

Title: Beta-blockers for heart failure with reduced, mid-range and preserved ejection fraction: An individual patient-level analysis of double-blind randomised trials

Short title: Beta-blockers, heart failure and ejection fraction

Authors and Institutions

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Beta-blockers in Heart Failure Collaborative Group



Abstract

Aims: Recent guidelines recommend that patients with heart failure and left ventricular ejection fraction (LVEF) 40-49% should be managed similar to LVEF \geq 50%. We investigated the effect of beta-blockers according to LVEF in double-blind, randomised, placebo-controlled trials.

Methods and Results: Individual patient data meta-analysis of eleven trials, stratified by baseline LVEF and heart rhythm (Clinicaltrials.gov:NCT0083244; PROSPERO:CRD42014010012). Primary outcomes were all-cause mortality and cardiovascular death over 1.3 years median follow-up, with an intention-to-treat analysis. For 14,262 patients in sinus rhythm, median LVEF was 27% (interquartile range 21-33%), including 575 patients with LVEF 40-49% and 244 \geq 50%. Beta-blockers reduced all-cause and cardiovascular mortality compared to placebo in sinus rhythm, an effect that was consistent across LVEF strata, except for those in the small subgroup with LVEF \geq 50%. For LVEF 40-49%, death occurred in 21/292 [7.2%] randomised to beta-blockers compared to 35/283 [12.4%] with placebo; adjusted hazard ratio (HR) 0.59 (95% CI 0.34-1.03). Cardiovascular death occurred in 13/292 [4.5%] with beta-blockers and 26/283 [9.2%] with placebo; adjusted HR 0.48 (95% CI 0.24-0.97). Over a median of 1.0 years following randomisation, LVEF increased with beta-blockers in all groups in sinus rhythm except LVEF \geq 50% (n=4,601). For patients in atrial fibrillation at baseline (n=3,050), beta-blockers increased LVEF when $<$ 50% at baseline, but did not improve prognosis.

Conclusion: Beta-blockers improve LVEF and prognosis for patients with heart failure in sinus rhythm with a reduced LVEF. The data are most robust for LVEF $<$ 40%, but similar benefit was observed in the subgroup of patients with LVEF 40-49%.

Key Words: Heart failure; Ejection fraction; Heart failure; Beta-blockers; Mortality.

Introduction

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3 Double-blind, randomised, placebo-controlled trials (RCTs) show that beta-blockers increase
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5 left ventricular ejection fraction (LVEF) and reduce morbidity and mortality for a broad range of
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7 patients with a reduced LVEF in sinus rhythm.^{1,2} Until recently, international guidelines on
8
9 heart failure have recognized two left ventricular phenotypes; heart failure with reduced LVEF
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11 (HFrEF) or preserved LVEF (HFpEF).^{3,4} Values for LVEF are continuously distributed but
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13 measurement precision is imperfect; differences of up to 10% for an individual patient may be
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15 attributed to measurement error⁵ and therefore precise cut-points of LVEF cannot reliably
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17 differentiate between phenotypes. Recently, the European Society of Cardiology (ESC)
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19 suggested there should be a third intermediate phenotype, called mid-range ejection fraction
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21 (HFmrEF; 40-49%), thereby creating a clear separation between HFrEF (<40%) and HFpEF
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23 ($\geq 50\%$).⁴ These guidelines suggest that until more information becomes available, patients with
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25 HFmrEF should be managed similarly to those with HFpEF, for which no therapy has been
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27 shown to improve mortality.⁴
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38 The Beta-blockers in Heart Failure Collaborative Group (BB-meta-HF) was created to pool
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40 individual patient data (IPD) from the major heart failure RCTs comparing beta-blockers and
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42 placebo to address key issues in relevant patient subgroups.⁶ Most, but not all of these trials
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44 recruited patients with an LVEF $\leq 35\%$ predominantly in sinus rhythm; IPD provides an
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46 opportunity to collate high-quality data from double-blind trials on the smaller number of
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48 patients with higher LVEF where the efficacy of beta-blockers is uncertain. Why beta-blockers
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50 appear ineffective in patients with heart failure and concomitant atrial fibrillation (AF)^{2,7,8}, and
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52 whether this holds true regardless of LVEF is also unclear. In this paper, we investigate the
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54 effect of beta-blockers on LVEF and prognosis, stratified according to baseline LVEF and heart
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56 rhythm.
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Methods

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3 The Beta-blockers in Heart Failure Collaborative Group (BB-meta-HF) includes the lead
4 investigators from the relevant trials, with the support of the four pharmaceutical companies that
5 conducted them (AstraZeneca, GlaxoSmithKline, Merck Serono and Menarini). This report was
6 prepared according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses
7 (PRISMA) IPD guidance⁹, and prospectively registered with Clinicaltrials.gov (NCT0083244)
8 and the PROSPERO database of systematic reviews (CRD42014010012).¹⁰
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Eligibility & search strategy

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22 Detailed rationale and methods have previously been published.^{1, 6, 7} Only unconfounded
23 placebo-controlled trials were eligible that recruited >300 patients, with a planned follow-up of
24 >6 months and explicit reporting of mortality. All trials had appropriate ethical approval.
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32 Eleven studies were included that account for 95.7% of eligible participants recruited in RCTs
33 based on a systematic literature review: the Australia/New Zealand Heart Failure Study
34 (ANZ)¹¹, the Beta-Blocker Evaluation Survival Trial (BEST)¹², the Carvedilol Post-Infarct
35 Survival Control in LV Dysfunction Study (CAPRICORN)¹³, the Carvedilol Hibernating
36 Reversible Ischaemia Trial: Marker of Success Study (CHRISTMAS)¹⁴, the Cardiac
37 Insufficiency Bisoprolol Study (CIBIS I)¹⁵, the Cardiac Insufficiency Bisoprolol Study II
38 (CIBIS-II)¹⁶, the Carvedilol Prospective Randomized Cumulative Survival Study
39 (COPERNICUS)¹⁷, the Metoprolol in Idiopathic Dilated Cardiomyopathy Study (MDC)¹⁸, the
40 Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF)¹⁹,
41 the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors
42 with Heart Failure (SENIORS)²⁰ and the U.S. Carvedilol Heart Failure Program (US-HF).²¹
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1 All included studies had low risk of bias, as determined using the Cochrane Collaborations Risk
2 of Bias Tool.²²
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7 Data collection & IPD integrity

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10 A standardized data request form to obtain IPD from each trial has been published, along with
11 search results and individual study demographics.⁶ IPD were obtained for all eleven trials
12 identified in the systematic review, and data were extracted from original source files provided
13 by the pharmaceutical companies and lead investigators. All data were cross-checked across
14 different trial databases and compared with published reports. Discrepancies, inconsistencies
15 and incomplete data were checked against original case report forms and trial documentation to
16 ensure IPD integrity. All eleven trial databases were then harmonized according to the
17 standardized data request form to match patient characteristics and outcomes across all trials.
18 Due to the small amount of missing data for relevant covariates, imputation was not performed.
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35 Participants

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39 We included all patients with baseline LVEF and an electrocardiogram (ECG) that showed
40 either sinus rhythm or AF/atrial flutter (for the purposes of this report, reference to AF therefore
41 includes atrial flutter). As we have already demonstrated an interaction of treatment effect with
42 heart rhythm⁷, patients with sinus rhythm and AF were analysed separately. Patients with heart
43 block, or a paced rhythm at baseline were excluded.
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54 Outcomes & effect measures

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57 The primary outcomes for this analysis were all-cause mortality and cardiovascular death, which
58 included additional deaths reported after the censor date for seven studies.^{19-21, 25, 26, 28, 29}
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Secondary outcomes were the first cardiovascular hospitalization and the composite of cardiovascular death and cardiovascular hospitalization (time to first event). All secondary outcomes were based on events from the study period only and do not include the MDC trial which did not collect this information. Three patients (one with sinus rhythm and two with AF) had missing event dates and were excluded from outcome analyses.

Most of the trials had limits for LVEF as inclusion or exclusion criteria, however these were typically defined preceding randomization ($<25\%$ ¹⁷, $\leq 35\%$ ^{12, 16, 21}, $\leq 40\%$ ^{13, 15, 18, 19} and $<45\%$ ¹¹; **Supplementary Figure A**). In this analysis, we used the baseline value of LVEF recorded in individual patient case report forms or core laboratory assessment, which in some patients was above the entry criterion according to that particular study. **LVEF was analysed as a continuous variable to model interactions with outcomes, and classified as $<20\%$, 20-25%, 26-34%, 35-39%, 40-49% and $\geq 50\%$, as well as $<40\%$, 40-49%, $\geq 50\%$ to align with guideline phenotypes.**

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).

All analyses followed the principle of intention-to-treat. Patients were classified by heart rhythm and LVEF. Outcomes were analysed using a Cox proportional hazards regression model²³, 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.

Fractional polynomials were used to find the best transformation²⁴, although a linear relationship with mortality was the best fit. Hazard ratios (HR) and 95% confidence intervals (CI) are presented, along with corresponding p-values. We pre-specified adjustment in Cox models for

1 age, sex, systolic blood pressure, prior myocardial infarction, and baseline use of angiotensin
2 converting enzyme inhibitors or angiotensin receptor blockers, and diuretic therapy.

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4 Adjustments for treatment allocation and LVEF were also made where appropriate. Kaplan-
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6 Meier plots were used to graph the pooled, unadjusted trial data, with log-rank tests for
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8 comparison stratified by study. Only a minority of patients were followed for more than three
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10 years and therefore data were censored at 1200 days (3.3 years) from randomization. Pre-
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12 defined sensitivity analyses included additional **multivariable** adjustment (including diabetes,
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14 NYHA class (I/II vs. III/IV), estimated glomerular filtration rate and digoxin); data are not
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16 shown as these results did not differ with our main model. We performed a post-hoc sensitivity
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18 analysis which excluded patients with an LVEF reported at exactly 40% from the 40-49% (mid-
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20 range) group. **A post-hoc analysis of cardiovascular hospitalisation accounting for the**
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22 **competing risk of death was performed using the method of Fine and Gray²⁵; results were**
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24 **similar to the results of the stratified Cox regression model.**

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31 We show the association between baseline LVEF and all cause-mortality by plotting the hazard
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33 of baseline LVEF relative to a baseline LVEF of 35%, fitted using an adjusted Cox proportional
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35 hazards model stratified by study. Follow-up LVEF was available in six trials.^{11, 12, 14, 18, 20, 21}
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37 We used the last available result to calculate change in LVEF from baseline. As availability of
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39 follow-up LVEF is determined by survival, we chose not to perform any statistical hypothesis
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41 testing.
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46 There was no evidence of violation of the proportional hazards assumption in any **multivariable**
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48 model as determined by Schoenfeld residuals.²⁶ Effect modification was assessed using p-
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50 values from interaction terms fitted in the **multivariable** models.^{24, 27} A two-tailed p-value of
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52 0.05 was considered statistically significant. Analyses were performed on Stata Version 14.1
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54 (StataCorp LP, Texas) and R Version 3.2.1 (R Core Team, Vienna).
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Results

Individual patient data were obtained for 18,637 patients. Patients were excluded if they had a missing baseline electrocardiogram (n=118), heart block (n=510), paced rhythm (n=616) or were missing their baseline LVEF (n=91). The cohort included 14,262 patients in sinus rhythm and 3,050 patients in atrial fibrillation (**Supplementary Figure A**), with a mean follow-up of 1.5 years (SD 1.1) and median follow-up of 1.3 years (IQR 0.8-1.9). Median age was 65 (IQR 55-72) years, 24% were women and 66% had ischaemic heart disease (IHD) as the cause for heart failure. Median LVEF at baseline was 27% (21-33%) and was similar for patients in sinus rhythm (**Table 1**) and AF (**Supplementary Table A**). Combining both heart rhythms, 721 patients had an LVEF 40-49% and 317 had an LVEF $\geq 50\%$. Patients with a higher baseline LVEF were older, more likely to be women, have milder NYHA class, higher blood pressure, and were less likely to have heart failure due to IHD. There were no differences in patient characteristics between those assigned to beta-blockers or placebo (**Supplementary Table B**).

LVEF at baseline was inversely associated with all-cause mortality, with an adjusted HR of 1.16 for each 5% lower LVEF (95% CI 1.26-1.19; $p < 0.0001$). **Figure 1** displays the hazard of all-cause mortality with LVEF 35% as the reference. The association between LVEF and prognosis was stronger for patients in sinus rhythm than AF (**Supplementary Table C**). Patients with LVEF $\geq 50\%$ had the lowest mortality despite their older age (**Supplementary Figure B**); all-cause and cardiovascular mortality were 10.4% and 6.3% respectively for those with LVEF $\geq 50\%$, compared to 26.7% and 21.7% for those with LVEF $< 20\%$. Mortality was predominantly cardiovascular regardless of aetiology, both for patients in sinus rhythm (**Supplementary Table D**) and AF (**Supplementary Table E**), and mostly attributed to sudden death or worsening heart failure.

Beta-blockers were associated with reductions in all-cause and cardiovascular mortality

compared to placebo for patients in sinus rhythm (interaction $p > 0.5$ for LVEF as a continuous

measure). Beta-blockers were effective in all LVEF categories, except in the small subgroup

where LVEF was $\geq 50\%$ (**Table 2** and **Figure 2**). There was no evidence for a difference in

benefit when LVEF was 40-49%; all-cause mortality occurred in 21/292 [7.2%] randomised to a

beta-blockers compared to 35/283 [12.4%] assigned to placebo (adjusted HR 0.59, 95% CI 0.34-

1.03), and cardiovascular death in 13/292 [4.5%] with beta-blockers and 26/283 [9.2%] with

placebo; (adjusted HR 0.48, 95% CI 0.24-0.97) (**Figure 3**). Beta-blockers reduced both sudden

death and deaths ascribed to heart failure for patients in sinus rhythm, but had no effect on non-

cardiovascular mortality (**Supplementary Table D**). Secondary outcomes (cardiovascular

hospitalization and the composite of cardiovascular death and cardiovascular hospitalization)

were lower with beta-blockers in all LVEF categories for patients in sinus rhythm, but

confidence intervals were wide when LVEF exceeded 40% (**Table 2** and **Figure 2**).

Patients with AF at baseline demonstrated no consistent benefit on clinical outcomes with beta-

blockers, regardless of LVEF (**Figure 4**). Fewer patients and events reduced the power to

identify or refute modest differences in outcome.

Change in LVEF was measured in 4,601 patients in sinus rhythm and 996 patients in AF who

survived to a follow-up assessment (median 1.0 years after baseline; IQR 0.3-2.0)

(**Supplementary Figure C**). In sinus rhythm, LVEF increased more in patients randomized to

beta-blockers than placebo, unless LVEF was $\geq 50\%$ at baseline (**Table 3** and **Figure 5**).

Increases in LVEF with beta-blockers were smaller for patients with IHD as the cause for heart

failure compared to non-ischaemic cardiomyopathy (**Supplementary Table F**). Beta-blockers

also increased LVEF for patients in AF in most LVEF categories except $\geq 50\%$ (Table 3 and

Figure 5).

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Discussion

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3 This analysis suggests that for patients with heart failure in sinus rhythm, the effect of beta-
4 blockers on mortality in patients with LVEF 40-49% is similar to that observed with LVEF
5 <40%. Consistent with the outcome data, LVEF increased with beta-blockers in all groups,
6 except those with LVEF \geq 50%. Only the SENIORS trial²⁰ intentionally enrolled patients with
7 any LVEF, but despite showing efficacy for beta-blockers in those with LVEF >35%²⁸, there
8 were too few patients and events to draw any conclusions in patients with more preserved
9 LVEF. The lower the LVEF, the higher the rate of adverse outcomes and therefore the benefit
10 of beta-blockers might be expected to be greatest in those with lower LVEF, as seen in a
11 subgroup analysis of the MERIT-HF trial.²⁹ However, we demonstrate a substantial 4.7%
12 absolute reduction in cardiovascular mortality in patients with LVEF 40-49% and sinus rhythm
13 (number needed to treat to prevent one cardiovascular death = 21 during a median follow-up of
14 1.3 years). This finding was statistically significant despite the relatively low number of trial
15 patients studied in this LVEF category. Our preference in statistical analysis is always to report
16 the interaction of treatment effect across continuous variables such as LVEF, instead of relying
17 on efficacy in subgroups. However in this case, the data are dominated by patients with LVEF
18 <40% and interaction tests are known to have low power.³⁰ Similar improvements in LVEF
19 were seen for those in AF, but this did not translate into better outcomes with beta-blockers for
20 patients in AF.

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51 The mechanisms by which beta-blockers exert benefit are uncertain.² Blocking adrenergic
52 receptors has direct effects on cardiomyocytes, reduces heart rate, alters vascular function and
53 modifies the neuro-endocrine response to heart failure.³¹ The importance of these mechanisms
54 may vary by aetiology, left ventricular phenotype, heart rhythm and clinical indication. For
55 example, beta-blockers are recommended for the treatment of ventricular tachycardia and
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1 prevention of ventricular fibrillation in the context of an acute coronary syndrome³², but may
2 have deleterious effects compared to other therapy in hypertension or non-cardiac surgery.³³ An
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4 improvement in LVEF is usually considered evidence of therapeutic benefit, but this analysis
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6 suggests we should be cautious about making such assumptions. The increase in LVEF with
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8 beta-blockers was smaller for patients with IHD, but the benefit on mortality was similar to
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10 those with a non-ischaemic cause for heart failure. The increase in LVEF with beta-blockers
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12 was similar for patients in sinus rhythm and AF, yet those with AF obtained no benefit on
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14 morbidity or mortality. The underlying reasons for this discrepancy remains a subject of
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16 discussion^{4, 8}, and the increase in both incidence and prevalence of AF³⁴ highlights a growing
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18 unmet clinical and research need.
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27 Recent guidelines from the ESC suggest that left ventricular dysfunction should be classified as
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29 HF_rEF when LVEF is <40%, HF_mrEF when 40-49% and HF_pEF only when LVEF is 50% or
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31 greater.⁴ The guideline points out that trials have, until recently, mostly used an LVEF of 40%
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33 or 45% to define HF_pEF and none have identified an intervention that reduced morbidity or
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35 mortality for such patients.⁴ Accordingly, the guideline recommends that patients with HF_mrEF
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37 be managed in the same way as HF_pEF until new evidence becomes available. Interestingly, a
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39 post-hoc analysis of the Treatment of Preserved cardiac function heart failure with an
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41 Aldosterone antagonist Trial (TOPCAT) also suggested a reduction in cardiovascular mortality
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43 with spironolactone in patients with an investigator-recorded LVEF 45-49%, but not when
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45 LVEF was greater than this.³⁵ Initial data from the Candesartan in Heart failure - Assessment of
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47 moRtality and Morbidity (CHARM) program of trials suggests that angiotensin inhibition has a
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49 similar benefit in patients with LVEF 40-49% as with <40%.³⁶ In line with our data, it is
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51 possible that future guideline recommendations for patients with this intermediate phenotype
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53 should be more similar to those for HF_rEF than HF_pEF, and that the threshold for differences in
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55 heart failure therapy should be at, or around, an LVEF of 50%.
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2 This analysis has limitations, with varied design and objectives of the component trials and
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4 relatively sparse outcome data for patients with LVEF >40%. The distribution of LVEF was not
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6 normal due to the inclusion criteria of the component RCTs; although the 40-49% group was
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8 weighted towards the lower end of mid-range LVEF, we found that primary outcomes were
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10 reduced in this group in sinus rhythm even when excluding those with an LVEF of 40%. In any
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12 trial, there is concern about whether the patients enrolled reflect the population encountered in
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14 clinical practice due to selection criteria, and this analysis is no different. However, our data
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16 represent the vast majority of patients enrolled in double-blind RCTs of beta-blockers.
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21 Our use of individual-patient baseline LVEF, rather than the screening LVEF that qualified for
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23 inclusion, meant that most trials contributed some data to the LVEF 40-49% group. Although
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25 the SENIORS trial, with a distinct type of beta-blocker, was the only RCT to specifically recruit
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27 patients with higher LVEF, it only accounted for 44% of patients in this category. In trials of
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29 HF_rEF, LVEF measured in a core echocardiography laboratory will exceed the LVEF inclusion
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31 criterion in 20-40% of patients.³⁷⁻⁴⁰ Some of the differences between the core laboratory and
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33 investigators may be explained by measurement error, but there also appears to be a bias on the
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35 part of investigators, conscious or unconscious, towards measuring an LVEF that allows for
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37 patient inclusion. Regression towards the mean will also result in repeat measures being less
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39 extreme; thus our approach of using double-blind data will have reduced, but not eliminated
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41 measurement bias and inadvertent misclassification. Both in research trials and clinical practice,
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43 measurements such as LVEF have inherent variability that require clinical review and oversight.
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48 Reported measurements such as blood pressure and LVEF are prone to digit preference (e.g.
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50 40% rather than 39%) and variability in timing, technique and quantification. The impact of this
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52 can be lessened by including a large amount of raw data (see **Supplementary Figure C**) or by
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54 using, where available, software generated LVEF (e.g. by Teichholz or Simpson's biplane
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method) rather than an ‘eyeball’ assessment. Patients who died had no follow-up LVEF and therefore this could have introduced bias in measured changes in LVEF.

Determination of LVEF may be less accurate for patients in AF due to variability in cardiac cycle length.⁴¹ The smaller number of patients with AF, although large in comparison to many published interventional trials⁴², limits our ability to make detailed comparisons to patients in sinus rhythm. Finally, data on natriuretic peptides, diastolic ventricular filling dynamics and atrial structure and function were lacking, which often help to describe different heart failure phenotypes.

Conclusion

For patients with heart failure in sinus rhythm and LVEF <40%, beta-blockers improve left ventricular systolic function and reduce cardiovascular morbidity and mortality. These benefits also apply to patients with LVEF 40-49%, a group in which beta-blocker therapy seems more likely to help than to harm. No benefit was seen in patients with LVEF ≥50%, but too few patients have been studied in double-blind RCTs to draw firm conclusions on the efficacy or safety of beta-blockers for HFpEF. No consistent evidence of prognostic benefit was observed for patients with heart failure and concomitant AF.

Acknowledgments

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3 We are indebted to the other members of the Beta-blockers in Heart Failure Collaborative Group
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5 for database access and extraction support (for full list, please see design paper⁶), the steering
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7 committees of the included trials (in particular representatives of the MERIT-HF trial), as well
8
9 as the late Philip Poole-Wilson (1943-2009; Imperial College, London, UK). This work is
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References

1. Kotecha D, Manzano L, Krum H, Rosano G, Holmes J, Altman DG, Collins PD, Packer M, Wikstrand J, Coats AJ, Cleland JG, Kirchhof P, von Lueder TG, Rigby AS, Andersson B, Lip GY, van Veldhuisen DJ, Shibata MC, Wedel H, Bohm M, Flather MD, Beta-Blockers in Heart Failure Collaborative G. Effect of age and sex on efficacy and tolerability of beta blockers in patients with heart failure with reduced ejection fraction: individual patient data meta-analysis. *BMJ*. 2016;**353**:i1855
2. Kotecha D, Flather MD, Altman DG, Holmes J, Rosano G, Wikstrand J, Packer M, Coats AJS, Manzano L, Bohm M, van Veldhuisen DJ, Andersson B, Wedel H, von Lueder TG, Rigby AS, Hjalmarsen A, Kjekshus J, Cleland JGF, Beta-Blockers in Heart Failure Collaborative G. Heart Rate and Rhythm and the Benefit of Beta-Blockers in Patients With Heart Failure. *J Am Coll Cardiol*. 2017;**69**:2885-2896
3. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;**128**:e240-319
4. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;**37**:2129-2200
5. McGowan JH, Cleland JG. Reliability of reporting left ventricular systolic function by echocardiography: a systematic review of 3 methods. *Am Heart J*. 2003;**146**:388-397
6. Kotecha D, Manzano L, Altman DG, Krum H, Erdem G, Williams N, Flather MD, Beta-Blockers in Heart Failure Collaborative Group. Individual patient data meta-analysis of beta-blockers in heart failure: rationale and design. *Syst Rev*. 2013;**2**:7
7. Kotecha D, Holmes J, Krum H, Altman DG, Manzano L, Cleland JG, Lip GY, Coats AJ, Andersson B, Kirchhof P, von Lueder TG, Wedel H, Rosano G, Shibata MC, Rigby A, Flather MD, Beta-Blockers in Heart Failure Collaborative Group. Efficacy of beta blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. *Lancet*. 2014;**384**:2235-2243
8. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;**37**:2893-2962
9. Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, Tierney JF. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. *JAMA*. 2015;**313**:1657-1665

10. Kotecha D, Manzano L, Krum H, Altman DG, Holmes J, Flather M. The Beta-Blockers in Heart Failure Collaborative Group: Individual patient data meta-analysis. *PROSPERO register*. 2014: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014010012
11. Australia/New Zealand Heart Failure Research Collaborative Group. Randomised, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischaemic heart disease. *Lancet*. 1997;**349**:375-380
12. Beta-Blocker Evaluation of Survival Trial Investigators. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. *N Engl J Med*. 2001;**344**:1659-1667
13. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet*. 2001;**357**:1385-1390
14. Cleland JG, Pennell DJ, Ray SG, Coats AJ, Macfarlane PW, Murray GD, Mule JD, Vered Z, Lahiri A. Myocardial viability as a determinant of the ejection fraction response to carvedilol in patients with heart failure (CHRISTMAS trial): randomised controlled trial. *Lancet*. 2003;**362**:14-21
15. CIBIS Investigators and Committees. A randomized trial of beta-blockade in heart failure. The Cardiac Insufficiency Bisoprolol Study (CIBIS). *Circulation*. 1994;**90**:1765-1773
16. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet*. 1999;**353**:9-13
17. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Castaigne A, Roecker EB, Schultz MK, DeMets DL. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med*. 2001;**344**:1651-1658
18. Waagstein F, Bristow MR, Swedberg K, Camerini F, Fowler MB, Silver MA, Gilbert EM, Johnson MR, Goss FG, Hjalmarson A. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. Metoprolol in Dilated Cardiomyopathy (MDC) Trial Study Group. *Lancet*. 1993;**342**:1441-1446
19. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet*. 1999;**353**:2001-2007
20. Flather MD, Shibata MC, Coats AJ, Van Veldhuisen DJ, Parkhomenko A, Borbola J, Cohen-Solal A, Dumitrascu D, Ferrari R, Lechat P, Soler-Soler J, Tavazzi L, Spinarova L, Toman J, Bohm M, Anker SD, Thompson SG, Poole-Wilson PA. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J*. 2005;**26**:215-225
21. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. *N Engl J Med*. 1996;**334**:1349-1355
22. Higgins JPT, Altman DG, Sterne JAC. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*. The Cochrane Collaboration; 2011.
23. Tudur Smith C, Williamson PR. A comparison of methods for fixed effects meta-analysis of individual patient data with time to event outcomes. *Clin Trials*. 2007;**4**:621-630

24. Sauerbrei W, Royston P. Building multivariable prognostic and diagnostic models: transformation of the predictors by using fractional polynomials. *J Roy Stat Soc.* 1999;**162**:71-94
25. Fine J, Gray R. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc.* 1999;**94**:496-509
26. Schoenfeld D. Partial Residuals for The Proportional Hazards Regression Model. *Biometrika.* 1982;**69**:239-241
27. Royston P, Sauerbrei W. A new approach to modelling interactions between treatment and continuous covariates in clinical trials by using fractional polynomials. *Stat Med.* 2004;**23**:2509-2525
28. van Veldhuisen DJ, Cohen-Solal A, Bohm M, Anker SD, Babalis D, Roughton M, Coats AJ, Poole-Wilson PA, Flather MD. Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: Data From SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure). *J Am Coll Cardiol.* 2009;**53**:2150-2158
29. Goldstein S, Fagerberg B, Hjalmarsen A, Kjekshus J, Waagstein F, Wedel H, Wikstrand J. Metoprolol controlled release/extended release in patients with severe heart failure: analysis of the experience in the MERIT-HF study. *J Am Coll Cardiol.* 2001;**38**:932-938
30. Altman DG, Bland JM. Interaction revisited: the difference between two estimates. *BMJ.* 2003;**326**:219
31. von Lueder TG, Kotecha D, Atar D, Hopper I. Neurohormonal blockade in heart failure. *Cardiac Fail Rev.* 2016;**3**:19-24
32. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekval TM, Spaulding C, Van Veldhuisen DJ. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J.* 2015;**36**:2793-2867
33. Ziff OJ, Samra M, Bromage DI, Howard JP, Francis DP, Kotecha D. [Late-breaking Conference Report] Marked variation in the efficacy of beta-blockers across cardiovascular health: A Global systematic assessment of mortality, myocardial infarction and stroke. *European Society of Cardiology Congress 2017.* <http://spo.escardio.org/SessionDetails.aspx?eevtid=1220&sessId=22276> [Accessed 22215 Aug 22017]
34. Lane DA, Skjoth F, Lip GYH, Larsen TB, Kotecha D. Temporal Trends in Incidence, Prevalence, and Mortality of Atrial Fibrillation in Primary Care. *J Am Heart Assoc.* 2017;**6**:e005155
35. Solomon SD, Claggett B, Lewis EF, Desai A, Anand I, Sweitzer NK, O'Meara E, Shah SJ, McKinlay S, Fleg JL, Sopko G, Pitt B, Pfeffer MA. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. *Eur Heart J.* 2016;**37**:455-462

36. Lund LH. [Late-breaking Conference Report] Heart failure with mid ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire EF spectrum. *Heart Failure* 2017. <https://www.escardio.org/Congresses-&-Events/Heart-Failure/Congress-resources/candesartan-provides-similar-benefit-for-patients-with-mid-range-ejection-fracti> [Accessed 15 Aug 2017]

37. Oh JK, Pellikka PA, Panza JA, Biernat J, Attisano T, Manahan BG, Wiste HJ, Lin G, Lee K, Miller FA, Jr., Stevens S, Sopko G, She L, Velazquez EJ. Core lab analysis of baseline echocardiographic studies in the STICH trial and recommendation for use of echocardiography in future clinical trials. *J Am Soc Echocardiogr.* 2012;**25**:327-336

38. Kutuyifa V, Kloppe A, Zareba W, Solomon SD, McNitt S, Polonsky S, Barshesht A, Merkely B, Lemke B, Nagy VK, Moss AJ, Goldenberg I. The influence of left ventricular ejection fraction on the effectiveness of cardiac resynchronization therapy: MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy). *J Am Coll Cardiol.* 2013;**61**:936-944

39. Shah AM, Shah SJ, Anand IS, Sweitzer NK, O'Meara E, Heitner JF, Sopko G, Li G, Assmann SF, McKinlay SM, Pitt B, Pfeffer MA, Solomon SD. Cardiac structure and function in heart failure with preserved ejection fraction: baseline findings from the echocardiographic study of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial. *Circ Heart Fail.* 2014;**7**:104-115

40. Chung ES, Katra RP, Ghio S, Bax J, Gerritse B, Hilpisch K, Peterson BJ, Feldman DS, Abraham WT. Cardiac resynchronization therapy may benefit patients with left ventricular ejection fraction >35%: a PROSPECT trial substudy. *Eur J Heart Fail.* 2010;**12**:581-587

41. Kotecha D, Mohamed M, Shantsila E, Popescu BA, Steeds RP. Is echocardiography valid and reproducible in patients with atrial fibrillation? A systematic review. *Europace.* 2017;10.1093/europace/eux027

42. Kotecha D, Calvert M, Deeks JJ, Griffith M, Kirchhof P, Lip GYH, Mehta S, Slinn G, Stanbury M, Steeds RP, Townend JN. A review of rate control in atrial fibrillation, and the rationale and protocol for the RATE-AF trial. *BMJ Open.* 2017;10.1136/bmjopen-2016-015099

Table 1: Baseline characteristics for patients in sinus rhythm

Characteristic	Left ventricular ejection fraction at baseline					
	<20% N = 2553	20-25% N = 3885	26-34% N = 5076	35-39% N = 1929	40-49% N = 575	≥50% N = 244
LVEF, median (IQR)	0.15 (0.13 - 0.18)	0.23 (0.21 - 0.24)	0.30 (0.28 - 0.32)	0.36 (0.35 - 0.38)	0.40 (0.40 - 0.43)	0.58 (0.53 - 0.65)
Age, median years (IQR)	61 (51 - 69)	63 (54 - 71)	64 (55 - 71)	64 (56 - 72)	71 (61 - 75)	75 (72 - 78)
Women, n (%)	521 (20.4%)	886 (22.8%)	1272 (25.1%)	518 (26.9%)	198 (34.4%)	129 (52.9%)
Years with HF diagnosis, median (IQR)	3 (1 - 6)	3 (1 - 6)	2 (1 - 5)	2 (1 - 5)	2 (1 - 5)	2 (1 - 5)
Ischaemic HF aetiology, n (%)	1484 (58.1%)	2572 (66.2%)	3475 (68.5%)	1562 (81.0%)	522 (90.8%)	209 (85.7%)
Prior myocardial infarction, n (%)	1242 (48.7%)	2187 (56.4%)	2993 (59.2%)	1374 (71.4%)	412 (71.8%)	88 (36.1%)
Diabetes Mellitus, n (%)	575 (25.1%)	956 (26.0%)	1153 (23.9%)	409 (22.2%)	135 (24.1%)	71 (29.1%)
NYHA class III/IV, n (%)	1624 (82.1%)	2045 (77.6%)	3265 (64.8%)	721 (37.7%)	136 (24.1%)	64 (26.6%)
Heart rate, median bpm (IQR)	84 (76 - 92)	80 (72 - 90)	78 (72 - 87)	76 (70 - 84)	76 (68 - 82)	75 (68 - 83)
Systolic BP, median mmHg (IQR)	114 (104 - 127)	120 (110 - 136)	127 (115 - 140)	130 (116 - 140)	131 (120 - 145)	147 (132 - 160)
Diastolic BP, median mmHg (IQR)	72 (66 - 80)	77 (70 - 82)	79 (70 - 83)	80 (70 - 83)	80 (70 - 85)	82 (78 - 90)
Body mass index, median kg/m ² (IQR)	27 (24 - 32)	27 (24 - 31)	27 (24 - 31)	27 (25 - 30)	27 (25 - 30)	27 (24 - 31)
Estimated GFR, median mL/min (IQR)	62 (50 - 76)	61 (48 - 75)	66 (53 - 80)	65 (53 - 78)	66 (53 - 78)	69 (55 - 83)
Any diuretic therapy, n (%)	2410 (94.4%)	3547 (91.3%)	4331 (85.3%)	1273 (66.0%)	376 (65.4%)	199 (81.6%)
ACEi or ARB, n (%)	2304 (94.8%)	3490 (94.7%)	4643 (94.8%)	1774 (95.1%)	508 (90.6%)	203 (87.3%)
Aldosterone antagonists, n (%)	207 (8.8%)	381 (10.4%)	360 (7.5%)	85 (4.7%)	31 (5.8%)	27 (11.9%)
Digoxin, n (%)	1833 (73.8%)	2297 (60.4%)	2475 (49.9%)	555 (29.6%)	138 (25.6%)	48 (21.2%)

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.

Missing data report: n=2828 for years with HF diagnosis; n=30 for prior myocardial infarction; n=809 for diabetes mellitus; n=1504 for NYHA class; n=62 for systolic BP; n=67 for diastolic BP; n=8 heart rate; n=123 for body mass index; n=664 for GFR; n=918 for aldosterone antagonists; n=376 for digoxin.

Table 2: Beta-blockers versus placebo according to LVEF at baseline

Baseline heart rhythm and LVEF category		All-cause mortality		Cardiovascular death		Cardiovascular hospitalization		Composite of cardiovascular death or cardiovascular hospitalization	
		Events / N	HR (95% CI); p-value	Events / N	HR (95% CI); p-value	Events / N	HR (95% CI); p-value	Events / N	HR (95% CI); p-value
Sinus rhythm	<20%	623 / 2531	0.70 (0.60-0.83); p<0.001	517 / 2531	0.67 (0.56-0.80); p<0.001	762 / 2407	0.70 (0.60-0.81); p<0.001	990 / 2407	0.68 (0.60-0.77); p<0.001
	20-25%	619 / 3862	0.76 (0.65-0.89); p=0.001	521 / 3862	0.78 (0.65-0.92); p=0.004	1033 / 3807	0.75 (0.66-0.85); p<0.001	1273 / 3807	0.75 (0.67-0.84); p<0.001
	26-34%	631 / 5043	0.75 (0.64-0.88); p<0.001	504 / 5042	0.73 (0.61-0.87); p<0.001	1118 / 4972	0.84 (0.74-0.94); p=0.003	1384 / 4972	0.80 (0.72-0.88); p<0.001
	35-39%	189 / 1919	0.67 (0.50-0.90); p=0.007	156 / 1919	0.72 (0.52-0.99); p=0.041	401 / 1907	0.75 (0.61-0.91); p=0.004	490 / 1907	0.74 (0.62-0.88); p=0.001
	40-49%	55 / 570	0.59 (0.34-1.03); p=0.066	38 / 570	0.48 (0.24-0.97); p=0.040	144 / 566	0.95 (0.68-1.32); p=0.76	164 / 566	0.83 (0.60-1.13); p=0.23
	≥50%	24 / 241	1.79 (0.78-4.10); p=0.17	15 / 241	1.77 (0.61-5.14); p=0.29	50 / 241	0.66 (0.37-1.18); p=0.16	54 / 241	0.66 (0.38-1.15); p=0.14
Atrial fibrillation	<20%	143 / 492	1.23 (0.88-1.74); p=0.23	124 / 492	1.16 (0.80-1.67); p=0.44	148 / 471	0.97 (0.69-1.35); p=0.85	201 / 471	0.96 (0.72-1.28); p<0.001
	20-25%	159 / 867	0.74 (0.54-1.02); p=0.07	136 / 867	0.77 (0.54-1.08); p=0.13	234 / 856	0.75 (0.58-0.98); p=0.032	291 / 856	0.75 (0.59-0.95); p=0.003
	26-34%	208 / 1093	0.98 (0.74-1.29); p=0.87	166 / 1093	0.98 (0.72-1.34); p=0.92	321 / 1083	1.01 (0.81-1.26); p=0.92	390 / 1083	0.93 (0.76-1.13); p=0.001
	35-39%	59 / 363	0.92 (0.53-1.58); p=0.75	46 / 363	0.67 (0.35-1.25); p=0.21	99 / 358	0.90 (0.60-1.36); p=0.62	121 / 358	0.94 (0.65-1.37); p=0.046
	40-49%	32 / 146	1.30 (0.63-2.67); p=0.48	22 / 146	0.86 (0.36-2.03); p=0.73	34 / 143	1.15 (0.57-2.32); p=0.69	46 / 143	1.06 (0.58-1.94); p=0.040
	≥50%	8 / 73	0.86 (0.19-3.94); p=0.85	4 / 73	1.00 (0.10-9.91); p=1.00	26 / 73	1.33 (0.56-3.16); p=0.52	27 / 73	1.17 (0.51-2.71); p=0.42

CI = confidence interval; HR = Hazard ratio (adjusted for baseline characteristics and stratified by trial); LVEF = left ventricular ejection fraction; N = number of individuals.

Table 3: Absolute mortality difference and observed change in LVEF

Classification	'Reduced' LVEF				'Mid-range' LVEF	'Preserved' LVEF
	<20%	20-25%	26-34%	35-39%	40-49%	≥50%
LVEF at baseline						
Sinus rhythm: All aetiology*						
Change in absolute mortality; beta-blockers vs placebo (95% CI) [†]	n=2552 -6.9% (-10.3% to -3.5%)	n=3885 -3.9% (-6.3% to -1.6%)	n=5076 -3.2% (-5.1% to -1.4%)	n=1929 -3.4% (-6.1% to -0.7%)	n=575 -5.2% (-10.0% to -0.3%)	n=244 +2.3% (-5.3% to +9.9%)
Change in LVEF from baseline to follow-up; mean difference (SE) beta-blockers vs placebo [‡]	n=1106 +4.7% (0.5%)	n=1068 +4.0% (0.5%)	n=1600 +4.2% (0.5%)	n=375 +4.9% (0.9%)	n=251 +1.9% (1.1%)	n=201 +0.1% (1.2%)
Atrial fibrillation: All aetiology						
Change in absolute mortality; beta-blockers vs placebo (95% CI) [†]	n=494 +2.8% (-5.3% to +10.9%)	n=867 -4.1% (-9.3% to +1.1%)	n=1101 -0.8% (-5.5% to +3.9%)	n=367 -3.2% (-10.7% to +4.3%)	n=146 +3.2% (-10.4% to +16.7%)	n=73 +0.3% (-14.0% to +14.6%)
Change in LVEF from baseline to follow-up; mean difference (SE) beta-blockers vs placebo [‡]	n=177 +4.6% (1.7%)	n=200 +3.4% (1.2%)	n=369 +1.5% (1.0%)	n=98 +0.1% (1.9%)	n=93 +4.8% (1.9%)	n=59 -2.2% (3.0%)

* See Supplementary Table F for data according to ischaemic/non-ischaemic aetiology in sinus rhythm.

[†] Median follow-up of 1.3 years (IQR 0.8-1.9)

[‡] Median 1.0 years after baseline assessment (IQR 0.3-2.0)

CI = confidence interval; LVEF = left ventricular ejection fraction; SE = standard error of the mean difference.

Supplementary Table A: Baseline characteristics for patients in atrial fibrillation

Characteristic	Left ventricular ejection fraction at baseline					
	<20% N = 494	20-25% N = 868	26-34% N = 1101	35-39% N = 368	40-49% N = 146	≥50% N = 73
LVEF, median (IQR)	0.16 (0.14 - 0.18)	0.23 (0.21 - 0.24)	0.30 (0.28 - 0.32)	0.35 (0.35 - 0.37)	0.41 (0.40 - 0.45)	0.56 (0.52 - 0.64)
Age, median years (IQR)	66 (59 - 73)	67 (59 - 73)	69 (61 - 75)	70 (61 - 74)	75 (71 - 79)	76 (74 - 79)
Women, n (%)	63 (12.8%)	128 (14.7%)	204 (18.5%)	86 (23.4%)	72 (49.3%)	39 (53.4%)
Years with HF diagnosis, median (IQR)	5 (2 - 8)	4 (2 - 8)	3 (1 - 6)	3 (1 - 6)	3 (1 - 5)	1 (0 - 4)
Ischaemic HF aetiology, n (%)	267 (54.0%)	443 (51.0%)	581 (52.8%)	233 (63.3%)	104 (71.2%)	52 (71.2%)
Prior myocardial infarction, n (%)	218 (44.3%)	331 (38.1%)	417 (38.2%)	168 (46.0%)	43 (29.5%)	21 (28.8%)
Diabetes Mellitus, n (%)	108 (24.2%)	200 (23.9%)	243 (22.8%)	72 (20.7%)	32 (22.7%)	19 (26.0%)
NYHA class III/IV, n (%)	434 (88.0%)	765 (88.2%)	819 (74.7%)	209 (57.3%)	56 (38.6%)	31 (42.5%)
Heart rate, median bpm (IQR)	84 (73 - 95)	81 (72 - 92)	80 (72 - 91)	80 (72 - 89)	82 (73 - 92)	84 (78 - 96)
Systolic BP, median mmHg (IQR)	120 (107 - 130)	122 (110 - 138)	130 (118 - 143)	130 (120 - 145)	142 (128 - 155)	140 (130 - 153)
Diastolic BP, median mmHg (IQR)	73 (65 - 80)	78 (70 - 82)	80 (70 - 87)	80 (72 - 87)	80 (75 - 90)	80 (79 - 89)
Body mass index, median kg/m ² (IQR)	27 (24 - 32)	27 (24 - 31)	28 (25 - 31)	28 (25 - 31)	26 (24 - 29)	28 (26 - 31)
Estimated GFR, median mL/min (IQR)	57 (45 - 69)	57 (46 - 70)	64 (52 - 77)	63 (50 - 75)	62 (49 - 76)	60 (49 - 78)
Any diuretic therapy, n (%)	480 (97.2%)	833 (96.0%)	1028 (93.4%)	312 (84.8%)	131 (89.7%)	68 (93.2%)
ACEi or ARB, n (%)	464 (93.9%)	833 (96.0%)	1036 (94.1%)	352 (95.7%)	133 (91.1%)	64 (87.7%)
Aldosterone antagonists, n (%)	78 (16.7%)	176 (20.7%)	136 (12.6%)	62 (17.6%)	27 (18.8%)	16 (21.9%)
Digoxin, n (%)	435 (88.1%)	749 (86.3%)	920 (83.6%)	272 (73.9%)	117 (80.1%)	52 (71.2%)

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.

Missing data report: n=319 for years with HF diagnosis; n=13 for prior myocardial infarction; n=135 for diabetes mellitus; n=431 for NYHA class; n= 2 for diastolic BP; n=8 heart rate; n= 22 for body mass index; n=101 for GFR; n=85 for any diuretic therapy; n=85 for aldosterone antagonists.

Supplementary Table B: Baseline characteristics according to randomised treatment allocation in sinus rhythm

Characteristic	LVEF <40%		LVEF 40-49%		LVEF ≥50%	
	PLACEBO N=6582	BETA-BLOCKER N=6861	PLACEBO N=283	BETA-BLOCKER N=292	PLACEBO N=121	BETA-BLOCKER N=123
LVEF, median (IQR)	0.26 (0.20-0.32)	0.26 (0.20-0.32)	0.40 (0.40-0.44)	0.40 (0.40-0.43)	0.58 (0.52-0.65)	0.58 (0.54-0.65)
Age, median years (IQR)	63 (54-71)	63 (54-71)	72 (61-75)	70 (60-74)	75 (72-78)	75 (71-78)
Women, %	23.6%	24.0%	33.6%	35.3%	47.9%	57.7%
Years with HF diagnosis, median (IQR)	3 (1-6)	3 (1-6)	2 (1-5)	2 (1-5)	2 (1-5)	2 (0-6)
Ischaemic HF aetiology, %	67.7%	67.5%	92.6%	89.0%	86.8%	84.6%
Prior myocardial infarction, %	58.0%	58.2%	72.3%	71.2%	39.7%	32.5%
Diabetes Mellitus, %	24.3%	24.6%	23.0%	25.1%	30.6%	27.6%
NYHA class III/IV, %	68.1%	67.7%	21.6%	26.5%	24.0%	29.3%
Heart rate, median bpm (IQR)	80 (72-88)	80 (72-88)	75 (68-82)	76 (70-82)	75 (68-84)	74 (68-80)
Systolic BP, median mmHg (IQR)	122 (110-138)	122 (110-138)	132 (120-148)	130 (120-145)	146 (132-161)	147 (132-160)
Diastolic BP, median mmHg (IQR)	77 (70-82)	77 (70-82)	80 (70-85)	80 (70-84)	80 (79-90)	82 (77-90)
Body mass index, median kg/m ² (IQR)	27 (24-31)	27 (24-31)	27 (25-30)	27 (25-30)	26 (24-31)	27 (25-30)
Estimated GFR, median mL/min (IQR)	64 (52-78)	64 (51-77)	67 (53-78)	66 (53-78)	67 (54-81)	72 (56-85)
Any diuretic therapy, %	85.9%	86.1%	67.1%	63.7%	81.0%	82.1%
ACEi or ARB, %	95.2%	94.4%	90.1%	91.1%	87.6%	87.0%
Aldosterone antagonists, %	8.1%	8.3%	6.4%	5.3%	9.9%	13.9%
Digoxin, %	53.6%	55.5%	26.4%	24.7%	17.1%	25.2%

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.

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20 **Supplementary Table C: Baseline LVEF and hazard for all-cause and cardiovascular mortality**
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	All-cause mortality		Cardiovascular death	
	N (events / patients)	HR, 95% CI; p-value	N (events / patients)	HR, 95% CI; p-value
Sinus rhythm; per 5% lower LVEF at baseline	2,160 / 14,261	1.24, 1.21-1.28; p<0.0001	1,768 / 14,260	1.20, 1.22-1.30; p<0.0001
Atrial fibrillation; per 5% lower LVEF at baseline	609 / 3,034	1.09, 1.03-1.15; p=0.002	498 / 3,034	1.10, 1.05-1.18; p<0.0001

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33 Adjusted hazard ratio (HR) analysed using a one-stage Cox regression model, with studies as strata. See also Supplementary Figure B.
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Supplementary Table D: Mode of death by baseline LVEF category in sinus rhythm

Baseline LVEF	<20%		20-25%		26-34%		35-39%		40-49%		≥50%	
Randomised allocation	PLC	BB	PLC	BB	PLC	BB	PLC	BB	PLC	BB	PLC	BB
Ischaemic cardiomyopathy												
All-cause mortality*	229 / 727 (31.5%)	180 / 756 (23.8%)	254 / 1258 (20.2%)	208 / 1314 (15.8%)	248 / 1697 (14.6%)	214 / 1778 (12.0%)	97 / 776 (12.5%)	62 / 786 (7.9%)	29 / 262 (11.1%)	19 / 260 (7.3%)	9 / 105 (8.6%)	13 / 104 (12.5%)
CV death	201 / 727 (27.6%)	156 / 756 (20.6%)	220 / 1258 (17.5%)	181 / 1314 (13.8%)	207 / 1697 (12.2%)	172 / 1778 (9.7%)	78 / 776 (10.1%)	53 / 786 (6.7%)	22 / 262 (8.4%)	12 / 260 (4.6%)	6 / 105 (5.7%)	9 / 104 (8.7%)
Sudden death	103 / 727 (14.2%)	83 / 756 (11.0%)	117 / 1258 (9.3%)	86 / 1314 (6.5%)	121 / 1697 (7.1%)	88 / 1778 (4.9%)	36 / 776 (4.6%)	29 / 786 (3.7%)	10 / 262 (3.8%)	4 / 260 (1.5%)	2 / 105 (1.9%)	3 / 104 (2.9%)
HF-related death	73 / 727 (10.0%)	45 / 756 (6.0%)	66 / 1258 (5.2%)	63 / 1314 (4.8%)	52 / 1697 (3.1%)	48 / 1778 (2.7%)	20 / 776 (2.6%)	9 / 786 (1.1%)	6 / 262 (2.3%)	3 / 260 (1.2%)	1 / 105 (1.0%)	1 / 104 (1.0%)
Non-CV death	10 / 727 (1.4%)	18 / 756 (2.4%)	16 / 1258 (1.3%)	14 / 1314 (1.1%)	21 / 1697 (1.2%)	19 / 1778 (1.1%)	9 / 776 (1.2%)	4 / 786 (0.5%)	4 / 262 (1.5%)	3 / 260 (1.2%)	1 / 105 (1.0%)	1 / 104 (1.0%)
Non-ischaemic cardiomyopathy												
All-cause mortality*	136 / 508 (26.8%)	118 / 561 (21.0%)	99 / 644 (15.4%)	82 / 669 (12.3%)	113 / 782 (14.5%)	81 / 819 (9.9%)	16 / 189 (8.5%)	18 / 178 (10.1%)	6 / 21 (28.6%)	2 / 32 (6.3%)	2 / 16 (12.5%)	1 / 19 (5.3%)
CV death	99 / 508 (19.5%)	80 / 561 (14.3%)	72 / 644 (11.2%)	61 / 669 (9.1%)	83 / 782 (10.6%)	54 / 819 (6.6%)	11 / 189 (5.8%)	15 / 178 (8.4%)	4 / 21 (19.0%)	1 / 32 (3.1%)	1 / 16 (6.3%)	0 / 19 (0.0%)
Sudden death	48 / 508 (9.4%)	39 / 561 (7.0%)	38 / 644 (5.9%)	27 / 669 (4.0%)	48 / 782 (6.1%)	27 / 819 (3.3%)	9 / 189 (4.8%)	5 / 178 (2.8%)	2 / 21 (9.5%)	1 / 32 (3.1%)	1 / 16 (6.3%)	0 / 19 (0.0%)
HF-related death	38 / 508 (7.5%)	28 / 561 (5.0%)	26 / 644 (4.0%)	17 / 669 (2.5%)	22 / 782 (2.8%)	15 / 819 (1.8%)	2 / 189 (1.1%)	6 / 178 (3.4%)	1 / 21 (4.8%)	0 / 32 (0.0%)	0 / 16 (0.0%)	0 / 19 (0.0%)
Non-CV death	8 / 508 (1.6%)	9 / 561 (1.6%)	8 / 644 (1.2%)	7 / 669 (1.0%)	11 / 782 (1.4%)	13 / 819 (1.6%)	3 / 189 (1.6%)	1 / 178 (0.6%)	0 / 21 (0.0%)	0 / 32 (0.0%)	0 / 16 (0.0%)	1 / 19 (5.3%)

BB, beta-blockers; CV, cardiovascular; LVEF, left-ventricular ejection fraction; PLC, placebo. * Includes deaths due to an unknown cause. Note that some deaths were ascribed to unknown causes and therefore are attributed neither to cardiovascular or non-cardiovascular deaths.

Supplementary Table E: Mode of death by baseline LVEF category in atrial fibrillation

Baseline LVEF	<20%		20-25%		26-34%		35-39%		40-49%		≥50%	
Randomised allocation	PLC	BB	PLC	BB	PLC	BB	PLC	BB	PLC	BB	PLC	BB
Ischaemic cardiomyopathy												
All-cause mortality*	47 / 141 (33.3%)	47 / 126 (37.3%)	49 / 224 (21.9%)	44 / 219 (20.1%)	60 / 302 (19.9%)	72 / 279 (25.8%)	29 / 120 (24.2%)	18 / 113 (15.9%)	9 / 50 (18.0%)	14 / 54 (25.9%)	3 / 26 (11.5%)	3 / 26 (11.5%)
CV death	45 / 141 (31.9%)	39 / 126 (31.0%)	41 / 224 (18.3%)	37 / 219 (16.9%)	51 / 302 (16.9%)	60 / 279 (21.5%)	26 / 120 (21.7%)	14 / 113 (12.4%)	7 / 50 (14.0%)	9 / 54 (16.7%)	1 / 26 (3.8%)	2 / 26 (7.7%)
Sudden death	17 / 141 (12.1%)	16 / 126 (12.7%)	22 / 224 (9.8%)	18 / 219 (8.2%)	19 / 302 (6.3%)	28 / 279 (10.0%)	15 / 120 (12.5%)	7 / 113 (6.2%)	1 / 50 (2.0%)	3 / 54 (5.6%)	0 / 26 (0.0%)	0 / 26 (0.0%)
HF-related death	25 / 141 (17.7%)	21 / 126 (16.7%)	13 / 224 (5.8%)	11 / 219 (5.0%)	24 / 302 (7.9%)	18 / 279 (6.5%)	6 / 120 (5.0%)	5 / 113 (4.4%)	2 / 50 (4.0%)	1 / 54 (1.9%)	0 / 26 (0.0%)	0 / 26 (0.0%)
Non-CV death	2 / 141 (1.4%)	5 / 126 (4.0%)	4 / 224 (1.8%)	5 / 219 (2.3%)	4 / 302 (1.3%)	4 / 279 (1.4%)	0 / 120 (0.0%)	2 / 113 (1.8%)	1 / 50 (2.0%)	2 / 54 (3.7%)	1 / 26 (3.8%)	1 / 26 (3.8%)
Non-ischaemic cardiomyopathy												
All-cause mortality*	24 / 106 (22.6%)	31 / 121 (25.6%)	42 / 213 (19.7%)	28 / 211 (13.3%)	50 / 255 (19.6%)	31 / 265 (11.7%)	5 / 70 (7.1%)	8 / 64 (12.5%)	5 / 17 (29.4%)	5 / 25 (20.0%)	1 / 11 (9.1%)	1 / 10 (10.0%)
CV death	18 / 106 (17.0%)	24 / 121 (19.8%)	34 / 213 (16.0%)	25 / 211 (11.8%)	34 / 255 (13.3%)	22 / 265 (8.3%)	4 / 70 (5.7%)	3 / 64 (4.7%)	4 / 17 (23.5%)	2 / 25 (8.0%)	1 / 11 (9.1%)	0 / 10 (0.0%)
Sudden death	11 / 106 (10.4%)	7 / 121 (5.8%)	18 / 213 (8.5%)	16 / 211 (7.6%)	20 / 255 (7.8%)	8 / 265 (3.0%)	2 / 70 (2.9%)	1 / 64 (1.6%)	1 / 17 (5.9%)	0 / 25 (0.0%)	1 / 11 (9.1%)	0 / 10 (0.0%)
HF-related death	6 / 106 (5.7%)	14 / 121 (11.6%)	9 / 213 (4.2%)	6 / 211 (2.8%)	7 / 255 (2.7%)	8 / 265 (3.0%)	2 / 70 (2.9%)	1 / 64 (1.6%)	2 / 17 (11.8%)	2 / 25 (8.0%)	0 / 11 (0.0%)	0 / 10 (0.0%)
Non-CV death	0 / 106 (0.0%)	0 / 121 (0.0%)	2 / 213 (0.9%)	1 / 211 (0.5%)	4 / 255 (1.6%)	3 / 265 (1.1%)	0 / 70 (0.0%)	1 / 64 (1.6%)	0 / 17 (0.0%)	2 / 25 (8.0%)	0 / 11 (0.0%)	1 / 10 (10.0%)

BB, beta-blockers; CV, cardiovascular; LVEF, left-ventricular ejection fraction; PLC, placebo. * Includes deaths due to an unknown cause. Note that some deaths were ascribed to unknown causes and therefore are attributed neither to cardiovascular or non-cardiovascular deaths.

Supplementary Table F: Absolute mortality difference and observed change in LVEF according to aetiology in sinus rhythm

Classification	'Reduced' LVEF				'Mid-range' LVEF	'Preserved' LVEF
	<20%	20-25%	26-34%	35-39%	40-49%	≥50%
LVEF at baseline						
Sinus rhythm: Ischaemic aetiology						
Change in absolute mortality; beta-blockers vs placebo (95% CI) †	n=1483 -7.7% (-12.2% to -3.1%)	n=2572 -4.4% (-7.3% to -1.4%)	n=3475 -2.6% (-4.8% to -0.3%)	n=1562 -4.6% (-7.6% to -1.6%)	n=522 -3.8% (-8.7% to +1.2%)	n=209 +3.9% (-4.4% to +12.2%)
Change in LVEF from baseline to follow-up; mean difference (SE) beta-blockers vs placebo‡	n=593 +3.1% (0.6%)	n=667 +3.3% (0.6%)	n=1070 +3.0% (0.5%)	n=277 +4.4% (1.0%)	n=227 +2.5% (1.2%)	n=177 +0.6% (1.3%)
Sinus rhythm: Non-ischaemic aetiology						
Change in absolute mortality; beta-blockers vs placebo (95% CI) †	n=1069 -5.7% (-10.9% to -0.6%)	n=1313 -3.1% (-6.8% to +0.6%)	n=1601 -4.6% (-7.8% to -1.4%)	n=367 +1.6% (-4.3% to +7.6%)	n=53 -22.3% (-43.4% to -1.3%)	n=35 -7.2% (-26.3% to +11.8%)
Change in LVEF from baseline to follow-up; mean difference (SE) beta-blockers vs placebo‡	n=513 +6.2% (0.9%)	n=401 +5.6% (1.0%)	n=530 +6.2% (0.9%)	n=98 +6.3% (2.0%)	n=24 -4.2% (4.3%)	n=24 -4.4% (4.5%)

† Median follow-up of 1.3 years (IQR 0.8-1.9)

‡ Median 1.0 years after baseline assessment (IQR 0.3-2.0)

CI = confidence interval; LVEF = left ventricular ejection fraction; SE = standard error of the mean difference.

Figure legends

Figure 1: Hazard of all-cause mortality across the spectrum of LVEF

Hazard ratio and 95% confidence intervals for all-cause mortality according to baseline left ventricular ejection fraction (LVEF), relative to a patient with an LVEF of 35%. Hazard ratios are fitted using a Cox proportional hazards regression model, adjusted for treatment, age, gender, previous myocardial infarction, systolic blood pressure, heart rate, use of angiotensin inhibitors/receptor blockers and diuretics, and stratified by study.

Figure 2: Beta-blockers versus placebo according to baseline LVEF in sinus rhythm

Intention to treat, one-stage Cox proportional hazards model in categories of left ventricular ejection fraction (LVEF) at baseline, adjusted for age, gender, previous myocardial infarction, systolic blood pressure, heart rate, and use of angiotensin inhibitors/receptor blockers and diuretics. 'n' is the number of individual patients analysed from double-blind, randomized controlled trials for the primary outcomes with complete case data.

Figure 3: Beta-blockers versus placebo in sinus rhythm according to heart failure phenotype

Kaplan Meier plots for unadjusted (A) all-cause mortality and (B) cardiovascular mortality according to baseline left ventricular ejection fraction (LVEF). * Similar results in post-hoc analysis when excluding patients with an LVEF reported as exactly 40% from the 40-49% group: (A) log-rank $p=0.030$ and (B) log-rank $p=0.039$; $n=147$ placebo and $n=143$ beta-blockers.

Figure 4: Beta-blockers versus placebo according to baseline LVEF in atrial fibrillation

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2 Intention to treat, one-stage Cox proportional hazards model in categories of left ventricular ejection
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4 fraction (LVEF) at baseline, adjusted for age, gender, previous myocardial infarction, systolic blood
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6 pressure, heart rate, and use of angiotensin inhibitors/receptor blockers and diuretics. 'n' is the
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8 number of individual patients analysed from double-blind, randomized controlled trials for the
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10 primary outcomes.
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Figure 5: Observed change in LVEF in survivors

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20 Change in left ventricular ejection fraction (LVEF) from baseline in patients who survived to
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22 follow-up, with median time between measurements of 1.0 years (interquartile range 0.3-2.0 years).
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25 Those with follow-up LVEF were older in age compared to those without follow-up LVEF (67
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27 [IQR 56-74] versus 64 [55-71] years, respectively), but with similar baseline LVEF (27% [20-33]
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29 versus 27% [21-33]) and frequency of ischaemic cardiomyopathy (65% versus 67%). The variance
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31 for each category of change in LVEF (beta-blockers versus placebo) is presented in Table 3. (A)
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35 Sinus rhythm; n=4,601 patients. (B) Atrial fibrillation; n=996.
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Supplementary Figure A: Study flowchart

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2 Note that left ventricular ejection fraction (LVEF) entry criteria for trials were often based on an
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4 assessment of LVEF that preceded enrolment. Hence at randomization or core laboratory
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6 assessment, some patients had LVEF above these inclusion/exclusion criteria and were available for
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8 analysis in this individual patient-level dataset. ^(a) Patients with stable heart failure and ischemic
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10 wall motion abnormalities. ^(b) Either LVEF $\leq 35\%$, or a hospital admission for heart failure within
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12 12 months regardless of LVEF.
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Supplementary Figure B: Crude and age-adjusted primary events according to baseline

LVEF

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25 Kaplan Meier survival curves for observed events according to baseline LVEF category regardless
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27 of heart rhythm. For both all-cause mortality and cardiovascular death, the trend test using a
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29 stratified log-rank analysis was $p < 0.0001$.
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Supplementary Figure C: Scatterplot of change versus baseline LVEF

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39 Change in LVEF plotted against baseline value for individual patients in sinus rhythm or atrial
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41 fibrillation (n=5,597). Dashed red line is the linear regression line.
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Figure 1 eps

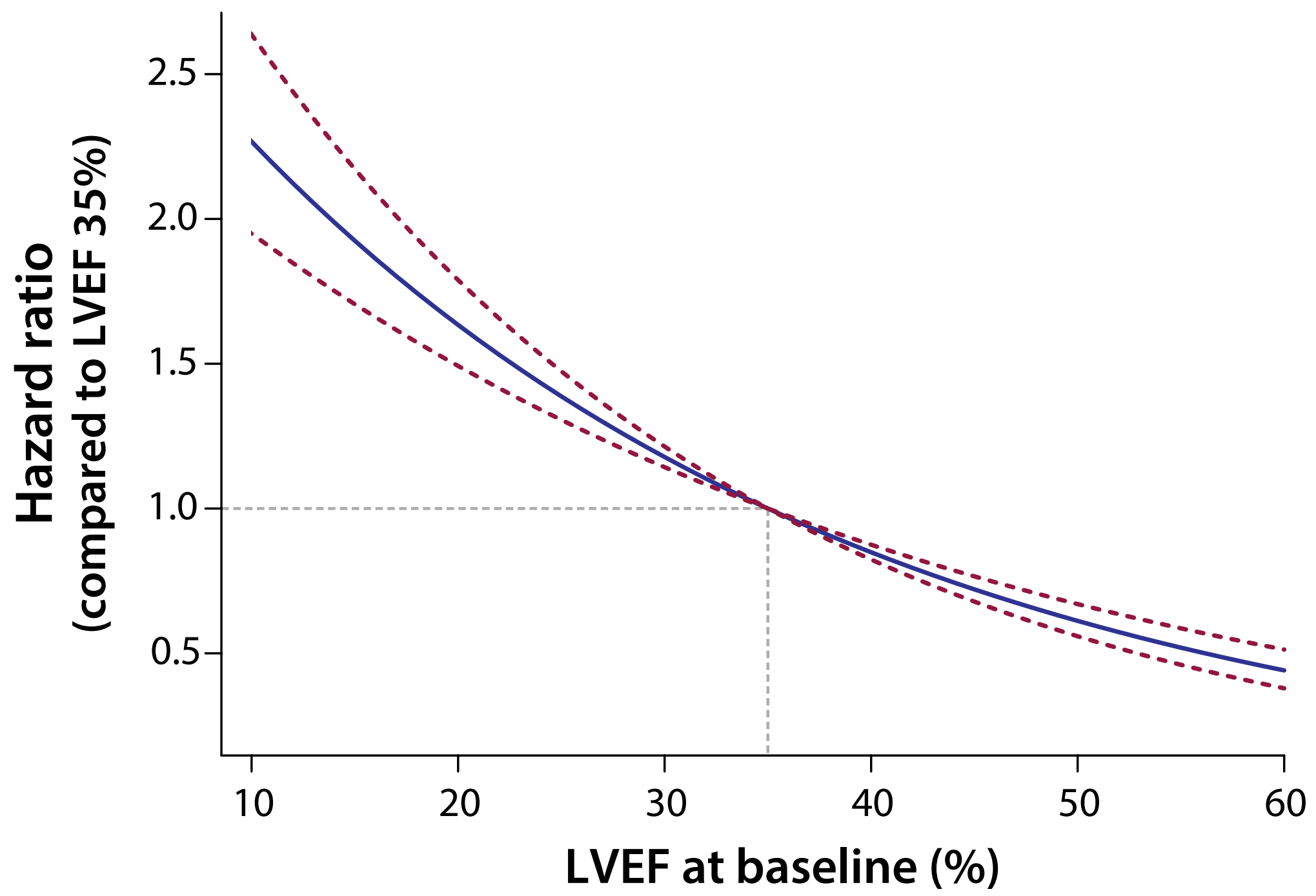
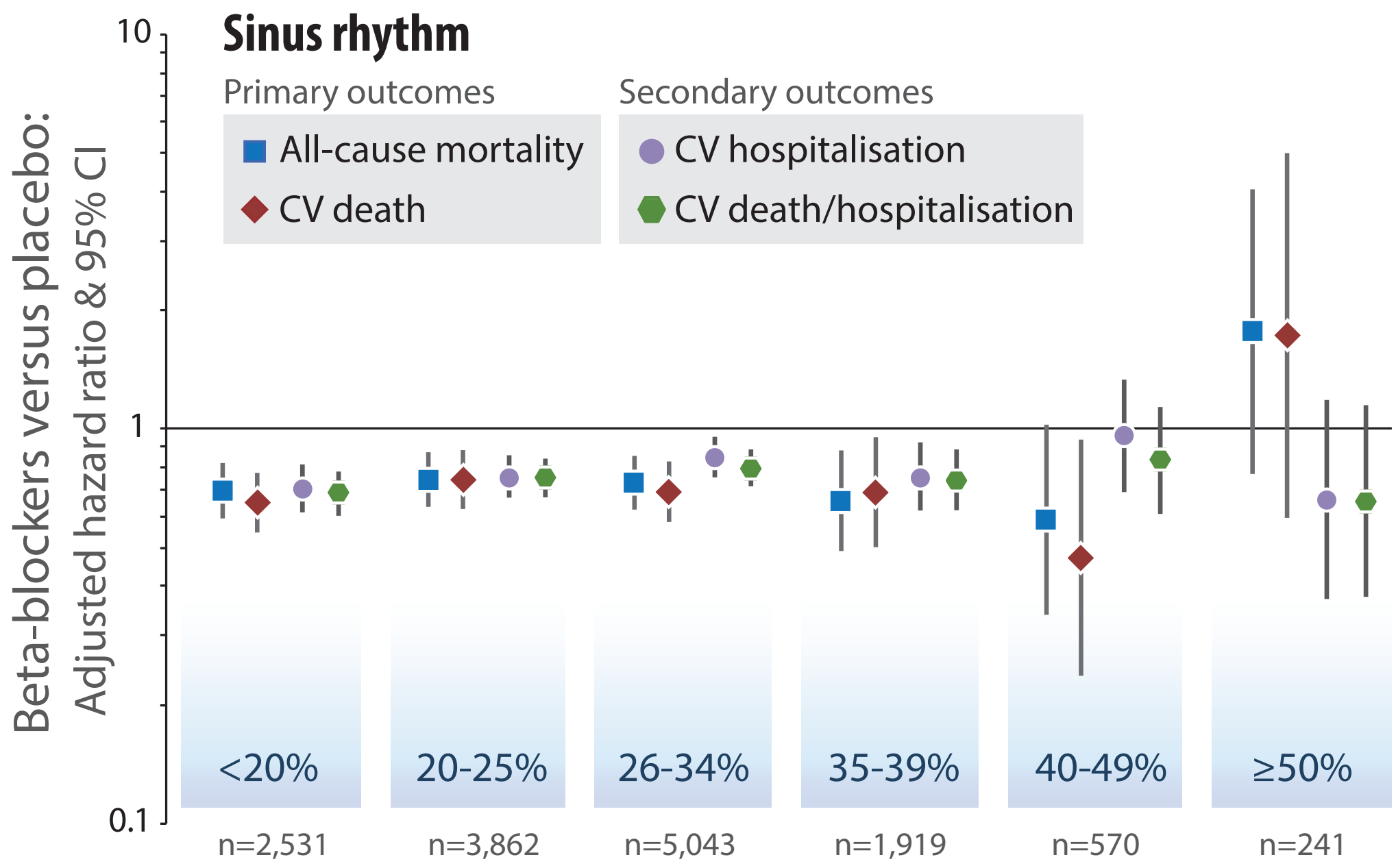
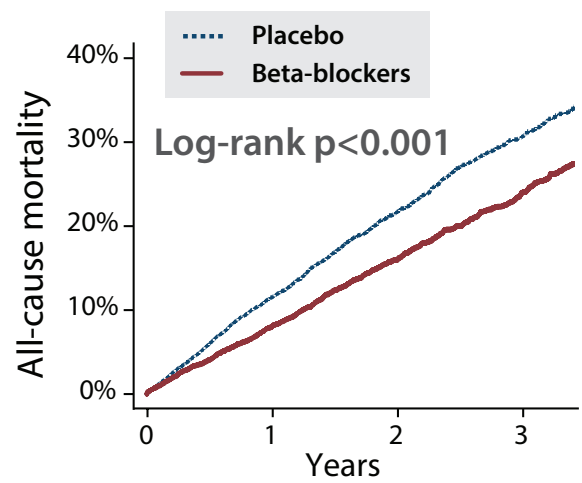


Figure 2 eps



A All-cause mortality

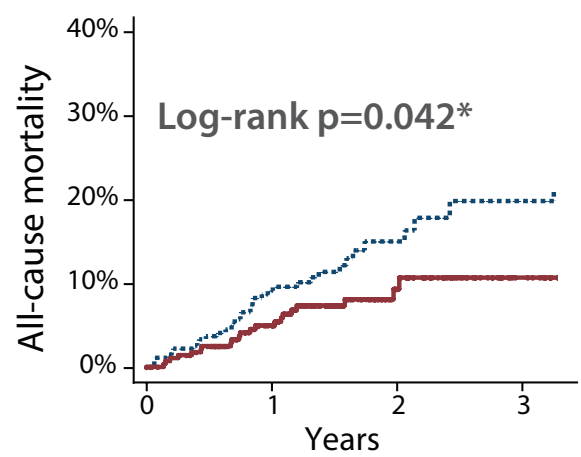
LVEF <40%, sinus rhythm



Number at risk

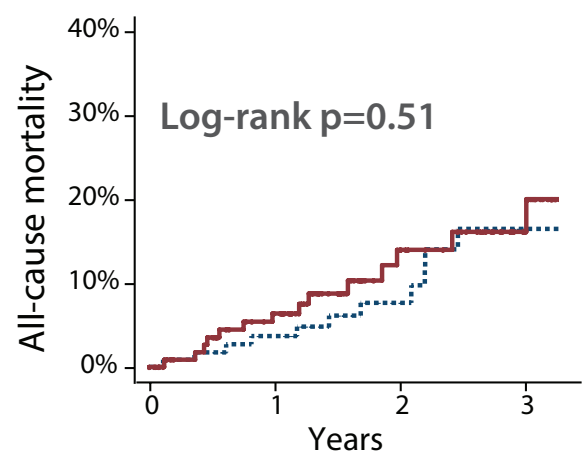
Placebo	6581	4282	1405	526
Beta-blocker	6861	4680	1673	678

LVEF 40-49%, sinus rhythm



283	199	63	11
292	211	65	15

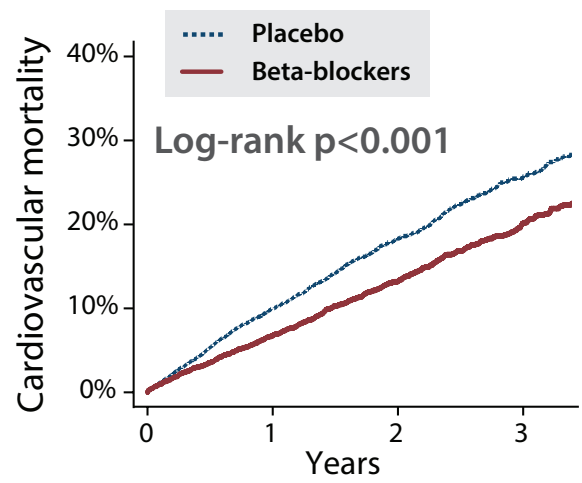
LVEF ≥50%, sinus rhythm



121	97	45	10
123	97	43	13

B Cardiovascular mortality

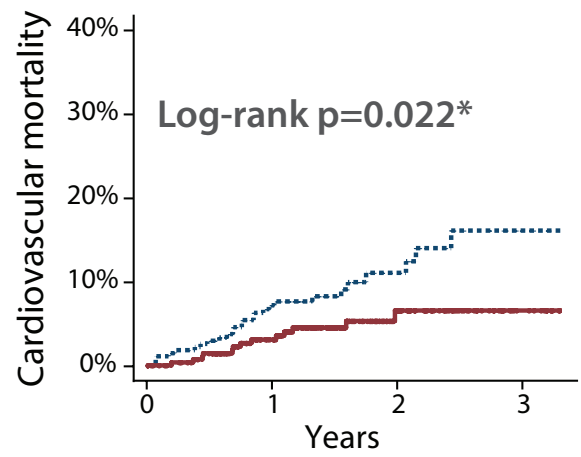
LVEF <40%, sinus rhythm



Number at risk

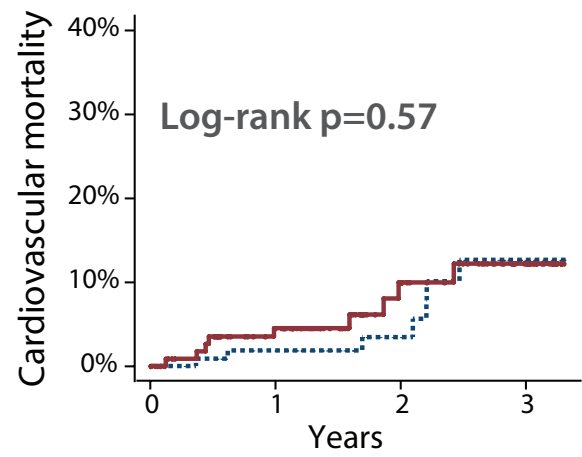
Placebo	6580	4281	1404	525
Beta-blocker	6861	4680	1673	678

LVEF 40-49%, sinus rhythm



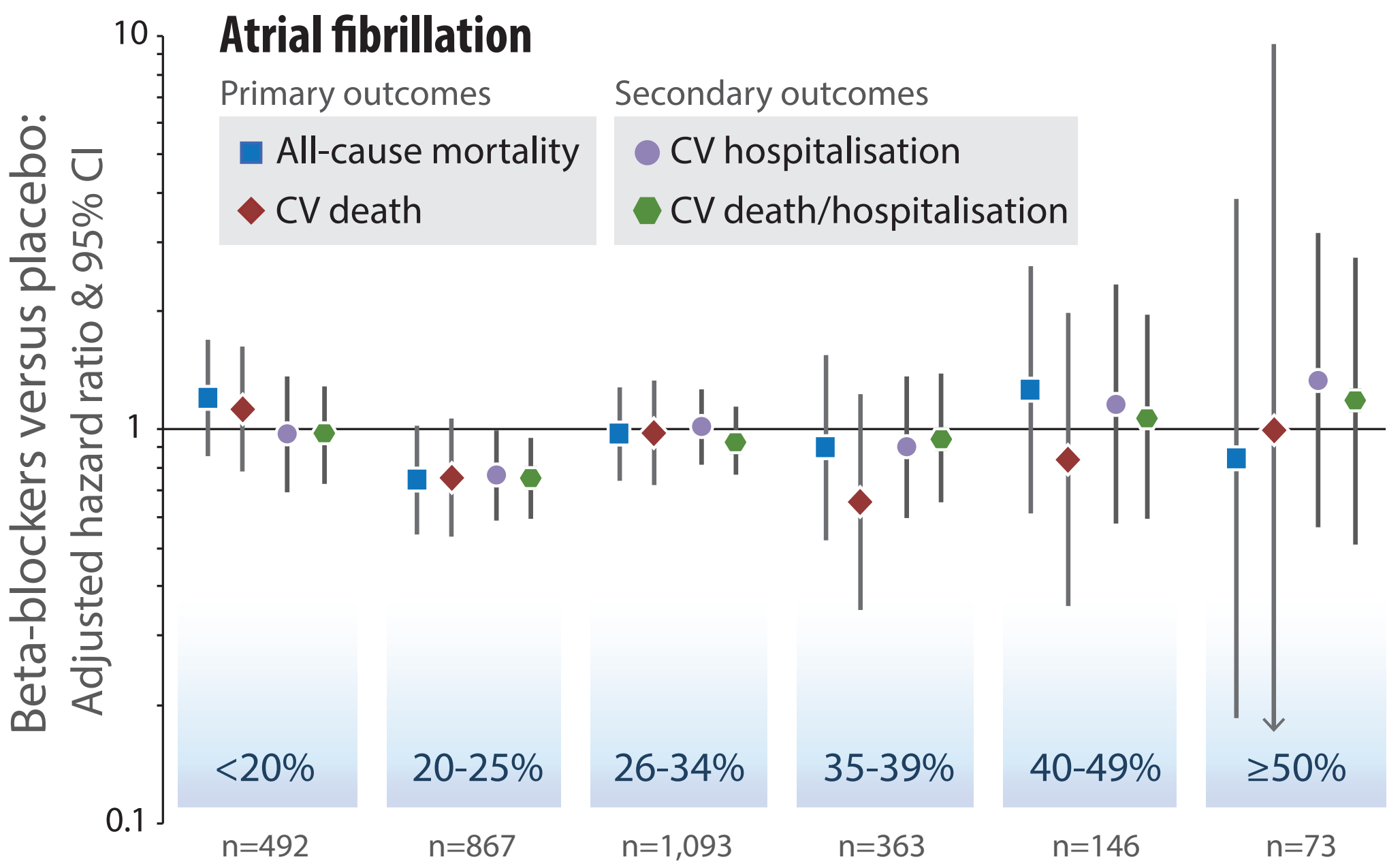
283	199	63	11
292	211	65	15

LVEF ≥50%, sinus rhythm

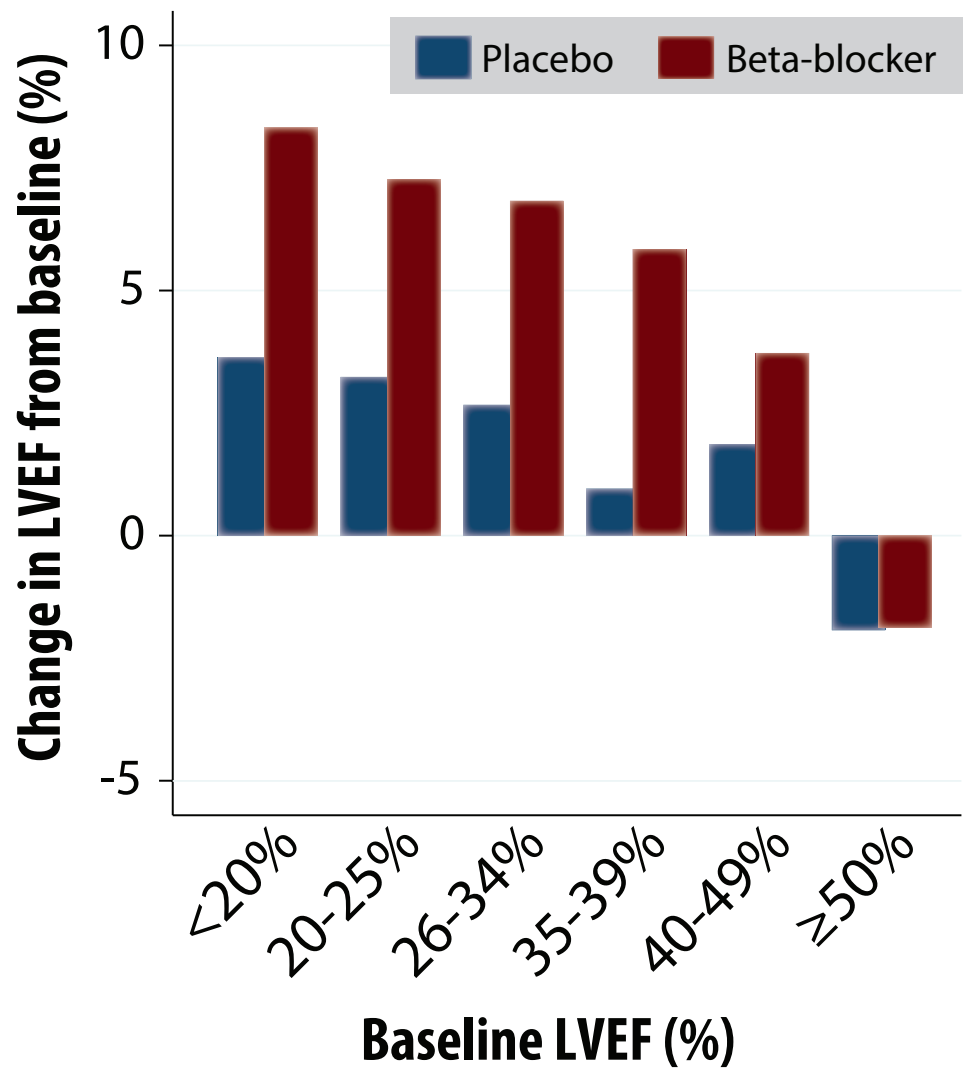


121	97	45	10
123	97	43	13

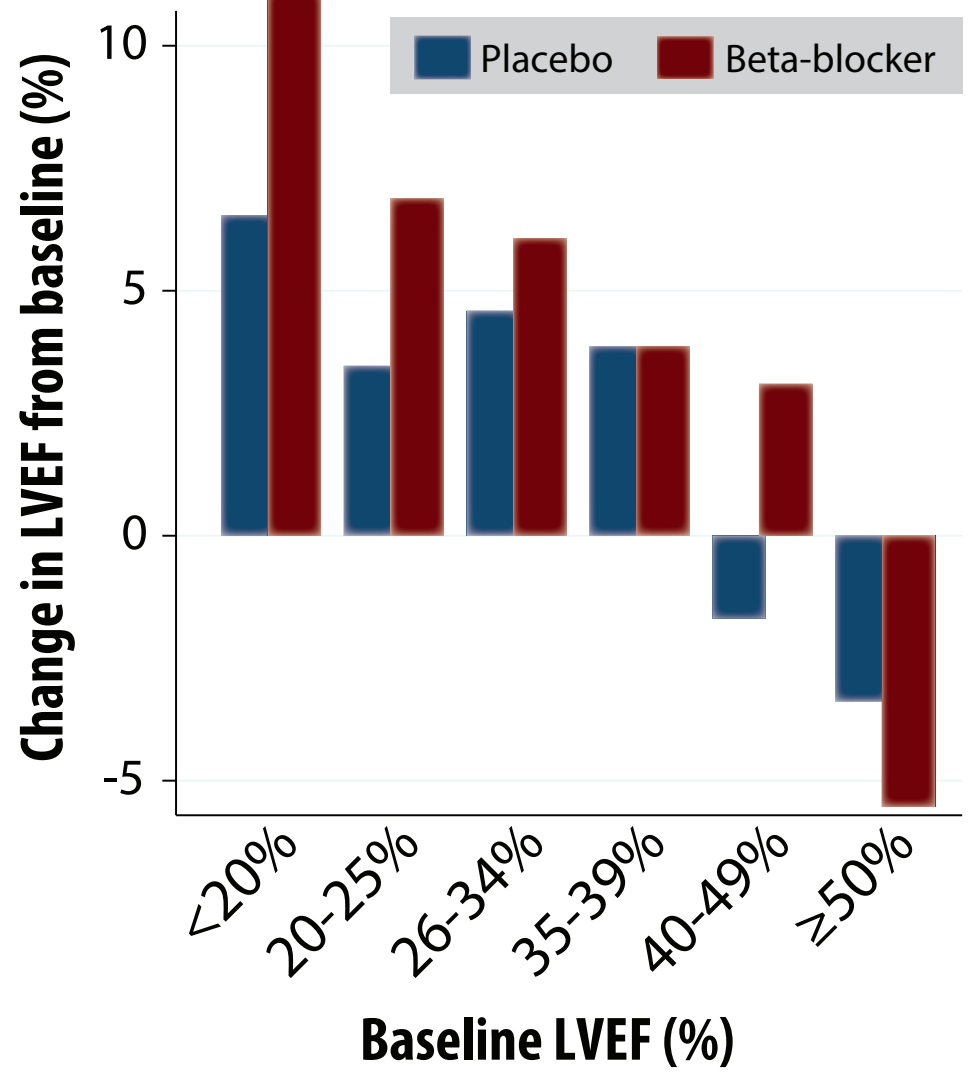
Figure 4 eps

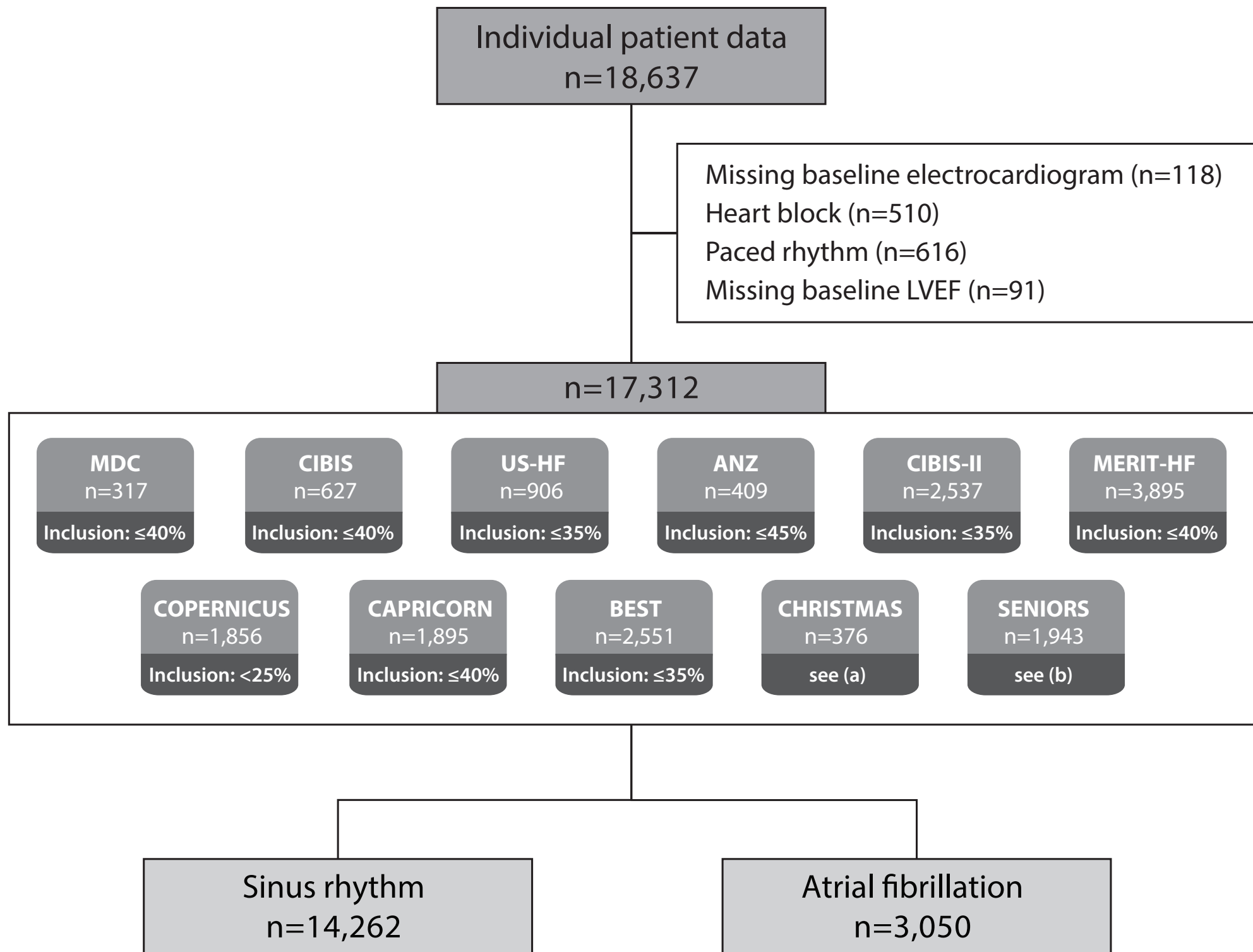


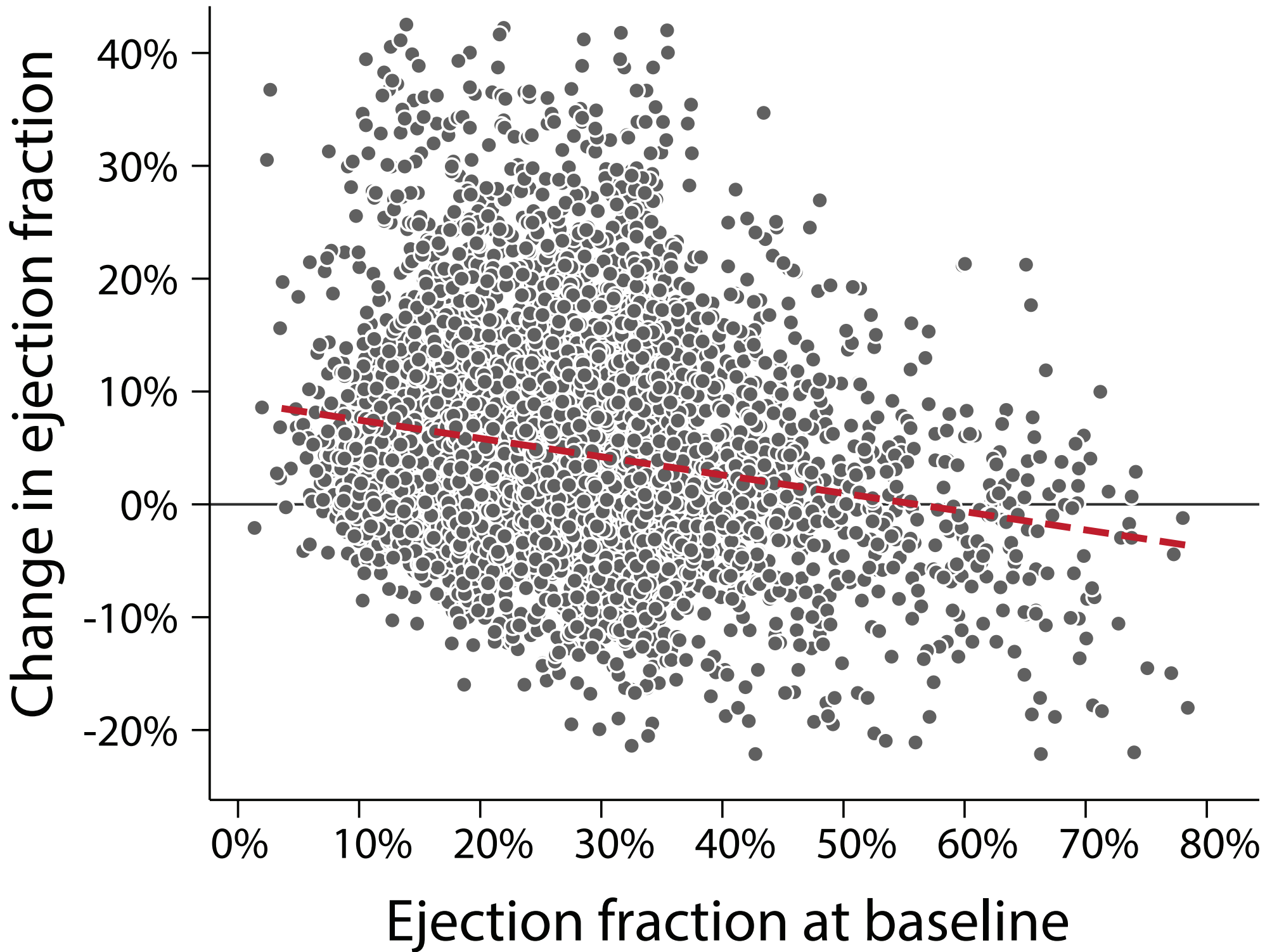
A Sinus rhythm



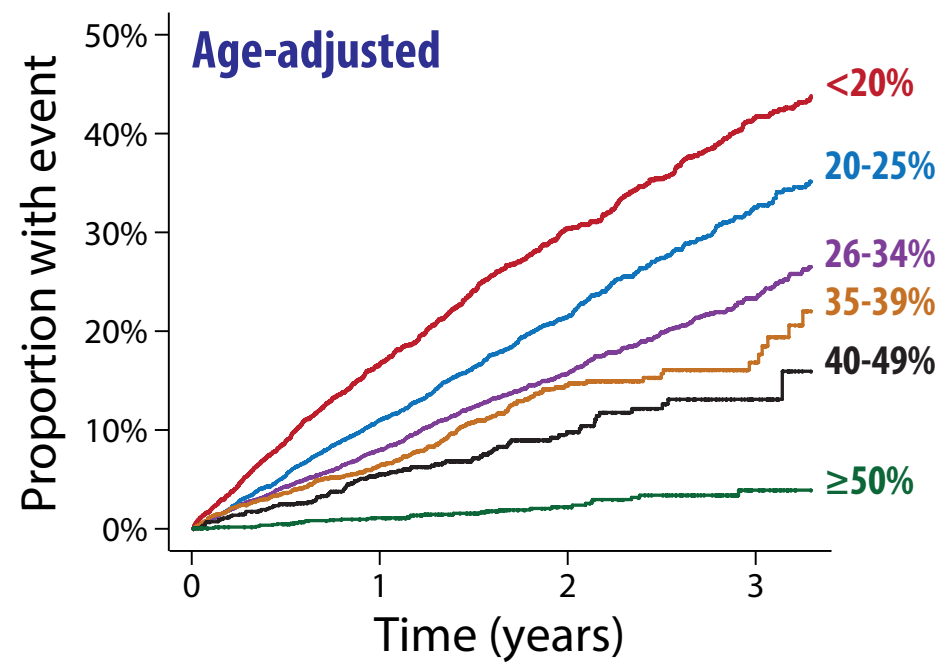
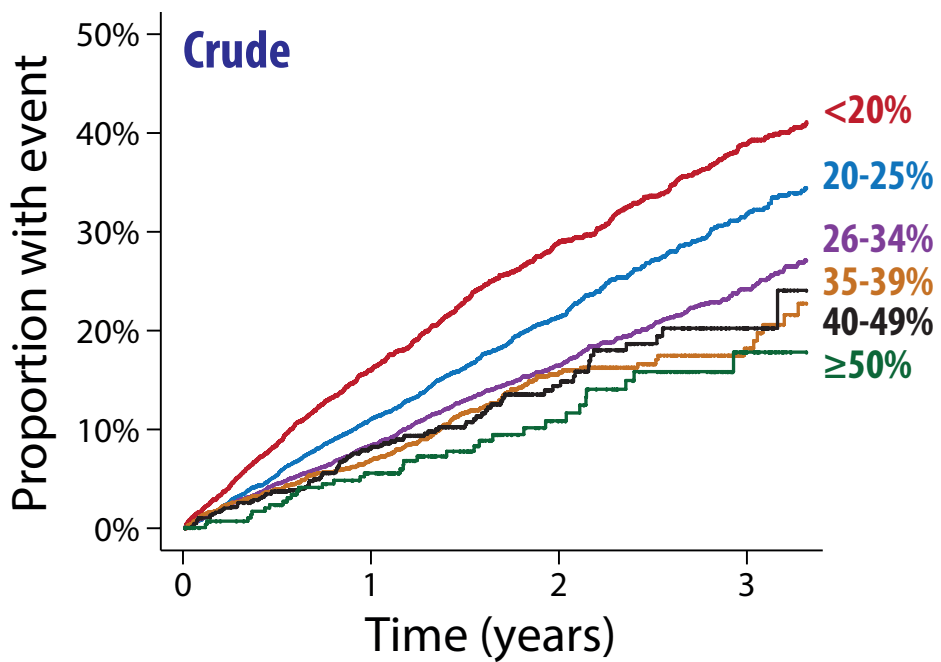
B Atrial fibrillation







A All-cause mortality



B Cardiovascular death

