



Kotecha, D. et al. (2017) Heart rate, heart rhythm and prognostic benefits of beta-blockers in heart failure: individual patient-data meta-analysis. *Journal of the American College of Cardiology*, 69(24), pp. 2885-2896. (doi:[10.1016/j.jacc.2017.04.001](https://doi.org/10.1016/j.jacc.2017.04.001))

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

Short title: Heart rate, rhythm, beta-blockers and heart failure

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Word count (abstract): 256 Word count (text): 4876 (including text, references and figure legends)

Disclosures

All authors have completed the ICMJE uniform disclosure form (www.icmje.org/coi_disclosure.pdf) and declare:

DK reports grants from Menarini, during the conduct of the study; non-financial support from Daiichi Sankyo and personal fees from AtriCure, outside the submitted work; and Chief Investigator for the RATE control Therapy Evaluation in Atrial Fibrillation (RATE-AF) Trial. MDF reports personal fees from AstraZeneca and grants from Novartis, all outside the submitted work. JW reports an appointment as Study team physician for MERIT-HF at AstraZeneca beside his role as Assistant Director for the Wallenberg Laboratory for Cardiovascular Research at Gothenburg University, Sweden. MP reports personal fees from Amgen, Admittance Technologies, Bayer, Boehringer Ingelheim, BioControl, Celyad, Daiichi Sankyo, AstraZeneca, Cardioentis, CardioKinetix, Relypsa, Novartis, Sanofi, Takeda and ZS Pharma, all outside the submitted work. MB reports personal fees from Servier, Medtronic, Bayer and Pfizer, all outside the submitted work. BA reports personal fees from Servier, outside the submitted work. HW reports personal fees from Astra-Zeneca, during the conduct of the study. JGFC reports grants, personal fees and non-financial support from GlaxoSmithKline, during the conduct of the study. DGA, JH, GR, AJSC, LM, DJvV, TGvL, ASR, AH and JK have nothing to disclose.

Funding

Menarini Farmaceutica Internazionale provided an unrestricted research grant for administrative costs, GlaxoSmithKline provided data extraction support and IRCCS San Raffaele a collaborative research grant. None of the pharmaceutical groups had any role in data analysis or manuscript preparation. The Steering Committee Lead (DK) and the Centre for Statistics in Medicine, Oxford, UK (DGA and JH), had full access to all the data and had joint responsibility for the decision to submit for publication after discussion with all the named authors. DK is funded by a National Institute for Health Research (NIHR) Career Development Fellowship (CDF-2015-08-074). The opinions expressed are those of the authors and do not represent the NIHR or the UK Department of Health.

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

Abstract (255 words)

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.

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 25th to 75th 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 m².

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 dose 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.

Acknowledgments

We are indebted to the other members of the Beta-blockers in Heart Failure Collaborative Group for database access and extraction support (for full list, please see design paper(13)), the steering committees of the included trials (in particular representatives of the MERIT-HF trial), as well as the late Philip Poole-Wilson (1943-2009; Imperial College, London, UK). This work is dedicated to the memory of Henry Krum (1958-2015; Monash University Melbourne, Australia), one of the founding members of the Collaborative Group.

This project was only possible with the support of the pharmaceutical companies that have marketed beta-blockers in heart failure, and the group wishes to extend their gratitude to AstraZeneca, GlaxoSmithKline, Menarini Farmaceutica and Merck Serono for full access to trial data. We gratefully acknowledge incorporation of data from the BEST trial through the National Heart Lung and Blood Institute BioLINCC programme.

Contributors

DK participated in the design of the study, leads the collaborative group and performed data management, statistical analysis and manuscript preparation. JH and DGA independently performed the primary statistical analyses. JGFC participated in evaluation of results and manuscript preparation. LM and MDF participated in the design and coordination of the study. All other named authors read, revised and approved the final manuscript.

Perspectives

Competency in Medical Knowledge 1: For patients in heart failure with reduced ejection fraction and sinus rhythm, beta-blockers reduce mortality regardless of baseline heart rate in double-blind randomized trials, and lower heart rates are associated with lower mortality.

Competency in Medical Knowledge 2: In heart failure patients with reduced ejection fraction and atrial fibrillation, there is a lack of effect of beta-blockers on mortality, and heart rate is unrelated to mortality.

Competency in Patient Care: The benefit of beta-blockers goes beyond simple heart rate lowering and for patients with heart failure and reduced ejection fraction in sinus rhythm, beta-blockers should be utilized regardless of baseline heart rate to improve prognosis.

Translational Outlook: Further studies on the impact of heart rate and rate control agents in atrial fibrillation are needed.

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Figure legends

CENTRAL ILLUSTRATION: Modelling 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 enrolment (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/m ² (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%)

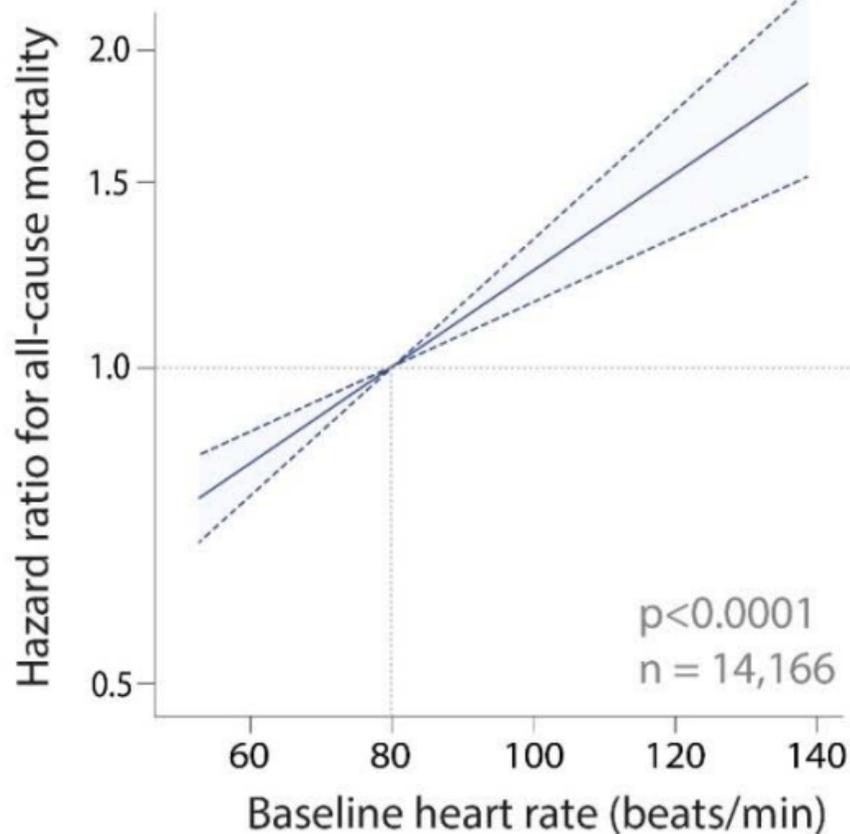
ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; bpm, beats/minute; GFR, glomerular filtration rate; HF, heart failure; IQR, interquartile range; LVEF, left-ventricular ejection fraction; NYHA, New York Heart Association. *See Online Table A for missing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

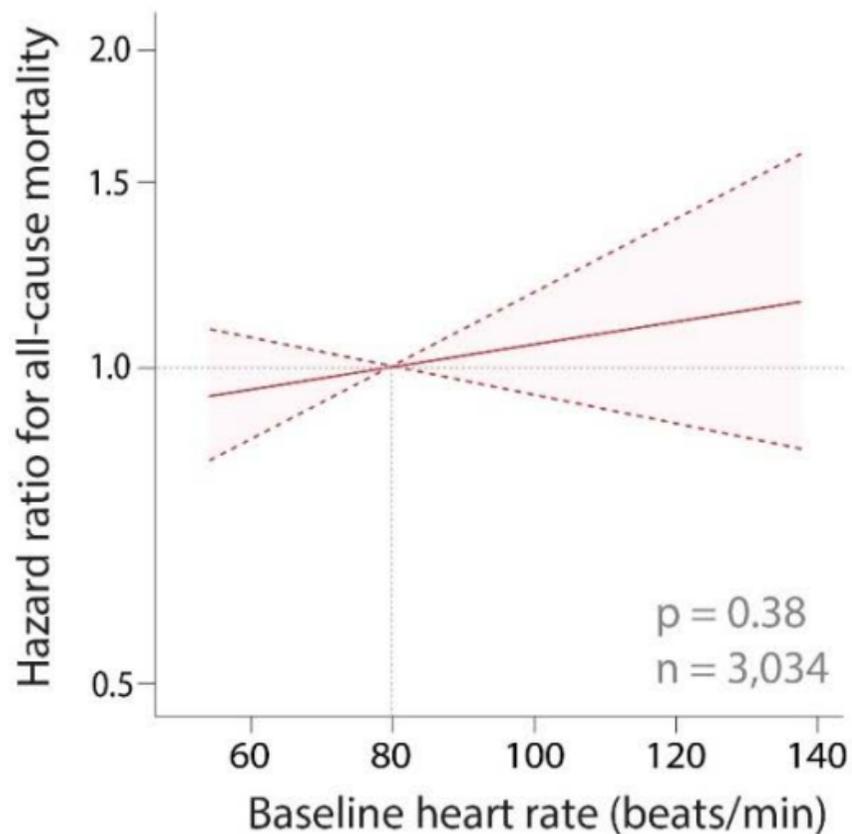
Beta-blockers versus placebo	Heart rate <70 bpm		Heart rate 70-90 bpm		Heart rate >90 bpm		Interaction p-value for heart rate as a continuous variable
	N (events /patients)	HR, 95% CI, p-value	N (events /patients)	HR, 95% CI, p-value	N (events /patients)	HR, 95% CI, p-value	
Sinus rhythm	328 / 2,386	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 HFrEF / Sinus rhythm



B HFrEF / Atrial fibrillation



Individual patient data
n=18,637

Missing baseline electrocardiogram (n=118)
Heart block (n=510)
Paced rhythm (n=616)
Missing baseline heart rate (n=15)

n=17,378

MDC
n=363

Exclusion: <45 bpm

CIBIS
n=628

Exclusion: <65 bpm

US-HF
n=907

Exclusion: <68 bpm

ANZ
n=409

Exclusion: <50 bpm

CIBIS-II
n=2,538

Exclusion: <60 bpm

MERIT-HF
n=3,895

Exclusion: <68 bpm

COPERNICUS
n=1,856

Exclusion: <68 bpm

CAPRICORN
n=1,902

Exclusion: <60 bpm

BEST
n=2,551

Exclusion: <50 bpm

CHRISTMAS
n=374*

Exclusion: <60 bpm

SENIORS
n=1,955

Exclusion: <60 bpm

Sinus rhythm
n=14,313

<70 bpm 70-90 bpm >90 bpm
n=2,420 n=9,128 n=2,765

Baseline: Final multivariate-adjusted Cox
regression model for all-cause mortality
n=14,166

Interim data on heart rate available
n=12,441

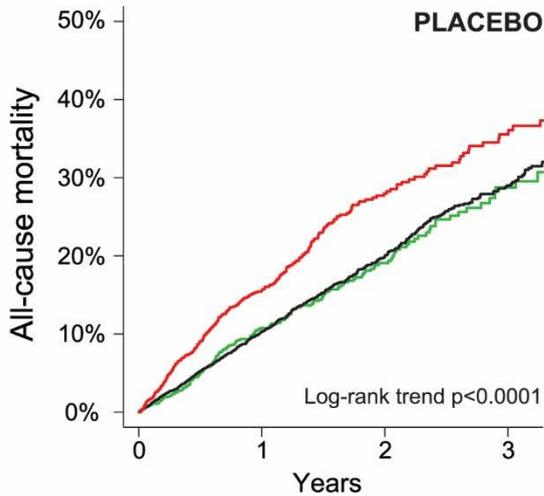
Atrial fibrillation
n=3,065

<70 bpm 70-90 bpm >90 bpm
n=427 n=1,811 n=827

Baseline: Final multivariate-adjusted Cox
regression model for all-cause mortality
n=3,034

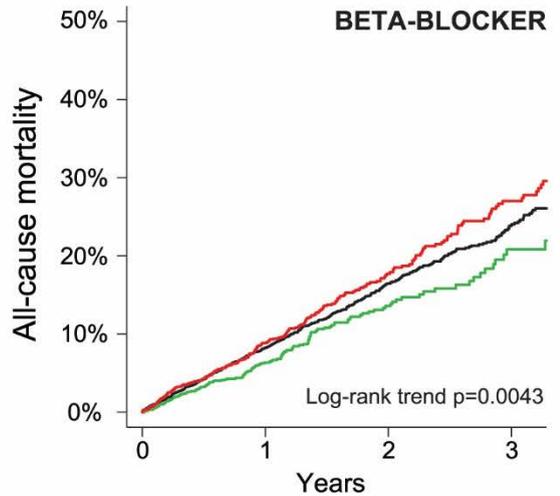
Interim data on heart rate available
n=2,566

A Sinus rhythm



Number at risk

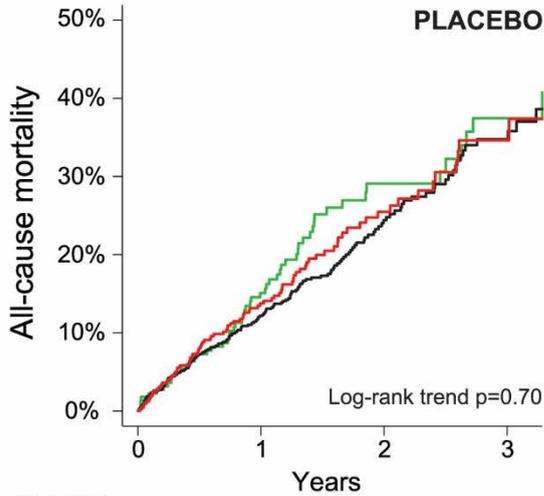
<70 bpm	1212	839	301	91
70-90 bpm	4476	2946	963	350
>90 bpm	1318	818	266	120



Number at risk

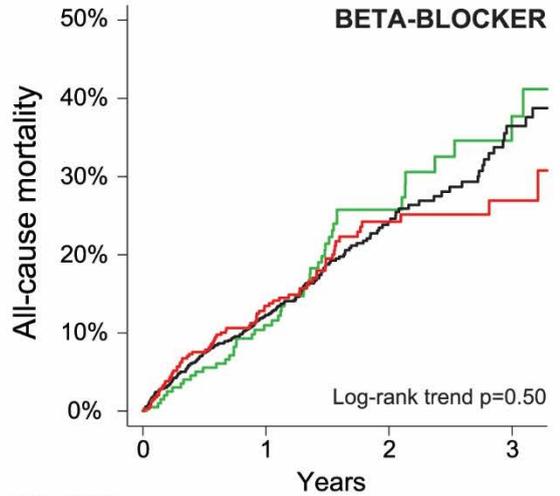
<70 bpm	1208	883	335	111
70-90 bpm	4650	3101	1038	408
>90 bpm	1446	1028	423	202

B Atrial fibrillation



Number at risk

<70 bpm	223	151	58	25
70-90 bpm	895	592	193	63
>90 bpm	424	277	95	27

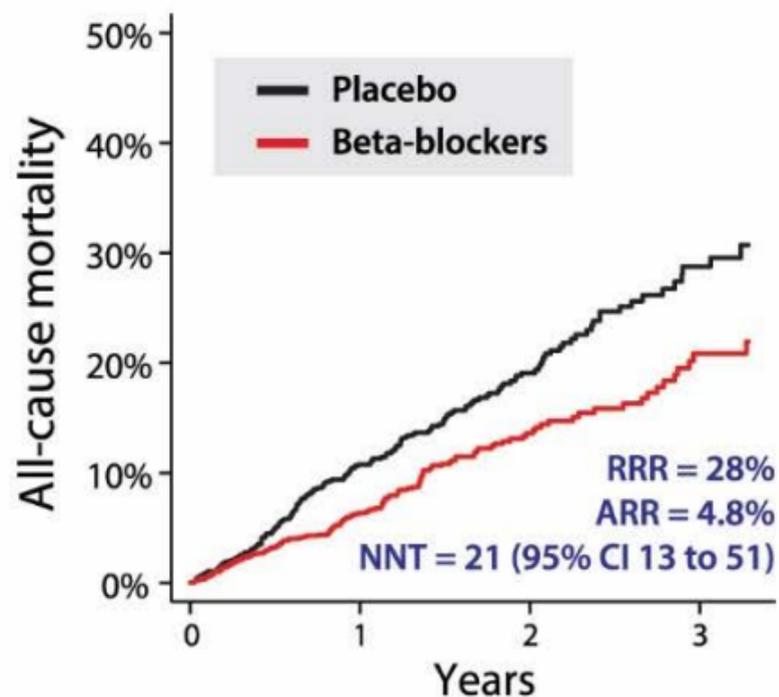


Number at risk

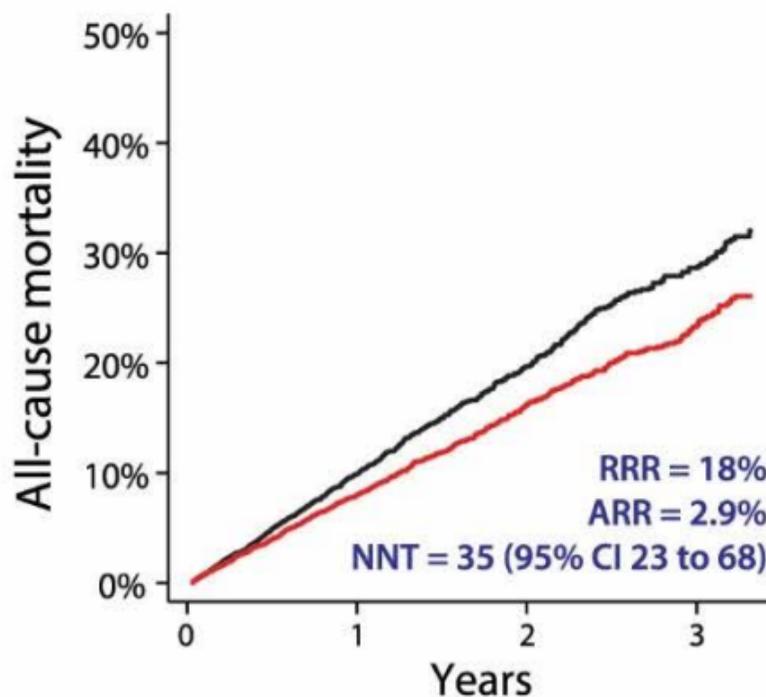
<70 bpm	203	150	50	20
70-90 bpm	914	591	188	65
>90 bpm	403	255	92	28

— <70 bpm
 — 70-90 bpm
 — >90 bpm

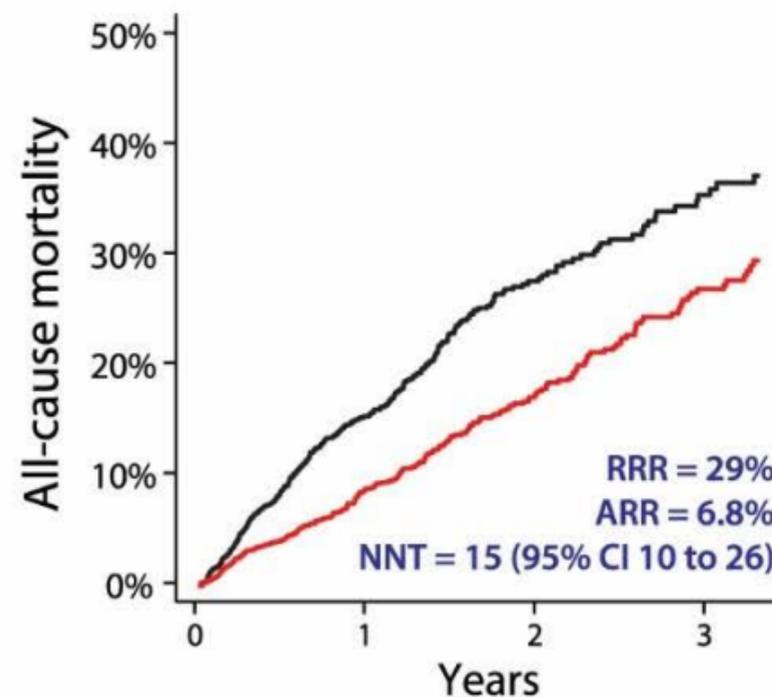
Baseline heart rate <70 bpm



Baseline heart rate 70-90 bpm



Baseline heart rate >90 bpm



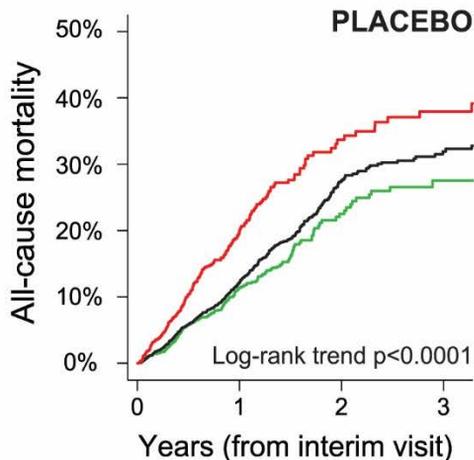
Number at risk

	0	1	2	3
Placebo	1212	839	301	91
Beta-blocker	1208	883	335	111

	0	1	2	3
Placebo	4476	2946	963	350
Beta-blocker	4650	3101	1038	408

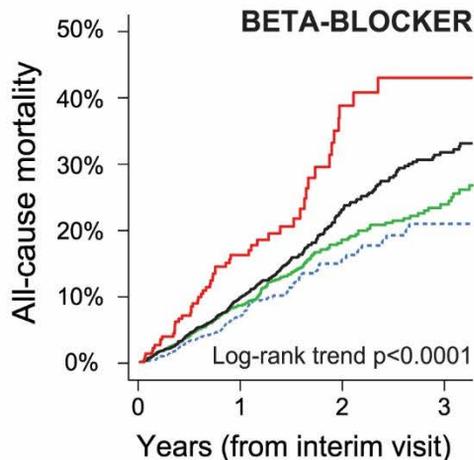
	0	1	2	3
Placebo	1318	818	266	120
Beta-blocker	1446	1028	423	202

A Sinus rhythm



Number at risk

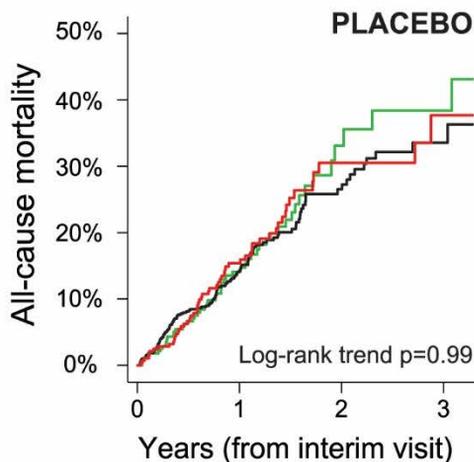
<70 bpm	1432	654	161	66
70-90 bpm	3505	1553	370	170
>90 bpm	940	382	105	63



Number at risk

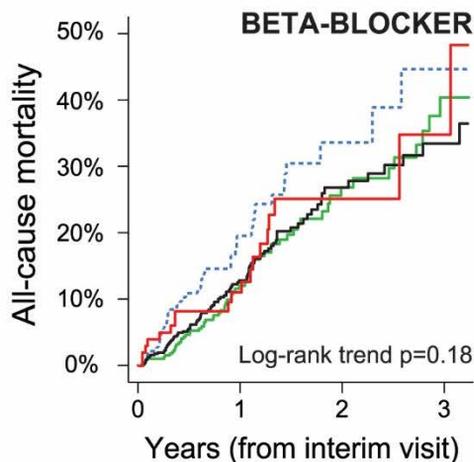
<60 bpm	1091	522	127	64
60-69 bpm	2350	1099	317	138
70-90 bpm	2447	1178	348	161
>90 bpm	241	127	33	22

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

— <70 bpm
 — 70-90 bpm
 — >90 bpm
 [- - - post-hoc defined <60 bpm]