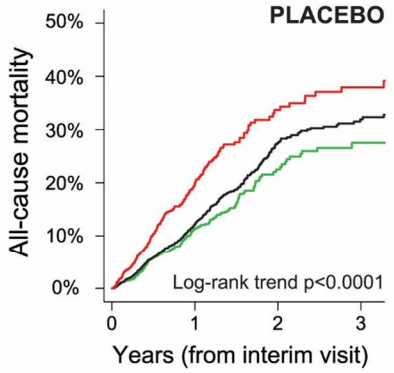
Hazard ratio (HR) analysed using the one-stage Cox regression model, with studies as strata (censor 1200 days); adjusted for age, gender, baseline left-ventricular ejection fraction, baseline systolic blood pressure, prior myocardial infarction, baseline angiotensin converting enzyme inhibitor/angiotensin receptor blocker, baseline diuretic therapy, randomized treatment allocation and baseline heart rate (within each heart rate group). Bpm, beats/minute; CI, confidence interval.

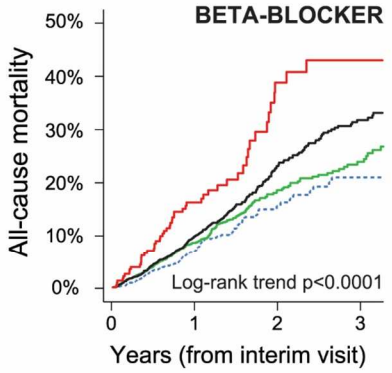



A Sinus rhythm
PLACEBO
BETA-BLOCKER
All-cause mortality
50%
40%
30%
20%
10%
0%
Log-rank trend p<0.0001
Log-rank trend p=0.0043
0
1
2
3
Years
Number at risk
<70 bpm 1212 839 301 91
70–90 bpm 4476 2946 963 350
>90 bpm 1318 818 266 120
<70 bpm 1208 883 335 111
70–90 bpm 4650 3101 1038 408
>90 bpm 1446 1028 423 202
B Atrial fibrillation
Log-rank trend p=0.70
Log-rank trend p=0.50
<70 bpm 223 151 58 25
70–90 bpm 895 592 193 63
>90 bpm 424 277 95 27
<70 bpm 203 150 50 20
70–90 bpm 914 591 188 65
>90 bpm 403 255 92 28
<70 bpm
70–90 bpm
>90 bpm



A Sinus rhythm

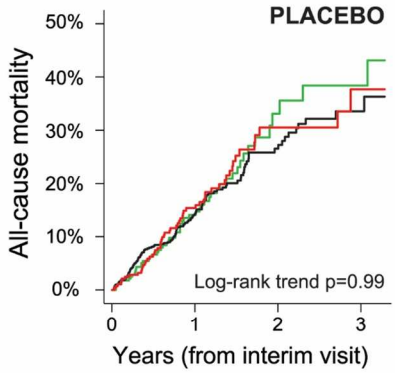


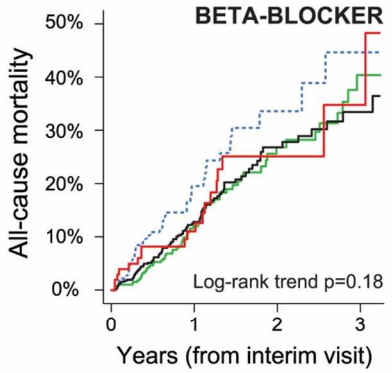


Number at risk				
<70 bpm	1432	654	161	66
70–90 bpm	3505	1553	370	170
>90 bpm	940	382	105	63

Number at risk				
<60 bpm	1091	522	127	64
60-69 bpm	2350	1099	317	138
70–90 bpm	2447	1178	348	161
>90 bpm	241	127	33	22

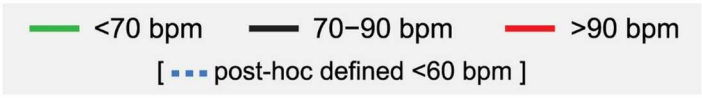
B Atrial fibrillation





Number at risk				
<70 bpm	283	140	27	13
70–90 bpm	712	329	102	25
>90 bpm	282	156	42	12

Number at risk				
<60 bpm	184	78	14	7
60-69 bpm	389	191	58	20
70–90 bpm	571	288	75	23
>90 bpm	103	54	12	4



Beta-blockers in Heart Failure Collaborative Group

Online Appendix (JACC013117-0413)

Heart rate, heart rhythm and prognostic effect of beta-blockers in heart failure: individual-patient data meta-analysis

Online Table 1: Baseline demographics by treatment allocation in sinus rhythm

Baseline characteristic *(sinus rhythm)*	**Heart rate <70 bpm**		**Heart rate 70-90 bpm**		**Heart rate >90 bpm**	
	Beta-blockers n=1,208	Placebo n=1,212	Beta-blockers n=4,650	Placebo n=4,478	Beta-blockers n=1,446	Placebo n=1,319
Heart rate, median bpm (IQR)	65 (62-68)	65 (62-68)	79 (74-84)	80 (75-84)	98 (94-102)	98 (94-103)
Age, median years (IQR)	67 (58-73)	66 (57-73)	64 (55-71)	64 (55-71)	60 (50-69)	59 (49-68)
Women, %	20.0%	21.9%	25.3%	25.2%	25.5%	27.3%
Years with HF diagnosis, median (IQR)	2 (1-6)	3 (1-5)	3 (1-6)	3 (1-6)	2 (1-5)	2 (1-5)
Ischemic HF etiology, %	77.1%	77.7%	70.6%	71.1%	55.8%	52.8%
Prior myocardial infarction, %	68.0%	68.7%	59.3%	60.6%	45.0%	41.9%
Diabetes Mellitus, %	19.1%	16.9%	24.6%	24.4%	28.3%	32.6%
NYHA class III/IV, %	56.2%	57.3%	65.0%	64.0%	75.6%	76.7%
LVEF, median % (IQR)	0.31 (0.25-0.35)	0.30 (0.23-0.35)	0.27 (0.21-0.33)	0.27 (0.21-0.33)	0.24 (0.19-0.30)	0.24 (0.18-0.30)
Systolic BP, median mmHg (IQR)	125 (112-140)	124 (112-140)	124 (112-140)	125 (110-140)	120 (110-136)	120 (108-135)
Diastolic BP, median mmHg (IQR)	75 (70-80)	75 (68-80)	78 (70-82)	78 (70-83)	79 (70-84)	77 (70-85)
Body mass index, median kg/m2 (IQR)	27 (24-30)	27 (24-30)	27 (24-31)	27 (24-31)	28 (24-33)	28 (25-33)
Estimated GFR, median mL/min (IQR)	65 (51-78)	65 (53-77)	64 (51-78)	63 (51-77)	65 (53-79)	65 (52-79)
Any diuretic therapy, %	78.1%	78.3%	85.1%	84.8%	91.4%	91.8%
ACEi or ARB, %	94.0%	94.3%	95.1%	94.1%	95.0%	94.2%
Aldosterone antagonists, %	6.7%	7.0%	7.5%	8.1%	11.4%	9.7%
Digoxin, %	38.1%	42.2%	52.1%	52.9%	64.0%	66.3%

Missing data report: n=2,835 missing for years with HF diagnosis; n=30 for prior myocardial infarction; n=842 for diabetes mellitus; n=1,505 for NYHA class; n=59 for LVEF; n=58 for systolic BP; n=63 for diastolic BP; n=665 for GFR; n=917 for aldosterone antagonists; n=374 for digoxin.

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; bpm, beats/minute; GFR, glomerular filtration rate; HF, heart failure; IQR, interquartile range; LVEF, left-ventricular ejection fraction; NYHA, New York Heart Association.

Online Table 2: Baseline demographics by treatment allocation in atrial fibrillation

Baseline characteristic *(atrial fibrillation)*	**Heart rate <70 bpm**		**Heart rate 70-90 bpm**		**Heart rate >90 bpm**	
	Beta-blockers n=204	Placebo n=223	Beta-blockers n=915	Placebo n=896	Beta-blockers n=403	Placebo n=424
Heart rate, median bpm (IQR)	65 (62-68)	65 (62-68)	80 (74-84)	80 (75-85)	100 (95-110)	100 (95-108)
Age, median years (IQR)	70 (63-75)	70 (61-76)	69 (61-75)	70 (61-75)	66 (58-73)	67 (59-72)
Women, %	16.6%	18.1%	17.2%	18.5%	23.8%	23.8%
Years with HF diagnosis, median (IQR)	4 (2-8)	3 (2-7)	3 (1-7)	4 (2-7)	3 (1-6)	3 (1-7)
Ischaemic HF etiology, %	60.1%	60.8%	57.6%	55.4%	50.5%	46.2%
Prior myocardial infarction, %	46.4%	52.5%	42.7%	40.2%	31.4%	27.4%
Diabetes Mellitus, %	19.7%	24.7%	23.4%	23.7%	20.0%	25.4%
NYHA class III/IV, %	71.5%	74.9%	73.9%	73.3%	82.8%	82.8%
LVEF, median % (IQR)	0.27 (0.22-0.32)	0.28 (0.23-0.33)	0.27 (0.22-0.33)	0.28 (0.22-0.34)	0.26 (0.21-0.33)	0.25 (0.20-0.32)
Systolic BP, median mmHg (IQR)	123 (110-138)	124 (110-140)	126 (113-140)	128 (115-140)	130 (115-145)	130 (114-143)
Diastolic BP, median mmHg (IQR)	74 (65-80)	75 (68-80)	78 (70-83)	80 (70-84)	80 (70-90)	80 (71-88)
Body mass index, median kg/m2 (IQR)	28 (25-32)	28 (25-32)	28 (25-31)	27 (24-30)	27 (25-31)	27 (25-31)
Estimated GFR, median mL/min (IQR)	59 (47-72)	59 (48-71)	60 (49-73)	59 (47-73)	64 (51-79)	63 (50-76)
Any diuretic therapy, %	91.0%	92.2%	92.7%	93.0%	94.8%	96.8%
ACEi or ARB, %	95.5%	93.1%	95.5%	93.6%	94.6%	94.5%
Aldosterone antagonists, %	17.1%	13.4%	15.4%	16.9%	19.7%	18.1%
Digoxin, %	83.0%	80.4%	83.1%	83.2%	85.4%	84.9%

Missing data report: n=319 missing for years with HF diagnosis; n=13 for prior myocardial infarction; n=149 for diabetes mellitus; n=431 for NYHA class; n=16 for LVEF; n=2 for diastolic BP; n=100 for GFR; n=85 for aldosterone antagonists.

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; bpm, beats/minute; GFR, glomerular filtration rate; HF, heart failure; IQR, interquartile range; LVEF, left-ventricular ejection fraction; NYHA, New York Heart Association.

Online Table 3: Sensitivity analyses

Sensitivity analysis	Events/patients	Hazard ratio for baseline heart rate per 10 bpm (95% CI), p-value	Hazard ratio for beta-blockers versus placebo (95% CI), p-value	p-value for interaction between baseline heart rate and beta-blocker efficacy
Sinus rhythm				
Censor at 365 days	1,251 / 14,166	1.13 (1.08 - 1.18), p < 0.0001	0.68 (0.61 - 0.77), p < 0.0001	0.26
Censor at 770 days	1 915 / 14,166	1.12 (1.08 - 1.16), p < 0.0001	0.72 (0.66 - 0.79), p < 0.0001	0.11
Heart rate 60-140 bpm	2 127 / 14,030	1.11 (1.07 - 1.15), p < 0.0001	0.73 (0.67 - 0.79), p < 0.0001	0.40
Two-stage fixed effects [1]	2,139 / 13,848	1.11 (1.07 - 1.15), p < 0.0001	0.74 (0.67 - 0.80), p < 0.0001	-
Two-stage random effects [1,2]	2,139 / 13,848	1.12 (1.07 - 1.17), p < 0.0001	0.71 (0.62 - 0.82), p < 0.0001	-
Additional adjustment [3]	2,045 / 13,307	1.10 (1.06 - 1.14) , p < 0.0001	0.73 (0.67 - 0.79), p < 0.0001	0.68
Atrial fibrillation [1]				
Censor at 365 days	355 / 3,034	1.06 (0.99 - 1.14), p = 0.11	0.97 (0.78 - 1.19), p = 0.75	0.81
Censor at 770 days	553 / 3,034	1.03 (0.97 - 1.09), p = 0.39	0.98 (0.83 - 1.16), p = 0.81	0.81
Heart rate 60-140 bpm	597 / 2,994	1.03 (0.98 - 1.10), p = 0.26	0.96 (0.82 - 1.13), p = 0.64	0.21
Two-stage fixed effects	609 / 3,034	1.03 (0.98 - 1.09), p = 0.26	0.97 (0.82 - 1.14), p = 0.70	-
Two-stage random effects [4]	609 / 3,034	1.01 (0.93 - 1.11), p = 0.74	0.97 (0.82 - 1.14), p = 0.70	-
Additional adjustment [3]	586 / 2,951	1.04 (0.98 - 1.10), p = 0.22	0.96 (0.81 - 1.13), p = 0.59	0.63

[1] Does not include the CHRISTMAS study. [2] Heterogeneity assessment in sinus rhythm: analysis of heart rate, I^2 =34.82%, p-value = 0.13; analysis of beta-blocker efficacy, I^2=53.35%, p-value = 0.02. [3] Includes adjustment for baseline aldosterone antagonists and digoxin, in addition to age, gender, left-ventricular ejection fraction, systolic blood pressure, prior myocardial infarction, baseline use of angiotensin converting enzyme inhibitors/angiotensin receptor blockers and diuretic therapy, and treatment allocation/heart rate where appropriate. [4] Heterogeneity assessment in AF: analysis of heart rate, I^2 =46.46%, p-value = 0.05; analysis of beta-blocker efficacy, I^2=0%, p-value = 0.74.

Bpm, beats/minute; CI, confidence interval.

Online Table 4: Effect of beta-blockers on heart rate

Rhythm at baseline	Placebo		Beta-blockers	
	N	Change in heart rate, baseline to interim visit; mean bpm (SD)	N	Change in heart rate, baseline to interim visit; mean bpm (SD)
Sinus rhythm	6,172	-1.7 (12.2)	6,399	-11.8 (13.0)
Atrial fibrillation	1,312	-2.6 (16.3)	1,280	-11.4 (16.3)

Bpm, beats/minute; SD, standard deviation.

Online Table 5: Attained versus change in heart rate

Statistical model	Events/patients	Hazard ratio (95% CI), p-value	
		Interim heart rate per 10 bpm	Change in heart rate per 10 bpm
Sinus rhythm			
Attained interim heart rate	1,643 / 12,441	1.13 (1.09 - 1.18), p <0.0001	-
Change from baseline heart rate	1,643 / 12441	-	0.97 (0.93 - 1.00), p = 0.09
Both attained and change in heart rate	1,643 / 12,441	1.16 (1.11 - 1.22), p <0.0001	1.05 (1.00 - 1.10), p = 0.0412
Atrial fibrillation			
Attained interim heart rate	457 / 2,566	1.03 (0.97 - 1.10), p = 0.33	-
Change from baseline heart rate	457 / 2,566	-	0.97 (0.91 - 1.02), p = 0.25
Both attained and change in heart rate	457 / 2,566	1.01 (0.94 - 1.09), p = 0.70	0.97 (0.91 - 1.05), p = 0.47

All models are adjusted and stratified as per Table 3 in the main paper. Bpm, beats/minute; CI, confidence interval.

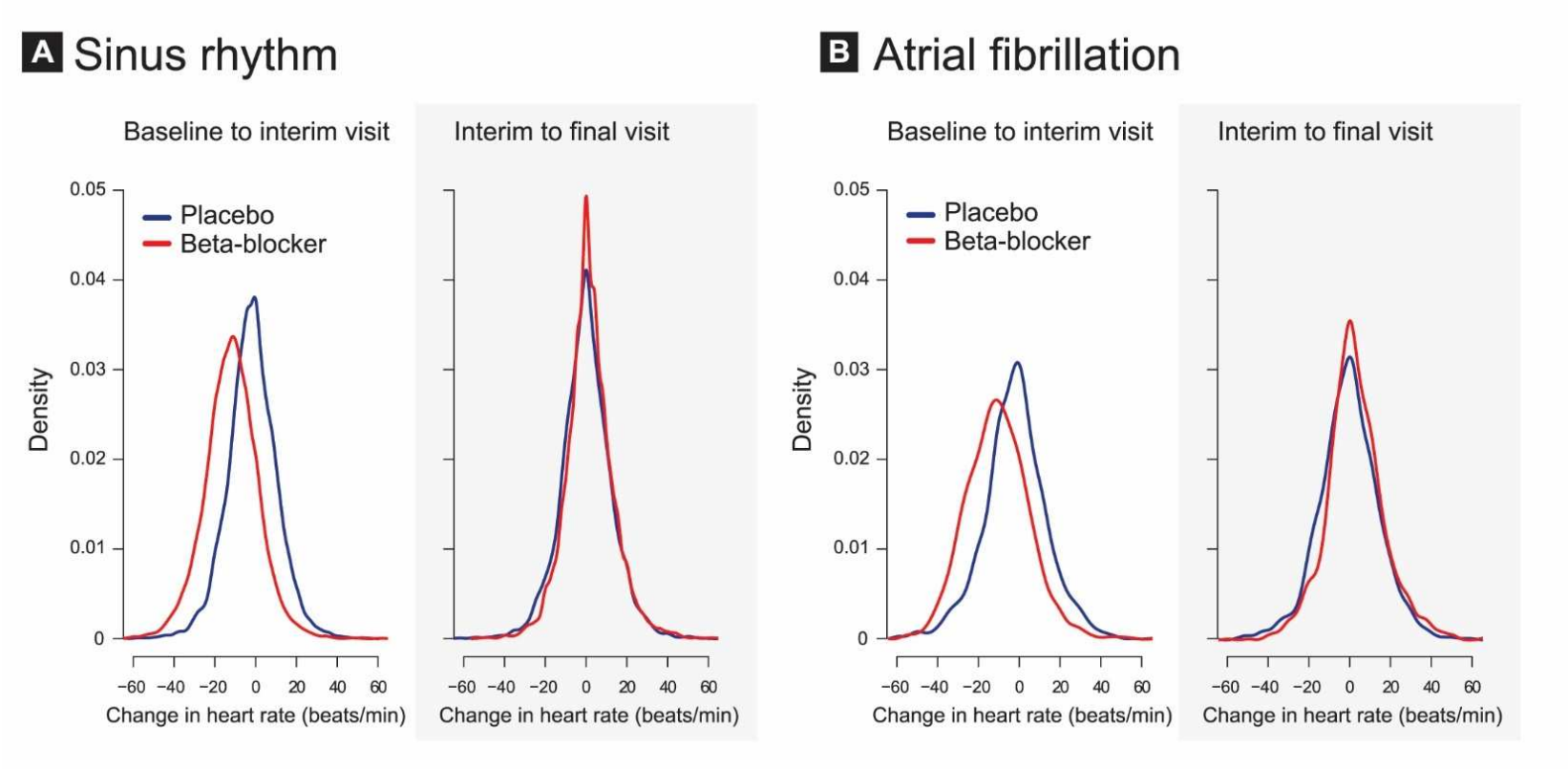
Online Table 6: Study dose achieved

Randomized group	N	Pooled average dose achieved as a percentage of maximal dose*		
		Heart rate <70 bpm	Heart rate 70-90 bpm	Heart rate >90 bpm
Sinus rhythm				
Placebo	4,547	84%	85%	82%
Beta-blockers	4,969	67%	74%	76%
Atrial fibrillation				
Placebo	1,038	84%	83%	85%
Beta-blockers	1,043	68%	71%	77%

* Achieved at the interim time point for each study, accounting for the differences in beta-blockers and maximum planned dosage between studies.

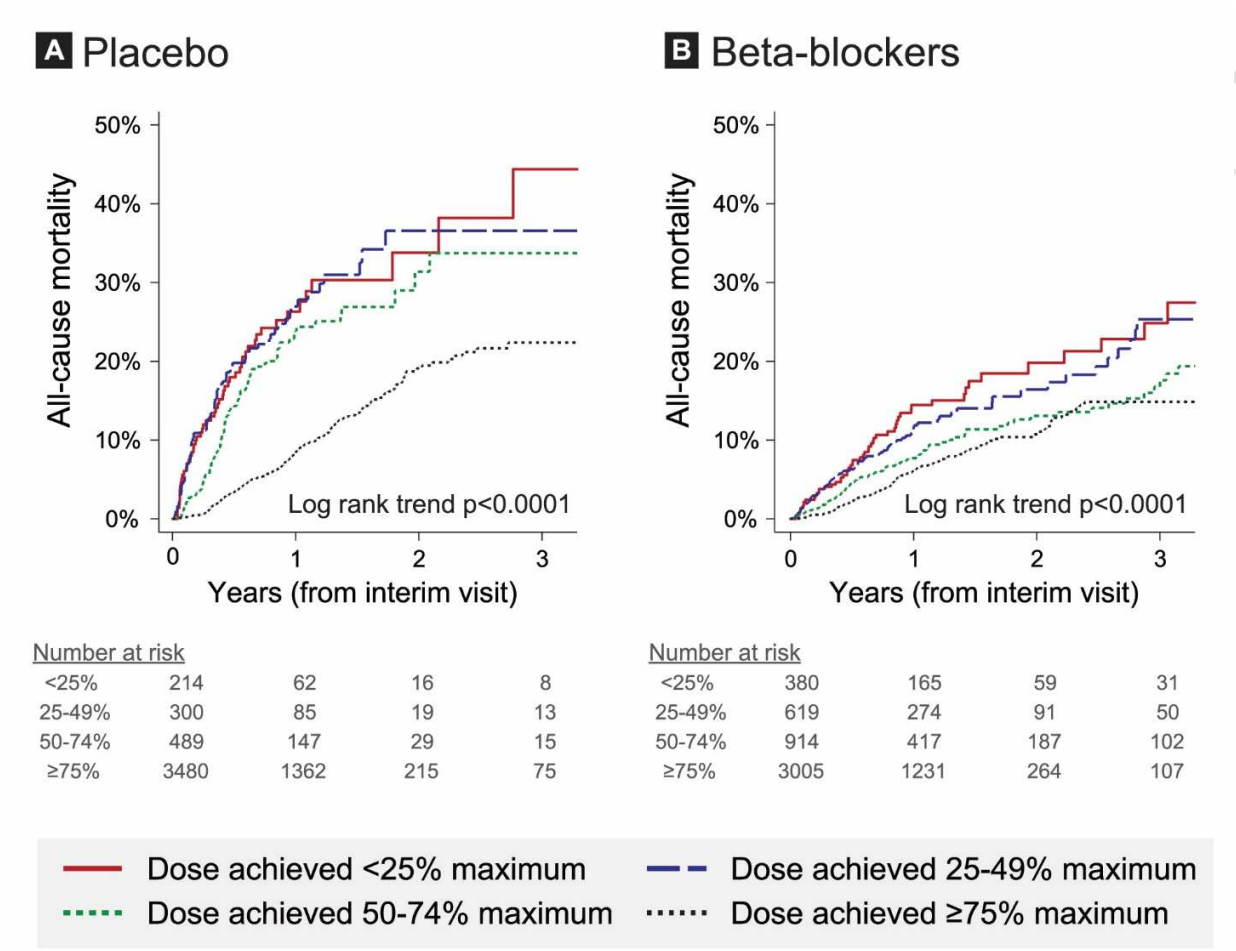
Bpm, beats/minute.

Online Figure 1: Change in heart rate during follow-up



Change in heart rate from baseline to interim visit and interim to final visit for individual patients in [A] sinus rhythm and [B] atrial fibrillation at baseline. Not all patients have all heart rates recorded on follow-up (for sinus rhythm, n=12,571 and n=12,119 respectively; for AF, n=2,592 and n=2,457 respectively).

Online Figure 2: Dose achieved and mortality in sinus rhythm



Kaplan Meier survival curves censored from time of the interim visit (mean of 184 days from randomization) for patients in sinus rhythm randomized to [A] placebo and [B] beta-blockers. Dose achieved is expressed as a percentage of maximal dose for each trial.