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Efficacy of beta-blockers in patients with heart failure plus atrial fibrillation: An individual-patient data meta-analysis

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Abstract

Background: Atrial fibrillation and heart failure often coexist, causing substantial cardiovascular morbidity and mortality. Beta blockers are indicated in patients with symptomatic heart failure with reduced ejection fraction; however, the efficacy of these drugs in patients with concomitant atrial fibrillation is uncertain. We therefore meta-analysed individual-patient data to assess the efficacy of beta blockers in patients with heart failure and sinus rhythm compared with atrial fibrillation.

Methods: We extracted individual-patient data from ten randomised controlled trials of the comparison of beta blockers versus placebo in heart failure. The presence of sinus rhythm or atrial fibrillation was ascertained from the baseline electrocardiograph. The primary outcome was all-cause mortality. Analysis was by intention to treat. Outcome data were meta-analysed with an adjusted Cox proportional hazards regression.

Findings: 18 254 patients were assessed, and of these 13 946 (76%) had sinus rhythm and 3066 (17%) had atrial fibrillation at baseline. Crude death rates over a mean follow-up of 1·5 years (SD 1·1) were 16% (2237 of 13 945) in patients with sinus rhythm and 21% (633 of 3064) in patients with atrial fibrillation. Beta-blocker therapy led to a significant reduction in all-cause mortality in patients with sinus rhythm (hazard ratio 0·73, 0·67–0·80; p<0·001), but not in patients with atrial fibrillation (0·97, 0·83–1·14; p=0·73), with a significant p value for interaction of baseline rhythm (p=0·002). The lack of efficacy for the primary outcome was noted in all subgroups of atrial fibrillation, including age, sex, left ventricular ejection fraction, New York Heart Association class, heart rate, and baseline medical therapy.

Interpretation: Based on our findings, beta blockers should not be used preferentially over other rate-control medications and not regarded as standard therapy to improve prognosis in patients with concomitant heart failure and atrial fibrillation.

Registration: PROSPERO CRD42014010012; Clinicaltrials.gov NCT00832442.

Abbreviations

ACEi	Angiotensin converting enzyme inhibitor
ARB	Angiotensin receptor blocker
AF	Atrial fibrillation
CI	Confidence interval
CV	Cardiovascular
ECG	Electrocardiogram
GFR	Glomerular filtration rate
HF	Heart failure
HR	Hazard ratio
IPD	Individual patient data
LVEF	Left-ventricular ejection fraction
NYHA	New York Heart Association
OR	Odds ratio
RCT	Randomised controlled trial

Introduction

Beta-blocker therapy for patients with chronic heart failure (HF) with reduced ejection fraction was instituted following a series of small mechanistic studies that led to large randomised controlled trials (RCTs) identifying a significant reduction in morbidity and mortality. Their use in symptomatic patients with HF has a class 1A recommendation from both European and American guidelines.[1, 2] Nonetheless, uptake of therapy in clinical practice remains sub-optimal, with those at the greatest risk of death less likely to receive evidence-based therapy.[3] There have also been concerns over treatment efficacy in certain groups, notably patients with atrial fibrillation (AF), women and the elderly. Previous analyses in these important patient subsets have lacked statistical power and further randomised evidence is now unlikely. The Beta-blockers in Heart Failure Collaborative Group was formed to provide definitive answers to a range of unanswered questions relating to HF and beta-blocker therapy, with the aim of optimising use and providing clear guidance on the efficacy and safety of treatment.[4]

Chronic HF and AF represent two common conditions that are associated with substantial morbidity and risk of death.[1, 5] Importantly, both are predicted to continue increasing in prevalence[6, 7], with the incidence of AF expected to double in the next 20 years.[8] Rehospitalisation is seen in over 50% of patients with HF within 6 months[9] and in nearly 40% of AF patients over 12 months.[10] Despite improved medical therapy, HF remains a significant driver of healthcare cost.[11] Those with concomitant AF have even higher mortality and hospital admission rates, regardless of which condition comes first.[12, 13] In addition, the prevalence of AF is closely related to the severity of HF, as determined by NYHA functional class.[14]

We sought to examine the efficacy and safety of beta-blockers in patients with HF and concomitant AF by performing an individual patient data (IPD) meta-analysis. Patients with AF are frequently prescribed beta-blockers both for prognostic benefit in HF and heart-rate control, although there is limited and underpowered evidence for efficacy with regards to clinical outcomes.[15] Considered the 'gold-standard' of meta-analysis, IPD allows appropriate examination of sub-groups and the ability to accurately combine original data (thereby improving data quality), perform full time-to-event analyses and generate hazard ratios adjusted for baseline covariates.[16] Assessment of over 18,000 patients randomised to beta-blockers or placebo permits a robust and adequately-powered analysis of the clinical benefit of beta-blocker therapy in patients with HF and AF, compared to those in sinus rhythm.

Methods

A detailed rationale and design paper has previously been published (click here for link to free online publication).[4] To summarise, the Beta-blockers in Heart Failure Collaborative Group (BB-meta-HF) is a multinational effort to combine individual data from the major RCTs investigating the use of beta-blockers in HF. The group consists of the leading investigators of these trials and international experts, with the support of the four pharmaceutical companies that have marketed therapies (AstraZeneca, GlaxoSmithKline, Merck Serono and Menarini). This report was prepared according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines[17] and prospectively registered with Clinicaltrials.gov (NCT0083244) and the PROSPERO database of systematic reviews (CRD42014010012).[18]

Eligibility, search strategy and data collection

Published or unpublished RCTs were identified through computer aided searches (e.g. 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. RCTs were included that reported mortality as a primary or composite outcome comparing beta-blockers versus placebo. Only unconfounded head-to-head trials were eligible, with recruitment of >300 patients and planned follow-up of >6 months to make the project technically feasible and clinically-relevant. The search results, individual study demographics and a standardised data request form to obtain IPD from each trial have previously been published.[4]

Eleven studies were included that account for 95.7% of eligible recruited participants: the Australia/New Zealand Heart Failure Study (ANZ)[19], the Beta-Blocker Evaluation Survival

Trial (BEST)[20], the Carvedilol Post-Infarct Survival Control in LV Dysfunction Study (CAPRICORN)[21], the Carvedilol Hibernating Reversible Ischaemia Trial: Marker of Success Study (CHRISTMAS)[22], the Cardiac Insufficiency Bisoprolol Study (CIBIS I)[23], the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II)[24], the Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS)[25], the Metoprolol in Idiopathic Dilated Cardiomyopathy Study (MDC)[26], the Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF)[27], the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure Study (SENIORS)[28] and the U.S. Carvedilol Heart Failure Study (US-HF)[29]. All included studies had low risk of bias, as determined using the Cochrane Collaborations Risk of Bias Tool.[30]

The CHRISTMAS trial was excluded from this analysis as AF was an exclusion criterion. Data were extracted from original source files and additional follow-up outcomes were available in seven studies.[19-21, 25, 26, 28, 29] The primary outcome was all-cause mortality, including an analysis of total mortality where deaths occurred after early study termination or following a fixed censor point. The mean follow-up period until death or censoring was 1.5 years (SD 1.1) across all studies, which ranged from 0.9 to 5.3 years in the individual trials. Major secondary outcomes were CV-death, the composite of all-cause mortality and CV-hospitalisation, and non-fatal stroke. Hospitalisation outcomes included the time to hospitalisation (any cause), CV-hospitalisation and HF-related hospitalisation, as well as the number and duration of CV/HF hospital admissions. An additional post-hoc defined outcome was the composite of CV-death and HF-related hospitalisation. Drug safety outcomes were focused on discontinuation of study drug therapy due to hypotension, bradycardia, renal impairment, HF-exacerbation or any adverse event.

Atrial fibrillation/flutter

The diagnosis of AF or atrial flutter was determined by the baseline electrocardiogram (ECG). Distinguishing between the two atrial arrhythmias was only possible in two trials.[20, 28] Consistent with clinical expectation, flutter accounted for only 4% of the combined group. For the purposes of this paper, reference to AF will therefore also include atrial flutter. Incident AF was defined as AF during follow-up in patients with sinus rhythm at baseline. Follow-up ECGs or adverse event data reflecting new-onset or recurrence of AF were available in all studies, with 862 of 13,946 individual patients (6%) missing data.

Statistical analysis

Data are presented as median and interquartile range (IQR) or percentages. Estimated glomerular filtration rate (GFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula, normalised to a body surface area of 1.73 m^2. Three patients had missing event dates and were excluded from outcome analyses. Hospitalisation was not recorded for the MDC trial and NYHA class was not explicitly obtained in the COPERNICUS study. As the amount of missing data for other major variables was low, there was no requirement for imputation of missing values.

All analyses followed the principle of intention to treat. The primary and major secondary outcomes were analysed using a stratified Cox proportional hazards regression model.[31] 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. Hazard ratios (HR) and 95% confidence intervals (CI) are presented, along with corresponding p-values, with adjustment for age, gender and baseline left-ventricular ejection fraction (LVEF), heart rate and use of angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB). Kaplan Meier plots are used to graph the data (pooling data from all trials). As the follow-up

periods in individual studies varied, data were censored at 1200 days. Heterogeneity for pooled outcomes 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.[32]

A range of sensitivity analyses were performed, including alternative censor points, separate exclusion of the BEST and CAPRICORN studies, additional baseline adjustment and random effects modelling.[33] Exploratory analyses included a per-protocol analysis assessing patients who remained on study therapy throughout the trial and factors associated with incident AF (using an adjusted logistic regression model as time to diagnosis of AF was not available).

A two-tailed p-value of 0.05 was considered statistically significant. Analyses were performed on Stata Version 11.2 (StataCorp LP, Texas) and R Version 3.0.2 (R Core Team, Vienna).

Results

A total of 18,254 individual participants were assessed, of which 13,946 (76.4%) were in sinus rhythm at baseline and 3,066 (16.8%) in AF. Other rhythms (predominantly paced rhythm or heart block) accounted for 1,124 (6.2%) and 118 patients had a missing or uninterpretable baseline ECG (0.6%). There were minimal differences in baseline characteristics between patients randomised to beta-blockers or placebo in any group (see Supplementary Table 1). A comparison of those in sinus rhythm and AF at baseline is presented in Table 1. The median duration of HF prior to enrolment was 3 years. Compared to those in sinus rhythm, AF patients were 5 years older, with a higher percentage of men. There were small differences in systolic blood pressure and GFR but LVEF and heart rate were similar. Patients with AF were more symptomatic, with 72% in NYHA class III/IV compared to 62% for those in sinus rhythm. AF patients had more frequent use of diuretics, aldosterone antagonists, digoxin and oral anticoagulants, however 95% in both groups were taking ACEi or ARB at baseline.

Outcomes according to baseline rhythm

Including deaths reported after early or date-based study termination, crude mortality rates were 20.7% in AF patients (633/3,064) and 16.0% in sinus rhythm (2,237/13,945). Considering deaths in the study period only, crude mortality rates were 18.1% in AF patients (556/3,064) and 14.5% in sinus rhythm (2,021/13,945). The most common causes of death in both groups were sudden death and death due to heart failure (see Table 2). Fatal stroke was relatively uncommon, although as expected more frequent in patients with AF.

Table 3 displays pooled hospitalisation data divided into all-cause, CV and HF-related

hospital admissions. The total number of hospitalisations and annualised rate per patient were higher in AF patients compared to sinus rhythm for all types, with longer average length of stay (for CV-hospitalisation 11.9 days in AF versus 9.7 days in sinus rhythm).

Efficacy of beta-blocker therapy

A consistent effect of beta-blockers versus placebo was noted across all death and/or hospitalisation outcomes, with benefit demonstrated in sinus rhythm but non-significant differences seen in AF patients (see Table 4). P-values for the interaction of treatment efficacy and baseline heart rhythm were significant for each of these outcomes. Including all reported deaths, the adjusted HR for all-cause mortality in sinus rhythm was 0.73 (95% CI 0.67-0.80) and in patients with AF 0.97 (95% CI 0.83-1.14), with a p-value for interaction of 0.002. Kaplan-Meier survival curves are displayed in Figure 1. Similar results were seen for CV-deaths or when restricting analysis to deaths during the study period only. For CV-hospitalisation, the adjusted HR in sinus rhythm was 0.78 (95% CI 0.73-0.83) and in AF 0.91 (95% CI 0.79-1.04), with a p-value for interaction of 0.05; see Figure 2 for Kaplan-Meier event curves. Results were similar for HF-related hospitalisation and the composite clinical outcomes (death or CV-hospitalisation and CV-death or HF-related hospitalisation). Beta-blocker therapy had no impact on incident non-fatal stroke in either sinus rhythm or AF (see Table 4).

Sensitivity and exploratory analyses

Sensitivity analyses for the primary outcome are presented in Supplementary Table 2. There were no observable effects for additional baseline adjustment, the exclusion of specific trials

or the use of different censor points. An alternative analysis method using a two-stage meta-analysis is presented in Figure 3, which resulted in virtually identical hazard ratios to the one-stage approach using both fixed and random effects modelling. Importantly, we identified no heterogeneity between the individual studies for all-cause mortality in patients with AF (I^2=0%, p=0.65).

An exploratory sub-group analysis was performed within the AF cohort for all-cause mortality, with no significant interactions identified for a range of baseline variables at clinical cut-points, including age, gender, LVEF, NYHA, the control of blood pressure or heart rate, and baseline medical therapy (see Figure 4). We also performed a per-protocol assessment for all reported deaths in the AF group. Compared to the intention-to-treat analysis, no difference was identified in the efficacy of beta-blocker therapy in AF patients that remained on therapy (HR 0.84; 95% CI 0.68-1.04), with no significant interaction for discontinuation of study treatment within the AF group (p=0.09).

Incident AF

In patients with sinus rhythm at baseline, 610 (4.7%) developed AF on a subsequent ECG. The factors independently associated with incident AF in an exploratory analysis were advanced age, male gender, increased BMI and NYHA class III/IV at baseline (see Supplementary Table 3). Allocation to beta-blockers was associated with a 33% reduction in the adjusted odds of incident AF (253/6,722 randomised to beta-blockers developed AF, compared to 357/6,362 allocated to placebo).

Study drug dosage, discontinuation, adverse treatment effects and heart rate

There were minimal differences in the dose of study drug achieved according to baseline heart rhythm, with overall 84% achieving maximal study dosage in the placebo arm and 73% in those randomised to beta-blockers (see Supplementary Table 4). The attained heart rate and change from baseline heart rate were similar in patients with sinus rhythm and AF, although interpretation is confounded by lack of measurement in patients who died prior to the interim study visit (see Supplementary Table 5). Rates of study drug discontinuation due to adverse effects were identical in patients allocated to either beta-blockers or placebo (15%). No differences in beta-blocker discontinuation rates were identified comparing sinus rhythm to AF (see Supplementary Table 6). The incidence of specific adverse effects causing withdrawal of therapy were low (for example hypotension or bradycardia in 1-2%).

Discussion

This individual patient analysis has investigated the largest cohort of patients with HF due to reduced ejection fraction and AF to-date. Our principal findings are that in contrast to those in sinus rhythm at baseline, patients with HF and AF obtained little or no benefit from beta-blockers, with no significant reduction in all-cause mortality, CV-hospitalisation or composite clinical outcomes compared to placebo. The AF group comprised 3,066 participants with 633 deaths, and although there may still be limited power, this analysis suggests that clinical benefit from beta-blockers is unlikely in patients with combined HF and AF. Patients in AF had higher crude rates of death, more frequent hospitalisation and longer length of stay compared to those in sinus rhythm.

Heart failure and AF are two common conditions that are increasing in prevalence. Although HF incidence has remained static over the past 25 years[34], the incidence of AF is increasing[35] and not simply as a function of the ageing population.[36] These two conditions frequently co-exist, with observational data suggesting the presence of AF in 14-50% of patients with symptomatic HF.[14] In HF, atrial remodelling frequently occurs due to sustained increases in pressure, volume and neurohormonal stress, making the development of AF more likely. Similarly, AF can lead to HF both as a direct cause (for example in tachycardia-induced cardiomyopathy) and due to loss of atrioventricular synchrony and impairment in diastolic filling. Heart failure with preserved ejection fraction is as common as the syndrome with reduced LVEF[2], however no prior trial has examined the impact of pharmacotherapy on diastolic function in patients with AF. However, regardless of the type of HF, the combination with AF is known to adversely affect prognosis[37] and overall represents a massive burden to affected patients, healthcare systems and societies, including substantial healthcare costs.[38] Hospitalisation in HF is the greatest cost contributor[11] and our analysis

suggests that AF increases both the risk of hospitalisation and length of stay, reinforcing the importance of finding efficacious therapies in this population.

The lack of prior focus on optimal management of the combination of HF and AF is concerning. Indeed all current guideline recommendations for treatment of HF with reduced LVEF stem from trials predominantly from patients in sinus rhythm. Guidelines from the European Society of Cardiology[1] and the American College of Cardiology Foundation/American Heart Association[2] recommend beta-blocker therapy in patients with HF and AF, based on the efficacy demonstrated from the trials assessed in this paper. Our analysis suggests that the substantial benefit identified in patients with sinus rhythm should not be extrapolated to those with AF. The reason for the lack of efficacy of beta-blockers in patients with AF may be due to several physiological differences.[15] In contrast to sinus rhythm, slower heart rates are not associated with improved survival in AF[39], although this remains to be adequately tested prospectively. The irregular rhythm in AF is also associated with a detrimental impact on systolic and diastolic cardiac function that is independent of heart rate.[40, 41] There are also structural[42] and cellular[43] consequences of AF that may impact on treatment efficacy. These observations however, do not fully explain why the positive effects of beta-blockers, particularly on myocardial metabolism, do not correspond to prognostic benefit in patients with AF, an anomaly that requires further investigation.

Finally it is important to consider the substantial reduction in hospitalisation and death that was seen in patients with sinus rhythm. Rates of beta-blocker uptake amongst HF patients in clinical practice have been consistently suboptimal[44, 45] and may reflect concern about symptom deterioration after initiation of therapy or the poor generalisability of RCT data to real-world patients.[46] One of the major aims of the Beta-blockers in Heart Failure

Collaboration was to improve rates of appropriate beta-blocker use by identifying key patient groups that benefit most from therapy. In this regard, use of beta-blockers in patients with sinus rhythm is strongly recommended and further sub-group analyses in relation to age, gender and diabetes are planned. We also found a reduction in incident AF in those with sinus rhythm treated with beta-blockers. This confirms a previous tabular analysis of beta-blocker trials in HF[47] and may be an important component of therapeutic benefit in patients with sinus rhythm.

Although we found no evidence that beta-blocker therapy prevents adverse clinical events in patients with HF and AF, it did appear safe with no *increase* in mortality or hospitalisation observed. This should reassure clinicians, particularly for patients with another indication for beta-blockers, for example acute myocardial infarction or the need for rate control of rapid AF with ongoing symptoms. However, for the primary reason of preventing major adverse cardiovascular outcomes in patients with chronic HF and reduced LVEF, beta-blockers do not appear to be effective in those with AF and should no longer be considered as standard therapy to improve prognosis.

Strengths & Limitations

The strength of our analysis was the use of IPD from large, high quality RCTs, with near-totality of available randomised data. We performed careful and methodical data extraction from original datasets[4], resulting in improved quality of baseline and outcome data across trials. Although the process of IPD meta-analysis is arduous, there are substantial benefits including the ability to adjust for covariates and produce time-to-event analyses.[16] We were also able to include post-publication data on mortality, explaining the small differences from previously published results in the component RCTs. We confirmed that our conclusions apply across various sub-groups of AF and regardless of meta-analysis

methodology. This study provides the most powerful analysis of the efficacy of beta-blockers in AF ever performed, thereby addressing a key clinical question regarding management of this important group of patients with HF.

As with all meta-analytical techniques, we are limited by the data provided from the individual studies. Although there were missing data for some variables, their impact was minimised by extracting data from source datasets with a published data extraction plan.[4] As previously noted, we were unable to separate those with AF and atrial flutter, however the latter made up only a small proportion of patients. The rate of incident AF was lower than expected from clinical practice and may reflect under-reporting, particularly of paroxysmal AF. Our inability to characterise the type, persistence and duration of AF is a limitation. Although the validity and reproducibility of LVEF measurement has not been adequately demonstrated in patients with AF, we did not see any difference in the variance of LVEF comparing those with sinus rhythm and AF. Finally, heart failure with preserved ejection fraction accounts for over half of patients with HF, but RCT data on beta-blockers versus placebo in this group are limited.[48] Of the studies included in our analysis, only SENIORS recruited patients with LVEF$\geq$0.50, which accounted for only 1.8% of the pooled dataset. Hence we are unable to comment on the efficacy of beta-blockers according to rhythm status for patients with HF and preserved LVEF.

Conclusion

In contrast to the beneficial effects noted for patients with sinus rhythm, beta-blocker therapy has no or minimal effect on mortality or cardiovascular hospital admission in patients with heart failure with reduced ejection fraction and atrial fibrillation. Based on our results, we dispute the preferential use of beta-blockers compared with other rate-control medications and emphasise the need for further trials in this common and increasingly important group of patients.

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Author contributions:

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

Competing interests:

DK has received grants from Menarini during the conduct of the study and honoraria from Menarini (>36 months ago). HK has received honoraria from GlaxoSmithKline, Roche, and Merck (>36 months ago). JGFC has received grants and personal fees from Roche and GlaxoSmithKline outside of the submitted work. AJSC has received grants and personal fees from Menarini during the conduct of the study and personal fees from Lone Star Heart outside of the submitted work. PK has received grants and personal fees from several research funders including the European Union, British Heart Foundation, German Research Foundation, Leducq Foundation, German Ministry of Education and Research, and from medical device and pharmaceutical companies outside the submitted work; PK also has

patents pending for atrial fibrillation therapy and markers. HW has received consulting fees from AstraZeneca as a member of the MDC and MERIT-HF steering committees. MDF has received grants from Menarini during the conduct of the study and personal fees from AstraZeneca outside the submitted work. TGvL was supported by a grant from Southern and Eastern Norway Health Authority during the conduct of the study. GYHL has served as a consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi , Bristol-Myers Squibb–Pfizer, Biotronik, Portola and Boehringer Ingelheim, and has been on the speakers' bureau for Bayer, Bristol-Myers Squibb–Pfizer, Boehringer Ingelheim, and Sanofi -Aventis. MCS has received honoraria and speaker fees from Forest Laboratories. The other authors declare no competing interests.

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Ethics Statement:

All original trials operated under supervision of an appropriate Human Ethics Committee.

The current analysis involves anonymised data only, hence ethics committee approval was deemed unnecessary by the National Research Ethics Service London – Chelsea (letter of confirmation available on request).

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Table 1: Pooled characteristics at baseline

Characteristic	Sinus rhythm n=13,946	Atrial fibrillation n=3,066
Age, median years (IQR)	64 (54-71)	69 (60-74)
Women	25.1%	19.4%
Diabetes mellitus	24.6%	23.1%
Years with HF diagnosis, median (IQR)	3.0 (1.0-6.0)	3.0 (1.0-7.0)
LVEF, median % (IQR)	0.27 (0.21-0.33)	0.27 (0.22-0.33)
NYHA class III/IV	62.6%	72.1%
Systolic BP, median mmHg (IQR)	123 (110-140)	127 (113-140)
Diastolic BP, median mmHg (IQR)	78 (70-82)	80 (70-85)
Heart rate, median bpm (IQR)	80 (72-88)	81 (72-92)
Body mass index, median kg/m^2 (IQR)	27 (24-31)	27 (25-31)
Estimated GFR, median mL/min (IQR)	64 (52-78)	61 (49-74)
Any diuretic therapy	85.2%	93.5%
ACEi or ARB	94.7%	94.5%
Aldosterone antagonists	8.2%	16.8%
Digoxin	52.9%	83.5%
Amiodarone	5.7%	10.4%
Oral anticoagulation	26.2%	57.8%

IQR, interquartile range; LVEF, left-ventricular ejection fraction; NYHA, New York Heart Association functional class; BP, blood pressure; GFR, glomerular filtration rate; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker. Within group characteristics according to treatment allocation are presented in Supplementary Table 1. Missing data were present for the following variables: Diabetes mellitus (n=993); Years with HF (n=2784); LVEF (n=76); NYHA class (n=2,376); Systolic BP (n=10); Diastolic BP (n=17); Heart rate (n=8); Body mass index (n=150); and GFR (n=735).

Table 2: Cause of death

Cause of death	Number of deaths (percentage of group)	
	Sinus rhythm	Atrial fibrillation
Acute myocardial infarction	126 (5.6%)	13 (2.1%)
Sudden death	927 (41.4%)	231 (36.5%)
Heart failure	539 (24.1%)	184 (29.1%)
Other cardiac cause	59 (2.6%)	11 (1.7%)
Stroke	43 (1.9%)	27 (4.3%)
Other vascular cause	99 (4.4%)	38 (6.0%)
Non-cardiovascular	180 (8.1%)	45 (7.1%)
Unknown	264 (11.8%)	84 (13.3%)
Total deaths	2,237 / 13,946 (16.0%)	633 / 3,066 (20.7%)

Includes all deaths, including those reported after early termination/study closure.

Table 3: Hospitalisation

Hospitalisation type	Pooled data for sinus rhythm	Pooled data for atrial fibrillation
All-cause hospitalisation		
Percentage with 1 or more admission	37.7%	40.1%
Average number of admissions per patient	0.78 (range 0-26)	0.79 (range 0-26)
Annualised hospitalisation rate per patient	0.86/year	0.94/year
CV-hospitalisation		
Percentage with 1 or more admission	25.7%	28.9%
Average number of admissions per patient	0.45 (range 0-16)	0.49 (range 0-14)
Annualised hospitalisation rate per patient	0.52/year	0.60/year
Average length of stay *	Mean 9.7, median 6 days (range 1-368)	Mean 11.9, median 8 days (range 1-179)
HF-related hospitalisation		
Percentage with 1 or more admission	16.4%	21.0%
Average number of admissions per patient	0.30 (range 0-16)	0.36 (range 0-14)
Annualised hospitalisation rate per patient	0.36/year	0.41/year
Average length of stay *	Mean 9.8, median 6.5 days (range 1-148)	Mean 12.0, median 8 days (range 1-179)

Note that presented data do not account for differences in baseline demographics between groups. *Average of first five hospitalisations for a CV/HF cause in those patients with at least one admission.

Table 4: Primary and secondary adverse outcomes

Outcome	Number of events/sample size	Sinus rhythm; Beta-blockers versus placebo		Atrial fibrillation; Beta-blockers versus placebo		Interaction; AF versus sinus rhythm
		HR (95% CI) *	p-value	HR (95% CI) *	p-value	p-value
All-cause mortality (including all reported deaths)	2870 / 17009	0.73 (0.67, 0.80)	<0.001	0.97 (0.83, 1.14)	0.73	0.002
All-cause mortality (deaths during study period)	2577 / 17009	0.73 (0.67, 0.80)	<0.001	0.93 (0.79, 1.10)	0.43	0.01
CV-death (including all reported deaths)	2297 / 17009	0.72 (0.65, 0.79)	<0.001	0.92 (0.77, 1.10)	0.35	0.02
First CV-hospitalisation	4374 / 16644	0.78 (0.73, 0.83)	<0.001	0.91 (0.79, 1.04)	0.15	0.05
Death or CV-hospitalisation	5670 / 16644	0.76 (0.72, 0.81)	<0.001	0.89 (0.80, 1.01)	0.06	0.01
First HF-related hospitalisation	2872 / 16644	0.71 (0.65, 0.77)	<0.001	0.91 (0.78, 1.07)	0.26	0.005
CV-death (during study period) or HF-related hospitalisation †	4151 / 16644	0.70 (0.65, 0.75)	<0.001	0.90 (0.79, 1.03)	0.13	0.001
Non-fatal stroke	296 / 16644	1.02 (0.78, 1.32)	0.91	1.04 (0.66, 1.63)	0.87	0.94

MDC does not contribute to analyses involving hospitalisation or incident stroke. *Hazard ratios derived from the one-stage Cox regression model, stratified by study and adjusted for the following variables (where applicable, missing data in brackets): Age, gender, baseline LVEF (n=76 missing), baseline heart rate (n=8 missing) and use of ACEi/ARB.
†Outcome was not pre-specified.

Supplementary Table 1: Baseline demographics according to treatment allocation

Characteristic	Sinus rhythm (n=13,946)		Atrial fibrillation (n=3,066)		Other (n=1,242) *	
	Beta-blocker (n=7,123)	Placebo (n=6,823)	Beta-blocker (n=1,523)	Placebo (n=1,543)	Beta-blocker (n=640)	Placebo (n=602)
Age, median years (IQR)	64 (54-72)	63 (54-71)	69 (60-75)	69 (61-74)	69 (60-76)	70 (62-76)
Women	24.7%	25.4%	18.9%	19.8%	20.6%	17.8%
Diabetes Mellitus	24.3%	24.8%	21.9%	24.3%	29.8%	30.4%
Years with HF diagnosis, median (IQR)	3.0 (1.0-6.0)	3.0 (1.0-6.0)	3.0 (1.0-7.0)	4.0 (2.0-7.0)	5.0 (2.0-9.0)	5.0 (2.0-10.0)
LVEF, median % (IQR)	0.27 (0.21-0.33)	0.27 (0.21-0.33)	0.27 (0.21-0.33)	0.27 (0.22-0.33)	0.23 (0.19-0.30)	0.22 (0.18-0.30)
NYHA class III/IV	62.6%	62.5%	72.2%	72.1%	67.5%	63.8%
Systolic BP, median mmHg (IQR)	123 (110-140)	123 (110-140)	126 (113-140)	127 (114-140)	120 (109-130)	120 (110-133)
Diastolic BP, median mmHg (IQR)	78 (70-82)	78 (70-83)	80 (70-85)	80 (70-85)	72 (65-80)	72 (66-80)
Heart rate, median bpm (IQR)	80 (72-88)	80 (72-88)	81 (72-92)	81 (73-92)	76 (70-85)	76 (70-83)
Body mass index, median kg/m^2 (IQR)	27 (24-31)	27 (24-31)	28 (25-31)	27 (25-31)	26 (24-29)	27 (24-30)
Estimated GFR, median mL/min (IQR)	65 (52-78)	64 (51-78)	61 (49-74)	60 (48-73)	54 (41-64)	52 (42-64)
Any diuretic therapy	85.1%	85.4%	93.1%	93.9%	92.2%	94.8%
ACEi or ARB	95.1%	94.4%	95.3%	93.8%	93.5%	93.1%
Aldosterone antagonists	8.1%	8.2%	16.8%	16.7%	15.8%	14.2%
Digoxin	51.9%	53.9%	83.7%	83.3%	67.6%	70.2%
Amiodarone	6.2%	5.3%	11.2%	9.7%	17.5%	17.2%
Oral anticoagulation	26.1%	26.3%	58.3%	57.3%	39.9%	40.4%

See Table 1 legend for missing data report. * Includes heart block (41.1% of group), paced rhythm (49.4%) and patients with a missing or uninterpretable baseline ECG (9.5%).

Supplementary Table 2: Sensitivity analyses for primary outcome

Time to all-cause mortality (all reported deaths)	Sinus rhythm; Beta-blockers versus placebo		Atrial fibrillation; Beta-blockers versus placebo		Interaction; AF versus sinus rhythm
	HR (95% CI)	p-value	HR (95% CI)	p-value	p-value
Main adjusted analysis (all trials, censor at 1200 days)	0.73 (0.67, 0.80)	<0.001	0.97 (0.83, 1.14)	0.73	0.002
Additional adjustment for baseline use of digoxin and oral anticoagulation	0.73 (0.67, 0.80)	<0.001	0.97 (0.83, 1.14)	0.75	0.002
Exclusion of BEST trial	0.66 (0.60, 0.74)	<0.001	1.03 (0.86, 1.24)	0.74	<0.001
Exclusion of CAPRICORN trial	0.72 (0.66, 0.79)	<0.001	0.98 (0.83, 1.15)	0.81	0.002
Censor at 770 days	0.72 (0.66, 0.79)	<0.001	1.00 (0.84, 1.18)	0.98	<0.001
Censor at 365 days	0.69 (0.61, 0.77)	<0.001	0.97 (0.79, 1.19)	0.75	0.005
Random effects model	0.72 (0.64, 0.80)	<0.001	0.96 (0.80, 1.14)	0.62	0.002

Hazard ratios derived from the adjusted one-stage Cox regression model, stratified by study.

Supplementary Table 3: Factors associated with incident AF

Variable (binary cut-point)	Incident AF in patients with sinus rhythm at baseline		
	OR (95% CI) for model with binary variables *	p-value for model with binary variables *	p-value for model with continuous variables †
Allocation to beta-blockers vs. placebo	0.67 (0.57, 0.79)	<0.001	<0.001
Age (≥70 years)	1.77 (1.44, 2.17)	<0.001	<0.001
Women vs. men	0.71 (0.58, 0.88)	0.001	0.001
Ischaemic vs. non-ischaemic cardiomyopathy	0.97 (0.80-1.18)	0.76	0.46
LVEF (≤0.35)	0.84 (0.63, 1.11)	0.21	0.87
Hypertension (≥140/90 mmHg)	0.98 (0.74, 1.29)	0.87	0.97
Body mass index (≥30 kg/m^2)	1.23 (1.00, 1.52)	0.05	<0.001
NYHA class (III/IV vs. I/II)	1.47 (1.11, 1.93)	0.007	0.02

Odds ratios (OR) derived from a multivariate logistic regression model with binary dependent variables, additionally adjusted for study. † Modelled using continuous variables, where applicable.

Supplementary Table 4: Study drug dosage

Treatment arm	Pooled average dose achieved as a percentage of maximal dose*	
	Sinus rhythm	Atrial fibrillation
Placebo	84.1%	83.7%
Beta-blocker	73.5%	72.1%

* Achieved at the interim time point for each study, accounting for the differences in maximum planned dosage between studies. Data not available for the BEST trial with an additional 5,413 patients missing data on interim dosage (total n=11,599).

Supplementary Table 5: Change in heart rate

	n	Baseline heart rate (bpm)		Attained heart rate (bpm)		Change from baseline (bpm)	
		Placebo	Beta-blocker	Placebo	Beta-blocker	Placebo	Beta-blocker
All patients surviving to interim follow-up	14,796	80 (72, 88)	80 (72, 88)	78 (70,88)	68 (60, 76)	-2 (-10, 6)	-12 (-20,-4)
According to baseline heart rhythm:							
Sinus rhythm	12,204	80 (72, 88)	80 (72, 88)	78 (70, 87)	68 (60, 76)	-2 (-10, 6)	-12 (-20, -4)
Atrial fibrillation	2,592	81 (72, 92)	81 (72, 92)	80 (79, 90)	70 (62, 80)	-2 (-12, 6)	-12 (-22, -1)

Data presented are median heart rates (IQR) pooled from individual patient data at the interim study time-point.
Median time to follow-up heart rate 0.5 years (IQR 0.3-0.6) with n=118 missing data.

Supplementary Table 6: Beta-blocker discontinuation

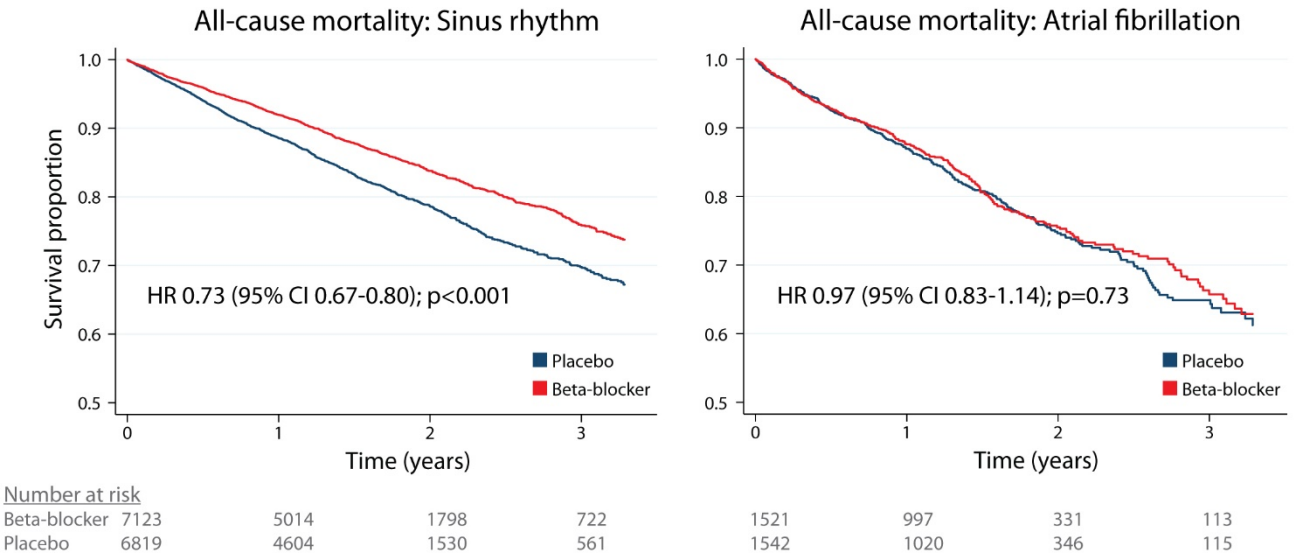
Discontinuation of beta-blockers	Sinus rhythm	Atrial fibrillation
- due to any adverse event*	1051 (14.4%)	231 (15.2%)
- due to hypotension†	65 (1.2%)	14 (1.2%)
- due to bradycardia†	68 (1.3%)	18 (1.6%)
- due to HF exacerbation*	262 (3.8%)	71 (4.9%)
- due to renal impairment†	22 (0.4%)	8 (0.7%)
- due to respiratory dysfunction†	43 (0.8%)	4 (0.4%)

Presented as absolute number (percentage within group). * Data available for all trials (total n=8,813 allocated to beta-blockers). † Data not available for MERIT-HF, CIBIS-I and MDC (total n=6,445 allocated to beta-blockers).

Figure 1

Kaplan Meier survival curve for sinus rhythm and AF comparing beta-blocker therapy versus placebo

Unadjusted survival curves for all reported deaths. Hazard ratios are derived from the adjusted one-stage Cox-regression model, stratified by study.



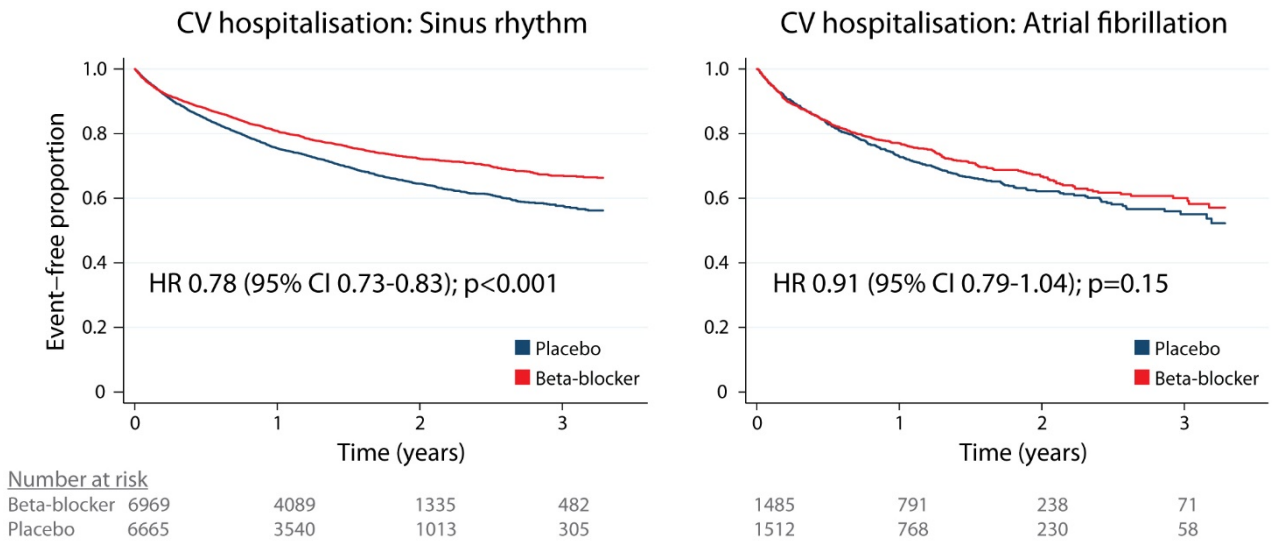
Number at risk

Beta-blocker	7123	5014	1798	722	1521	997	331	113
Placebo	6819	4604	1530	561	1542	1020	346	115

Figure 2

Figure 2: Kaplan Meier event curve for cardiovascular hospitalisation in sinus rhythm and AF comparing beta-blocker therapy versus placebo

Unadjusted event curves for CV-hospitalisation during the study period. Hazard ratios are derived from the adjusted one-stage Cox-regression model, stratified by study.



Number at risk

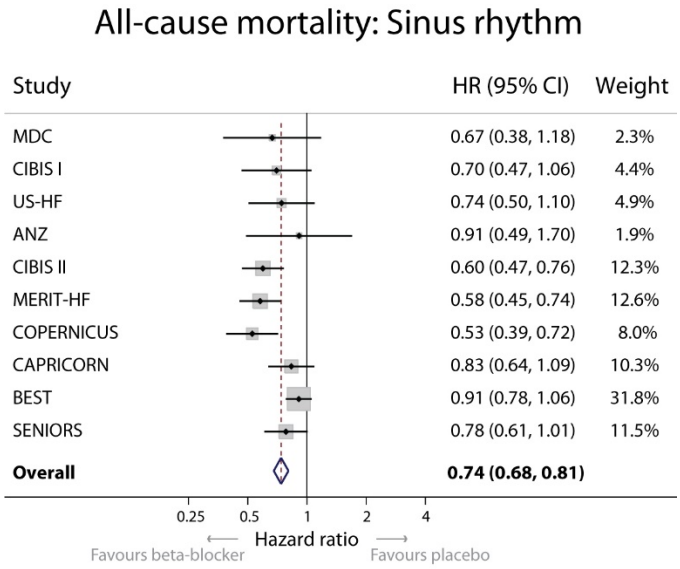
Beta-blocker	6969	4089	1335	482
Placebo	6665	3540	1013	305

1485	791	238	71
1512	768	230	58

Figure 3

Figure 3: Two-stage adjusted meta-analysis for all-cause mortality

Cox regression models in sinus rhythm and AF, adjusted for age, gender, LVEF, heart rate and use of ACEi/ARB, meta-analysed using a fixed-effects approach. Analysis includes all reported deaths, censored at 1200 days. Heterogeneity was significant for sinus rhythm (I^2=56%, p=0.016) but not for AF (I^2=0%, p=0.65).



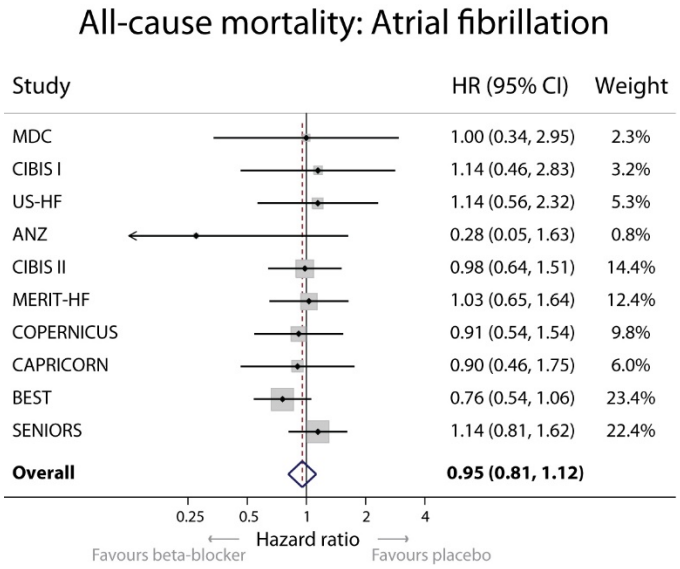
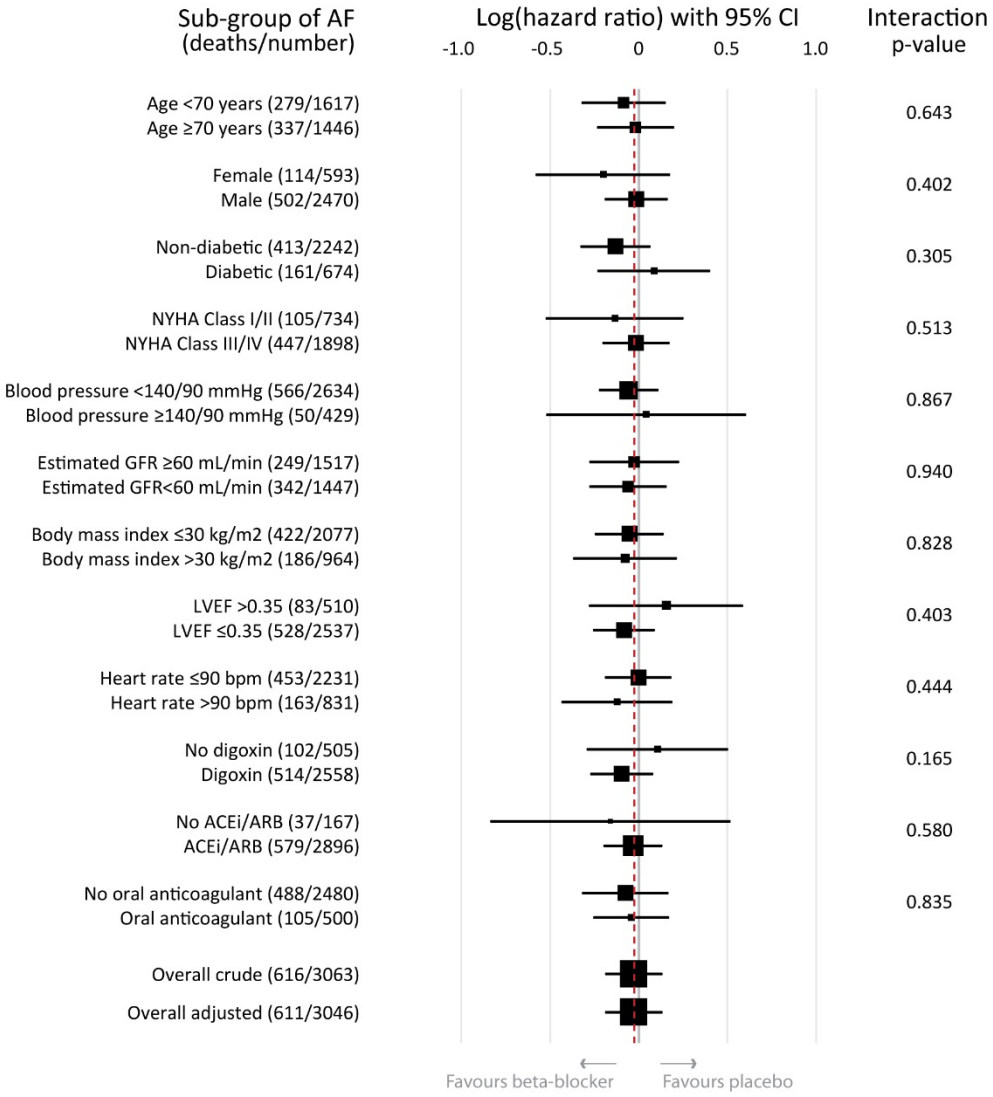


Figure 4

Figure 4: Sub-group analysis of all-cause mortality in AF patients comparing beta-blocker therapy versus placebo

Exploration of treatment efficacy for patients with AF according to baseline variables/measurements. Dashed line is the overall effect of beta-blockers versus placebo in AF patients. Hazard ratios and interaction p-values derived from the one-stage Cox regression model, stratified by study.



Efficacy of beta-blockers in patients with heart failure plus atrial fibrillation: An individual-patient data meta-analysis

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Beta-Blockers in Heart Failure Collaborative Group

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