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Beta-blockers after Myocardial Infarction with Normal Ejection Fraction

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Abstract

Background

The benefit of beta-blockers following myocardial infarction in patients with a preserved left ventricular ejection fraction (LVEF ≥50%) is unclear.

Methods

This meta-analysis includes individual patient-level data from 5 open-label trials that randomly assigned patients with a recent myocardial infarction, no other indications for beta-blocker therapy, and a LVEF ≥50% to beta-blockers or no beta-blockers. The primary end point was a composite of all-cause mortality, myocardial infarction, or heart failure. Event rates were analyzed with a one-stage fixed-effects Cox proportional hazards model.

Results

In total, 17,801 patients were included from REBOOT (7,459 patients), REDUCE-AMI (4,967 patients), BETAMI (2,441 patients), DANBLOCK (2,277 patients), and CAPITAL-RCT (657 patients). Of these, 8831 patients (49.6%) were assigned to a beta-blocker group and 8970 (50.4%) to a no beta-blocker group. During a median follow-up of 3.6 years (interquartile range, 2.3 to 4.6), the primary composite end point occurred in 717 patients (8.1%) in the beta-blocker group and 748 patients (8.3%) in the no beta-blocker group (hazard ratio 0.97; 95% CI, 0.87-1.07; P=0.54). All-cause mortality occurred in 335 and 326 patients (hazard ratio, 1.04; 95% CI, 0.89 to 1.21), myocardial infarction in 360 and 407 patients (hazard ratio, 0.89; 95% CI, 0.77 to 1.03), and heart failure in 75 and 87 patients (hazard ratio, 0.87; 95% CI, 0.64-1.19) in the beta-blocker and no beta-blocker groups, respectively. The results appeared consistent across subgroups.

Conclusion

In this meta-analysis of individual patient-level data from 5 trials, beta-blocker therapy did not reduce the composite of all-cause mortality, myocardial infarction, or heart failure in patients with a LVEF ≥50% after myocardial infarction without other indications for beta-blockers.

(Funded by Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC), and others.)

Introduction

Beta-blocker therapy has been considered the standard of care following myocardial infarction based on evidence from seminal trials performed in the early 1980s.[1–4] Since then, advances in diagnostics, coronary-artery reperfusion, revascularization techniques, and pharmacological treatments have markedly improved outcomes.[5–7] This has led to uncertainty about the continued need for beta-blockers in patients after a myocardial infarction without heart failure or a reduced left ventricular ejection fraction (LVEF<40%). Current guidelines provide divergent recommendations on the utility of beta-blockers for patients after myocardial infarction: the European Society of Cardiology provides a Class IIa recommendation for patients without a reduced LVEF, whereas the American Heart Association and American College of Cardiology guidelines provide a Class I recommendation for all patients with a myocardial infarction regardless of LVEF.[8,9]

Five recent open-label randomized trials assessing the effects of beta-blockers in patients with a recent myocardial infarction with a mildly reduced or preserved LVEF, have yielded apparently conflicting results. Some trials reported no apparent benefit of beta-blockers when compared to placebo, while others suggested benefit.[10–13] None of the trials were sufficiently powered for a definitive assessment of individual outcomes, such as mortality, myocardial infarction, or heart failure, and lacked sufficient data for robust subgroup analyses by age, sex, type of myocardial infarction, or specific beta-blocker regimens. A recently published meta-analysis focused on patients from these trials with mildly reduced LVEF (40% to 49%) suggested beneficial effects of beta-blockers on a composite end point of all-cause mortality, myocardial infarction, and heart failure.[14]

This individual patient data meta-analysis summarizes the evidence in patients with a recent myocardial infarction and LVEF ≥50% by combining data from five contemporary randomized trials to clarify the effects of beta-blocker therapy on morbidity and mortality in this patient population.

Methods

Individual trials, search strategy, and selection criteria

This pre-planned meta-analysis pooled individual-level data of patients with a preserved LVEF (≥50%) from the REBOOT (Treatment with Beta-Blockers after Myocardial Infarction without Reduced Ejection Fraction),[10] REDUCE-AMI (Randomized Evaluation of Decreased Usage of Beta-Blockers after Acute Myocardial Infarction),[11] BETAMI (Norwegian Beta-Blocker Treatment after Acute Myocardial Infarction in Revascularized Patients without Reduced Left Ventricular Ejection Fraction),[12] DANBLOCK (Danish Trial of Beta-Blocker Therapy after Myocardial Infarction without Heart Failure),[12] and CAPITAL-RCT (Carvedilol Post-Intervention Long-Term Administration in Large-scale Randomized Controlled Trial)[13] trials. These trials were all investigator-initiated, open-label, randomized, superiority trials designed to evaluate the effect of beta-blockers after myocardial infarction. Patients with myocardial infarction within the prior 14 days with a preserved or mildly reduced LVEF (≥40%) meeting eligibility criteria (presented for each trial in Supplementary Appendix available with the full text of this article at NEJM.org) were randomly assigned to either oral beta-blocker therapy or no beta-blocker therapy. The type and dose of beta-blocker was determined by the treating physician in all trials, except for the CAPITAL-RCT trial, where all patients received carvedilol. Key exclusion criteria comprised any indication for

a beta-blocker other than a myocardial infarction, such as heart failure, or a contraindication to beta-blockers. All patients received usual care. Key information on the trials including eligibility criteria, and primary and secondary end points is presented in Tables S1 through S3. All participants provided written informed consent, and all trials received approval from the relevant authorities and ethics committees. [10–13]

A systematic review of MEDLINE was conducted to confirm inclusion of all relevant trials performed in the coronary-artery reperfusion era investigating the efficacy of mid- and long-term oral beta-blocker therapy (median follow-up >1 year) in patients with a recent myocardial infarction (randomization within 14 days) and a preserved LVEF (≥50%). The pre-registered search strategy performed on August 12th, 2025, is presented in the Supplementary Appendix along with the PRISMA flow chart. Two researchers (AMDK and XR) screened the titles, abstracts, and keywords of all retrieved records, and reviewed full-text articles for eligibility. No further trials were identified from the search. The risk of bias was assessed by AMDK and JM using the Cochrane risk of bias tool (additional information is provided in the Supplementary Appendix and Tables S4 to S9).[15] Data were extracted and harmonized by AMDK, XR, and TH, analyzed by XR, and replicated by MWF. All co-authors vouch for the accuracy and completeness of the data. AMDK and JM drafted the manuscript. All co-authors revised and agreed to publish the final version.

This individual-patient data meta-analysis is reported according to the PRISMA guidelines (Supplementary Appendix). The study was registered at PROSPERO (CRD420251119176) and a prespecified Statistical Analysis Plan (available online at NEJM.org) was developed before data analysis, at a time when the authors were aware of the individual trial results.

The funders of the individual trials had no role in study design, data collection, analysis, interpretation, or writing of the paper.

End points

The pre-specified primary end point was a composite of all-cause mortality, myocardial infarction, or heart failure. This was selected for its clinical relevance and to ensure consistency with our previous individual-patient data meta-analysis on beta-blocker therapy in patients with mildly reduced LVEF.[14] Each of the components of the primary end point was analyzed individually as secondary end points. All myocardial infarction and heart failure events were adjudicated by an independent, blinded Clinical Endpoint Adjudication Committee in all trials except REDUCE-AMI.[11] Heart failure was diagnosed either at hospitalization (all trials) or at an outpatient clinic (BETAMI-DANBLOCK). End point definitions by trial are presented the Statistical Analysis Plan and summarized in Table S10.

Other secondary end points (for trials with available data) included cardiac death, unplanned coronary revascularization, and malignant ventricular arrhythmias. Safety end points included ischemic stroke and advanced atrioventricular block. An overview of availability of data and end points are presented in Table S11.

Statistical analysis

All end points were analyzed according to the intention-to-treat principle and in accordance with the prespecified Statistical Analysis Plan. A fixed-effect model was used for a one-stage individual-patient data meta-analysis. We used Poisson regression to estimate incidence rates and incidence rate ratios. Time-to-first-event survival curves for the primary end point were estimated

with the Kaplan–Meier method and compared with the log-rank test. An unadjusted Cox proportional hazard model stratified by trial was used to estimate the hazard ratio and 95% confidence interval (CI) for all end points. Between-trial heterogeneity was explored with a restricted maximum likelihood estimate of the between-trial variance of treatment effect. Additionally, we examined treatment-by-trial heterogeneity with Higgins and Thompson's I^2 statistic from a two-stage meta-analysis.

Three sensitivity analyses were performed: a multivariable Cox regression adjusted for age, sex, index myocardial infarction type, LVEF, and trial; a two-stage meta-analysis using a random-effects model; and an analysis on adjudicated events only (excluding all data from REDUCE-AMI, as myocardial infarction and heart failure events were not adjudicated by an independent, blinded end point adjudication committee in that trial). We further performed a landmark analysis of the primary end point in which follow-up time was limited to 12 months.

The number of patients lost to follow-up was less than 1% in all trials (Table S12), as was the extent of missing data on subgroup-defining baseline characteristics (< 1%). Under an assumption of missing completely at random, complete case analyses were performed for all end points and subgroups. Prespecified subgroup analyses were performed by adding an interaction term between treatment and subgroup to the model for the primary end point. Two stratified analyses of the primary end point were conducted, where the strata were defined by beta-blocker dose and type (more information on these analyses are presented in Supplementary Appendix). Stratified analyses were adjusted for major potential confounders (sex, age, and index myocardial infarction type) as neither dose nor type of beta-blocker were randomized. The treatment effects were reported for all strata as hazard ratios and 95% CIs. The proportional hazard assumption was

examined for all Cox regression models by plotting log-log of survival by log of analysis time. If the assumption was deemed not to be met, the between-group difference in restricted mean event-free survival time from baseline until three years follow-up was estimated, as prespecified in our Statistical Analysis Plan.

The widths of the CI for the secondary end points have not been adjusted for multiplicity and should not be used in place of hypothesis testing. Additional details are provided in the Statistical Analysis Plan.

Results

Characteristics of the patients

A total of 17,801 patients with a preserved LVEF were included in the five trials (REBOOT: 7,459 patients; REDUCE-AMI: 4,967 patients; BETAMI: 2,441 patients; DANBLOCK: 2,277 patients; and CAPITAL-RCT: 657 patients). Among them, 8,831 (49.6%) were randomly assigned to beta-blockers, and 8,970 (50.4%) were assigned to the no beta-blocker group. Baseline characteristics of the population appeared well balanced and comparable with the overall population with myocardial infarction and preserved LVEF (Table S13). The baseline characteristics by randomization group are summarized in Table 1 and Table S14, and by trial in Table S15. Missing information by trial and randomization group is presented in Tables S16 to S20. The median age of the total population was 62 years (interquartile range, 55 to 71), 20.7% were women, 8.1% had a prior myocardial infarction, and 2.0% had atrial fibrillation. A total of 45.7% had a ST-segment elevation myocardial infarction, and 94.2% underwent a percutaneous coronary intervention.

End points

During a median follow-up period of 3.6 years (interquartile range, 2.3 to 4.6) (3.6 years [interquartile range 2.3 to 4.6] for the beta-blocker group and 3.6 years [interquartile range 2.3 to 4.6] for the no beta-blocker group), the primary composite end point of all-cause mortality, myocardial infarction or heart failure occurred in 717 of 8,831 patients (8,1%; 2.37 per 100 patient-years) in the beta-blocker group and 748 of 8,970 patients (8.3%; 2.45 per 100 patient-years) in the no beta-blocker group (hazard ratio, 0.97; 95% CI, 0.87 to 1.07; P=0.54) (Figure 1A and Table 2). There were no missing outcome data for the primary analysis. Rate ratios and incidence rate ratios by trial are further detailed in Table S21. The between-trial variance was estimated to be 0.005 (95% CI, 0.00 to 0.10) and the amount of variance due to heterogeneity was estimated as I^2=20.0%. Results that appeared consistent with the primary analyses were found in both the two-stage meta-analysis (hazard ratio 0.97; 95% CI, 0.88 to 1.07), and the adjusted Cox regression analysis (hazard ratio, 0.96; 95% CI, 0.87 to 1.07). The results remained similar when data from REDUCE-AMI were excluded (hazard ratio, 0.97; 95% CI, 0.86 to 1.10).

All-cause mortality occurred in 335 patients (1.07 per 100 patient-years) and 326 patients (1.03 per 100 patient-years) in the beta-blocker and no beta-blocker groups, respectively (hazard ratio, 1.04; 95% CI, 0.89 to 1.21) (Figure 1B and Table 2). Myocardial infarction occurred in 360 patients (1.19 per 100 patient-years) and 407 patients (1.33 per 100 patient-years), respectively (hazard ratio, 0.89; 95% CI 0.77 to 1.03)(Figure 1C and Table 2). Heart failure occurred in 75 patients (0.24 per 100 patient-years) and 87 patients (0.28 per 100 patient-years), respectively (hazard ratio, 0.87; 95% CI, 0.64 to 1.19)(Figure 1D and Table 2). Cardiac death occurred in 97 patients (0.37 per 100 patient-years) and 78 patients (0.29 per 100 patient-years), respectively (hazard ratio, 1.26; 95% CI, 0.94 to 1.70)(Table 2). Unplanned coronary revascularization occurred

in 315 patients (14.5 per 1,000 patient-years) and 315 patients (14.1 per 1,000 patient-years), respectively (hazard ratio, 1.03; 95% CI, 0.88 to 1.20). All sensitivity analyses and treatment estimates for the individual trials and the estimates of the primary analysis are presented in Figure 2. Further details on secondary end points can be found in Table 2. The event rate of secondary end points by group and trial can be found in Table S22.

In a prespecified analysis restricted to 12 months of follow-up, a primary end-point event occurred in in 235 patients (2.73 per 100 patient-years) and 271 patients (3.10 per 100 patient-years) in the beta-blocker and no-beta-blocker groups, respectively (0.88, 95% CI, 0.74 to 1.05).

Safety

Ischemic stroke occurred in 115 patients (0.37 per 100 patient-years) in the beta-blocker group and in 94 patients (0.30 per 100 patient-years) in the no beta-blocker group (difference in restricted mean event-free survival time at three years follow-up, 2.6 days; 95% CI, -0.73 to 4.4)(Table 2). The rates of admission for advanced atrioventricular block occurred in 69 patients (0.23 per 100 patient-years) and 68 patients (0.23 per 100 patient-years) in the beta-blocker and no beta-blocker groups, respectively (hazard ratio, 1.03; 95% CI, 0.73 to 1.44)(Table 2).

Subgroup analyses and stratified analyses

Results for pre-specified subgroups are shown in Figure 3. The treatment effects appeared generally consistent based on the subgroups included. Stratified analyses regarding the dose and type of beta-blockers are reported in Table S23.

Discussion

In this individual-patient data meta-analysis that included data from 5 contemporary randomized trials, beta-blocker therapy was not associated with a reduction in the composite of all-cause mortality, myocardial infarction, or heart failure in patients with a recent myocardial infarction and a preserved LVEF (≥50%) compared to placebo. The results appeared consistent for each individual component of the primary end point, secondary and safety end points, as well as across prespecified subgroups.

Beta-blockers remain a cornerstone therapy for patients with heart failure or reduced LVEF (<40%) after myocardial infarction.[8,16–18] The REBOOT,[10] BETAMI,[12] DANBLOCK,[12] and CAPITAL-RCT[13] trials investigated the efficacy of beta-blockers in patients with a LVEF≥40%, whereas the REDUCE-AMI[11] trial exclusively enrolled patients with a LVEF≥50%. The individual trials differed in their primary end point and their results. REBOOT[10] found no effect of beta-blockers on the composite of all-cause mortality, myocardial infarction, or heart failure (hazard ratio, 1.04; 95% CI, 0.89 to 1.22; P=0.63). Similarly, REDUCE-AMI[11] found no effect on the composite of all-cause mortality or myocardial infarction (hazard ratio, 0.96; 95% CI, 0.79 to 1.16; P=0.64). In contrast, BETAMI and DANBLOCK (pooled analysis in a single publication)[12] found that beta-blockers reduced the composite of all-cause mortality or major adverse cardiovascular events (hazard ratio, 0.85; 95% CI, 0.75 to 0.98; P=0.03). CAPITAL-RCT[13] found no effect on a composite of all-cause mortality, myocardial infarction, heart failure, or acute coronary syndromes (hazard ratio, 0.75; 95% CI, 0.47 to 1.16; P=0.20). Recently, an individual patient-data meta-analysis of patients with mildly reduced LVEF (40% to 49%) across REBOOT,[10] BETAMI,[12] DANBLOCK,[12] and CAPITAL-RCT[13] demonstrated a 25% relative reduction (hazard ratio 0.75; 95% CI, 0.58 to 0.97) in the composite of all-cause

mortality, myocardial infarction, or heart failure.[19] In contrast, among patients with a preserved LVEF, we found no effect of beta-blockers on the primary composite end point (hazard ratio, 0.97; 95% CI, 0.87 to 1.07). In line with this, the ABYSS (Assessment of Beta-Blocker Interruption 1 Year after an Uncomplicated Myocardial Infarction on Safety and Symptomatic Cardiac Events Requiring Hospitalization) trial[20] - a non-inferiority trial that randomized patients at a median of 2.9 years after myocardial infarction to continuation or discontinuation of beta-blockers - found no effect on a composite of all-cause mortality, myocardial infarction, heart failure or stroke.

These findings are not unexpected as LVEF is a strong prognostic factor in both myocardial infarction and heart failure patients.[21,22] The population with preserved LVEF without other indications or contraindications for beta-blockers is generally less co-morbid with a better prognosis than patients with reduced or mildly reduced LVEF.[23] This is reflected in the low event rates with 2.41 (2.29 to 2.54) primary events per 100 person-years in this meta-analysis, compared with 3.76 (3.31 to 4.27) per 100 person-years in the meta-analysis on patients with a mildly reduced LVEF.[19] Myocardial infarction patients with a preserved LVEF have likely experienced smaller infarctions with less myocardial scarring than patients with a reduced LVEF, which reduces the vulnerability to ventricular arrhythmias and sudden cardiac death. Consequently, the pharmacological effects of beta-blockers after myocardial infarction may be less relevant for this population.[24]

It is important to recognize that a substantial proportion of patients were excluded from enrollment in the trials included in this meta-analysis. In BETAMI-DANBLOCK, approximately half of the individuals screened for eligibility were ineligible despite having a LVEF>40%, primarily due to established indications for beta-blockers, such as atrial fibrillation, uncontrolled hypertension, or

heart failure.[12] Thus, the absence of an overall benefit of beta-blockers in patients with preserved LVEF after myocardial infarction in this study does not apply to all patients with myocardial infarction and preserved LVEF.

We observed generally consistent findings in all subgroups, including women and elderly who have been underrepresented in previous trials. Notably, the significant interaction between sex and beta-blocker effect found in REBOOT[25] was not confirmed in this meta-analysis.

Older trials have documented a benefit of metoprolol and carvedilol on major adverse cardiovascular events in patients after a myocardial infarction,[2,26–28] while bisoprolol lacks similar evidence despite its common use in myocardial infarction populations.[29,30] We did not observe any apparent differences across type of beta-blocker. However, few patients were prescribed non-selective beta-blockers (e.g., carvedilol and propranolol) and patients were not randomized to type or dose of beta-blocker therapy. Although higher beta-blocker doses were associated with a higher incidence of events, this may relate to greater burden of comorbidities or baseline risk compared with those receiving lower doses. Observational studies have shown no association between beta-blocker dose and outcomes.[31–33] Beta-blocker doses were generally low in all trials, though reflecting current clinical practice.[31–33]

Certain limitations of our analysis should be acknowledged. First, all included trials were open-label trials with 6- and 12-months cross-over rates ranging from 11% to 18%. These factors could potentially bias the result towards equipoise. However, the per-protocol analyses of REBOOT showed consistent findings,[10] and the vast majority of trials included in this meta-analysis employed adjudicated end points. Additionally, the results appeared consistent across all trials,

individual end points, countries, and beta-blocker classes. Second, we applied the end points as defined in each trial and some definitions, such as those for heart failure, differed between the trials. Nonetheless, they were partially harmonized to ensure consistency where possible and a sensitivity analysis was performed in which data from REDUCE-AMI, with non-adjudicated end points, were excluded. Some end points (Table S11) and some baseline characteristics used to define subgroups (Table 1 and S14) were not available in all data sets, limiting the generalizability of the findings for these analyses. Third, the included population was predominantly European and Japanese, and only a minority were women, which may affect generalizability.

In this individual-patient data meta-analysis, which consolidates the totality of evidence from 5 contemporary randomized trials, beta-blocker therapy did not reduce the composite of all-cause mortality, myocardial infarction, or heart failure in patients with a preserved LVEF (≥50%) after a recent myocardial infarction without other indications for beta-blocker therapy.

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Tables

Table 1. Baseline Characteristics of the Patients

	Beta-blockers (N = 8831)	No Beta-blockers (N = 8970)
Demographics		
Median age – yr (IQR)§	62 (55-71)	62 (55-71)
Women – no. (%)	1837 (20.8)	1856 (20.7)
Country - no. (%)		
Spain	2933 (32.7)	2998 (33.4)
Sweden, Estonia, and New Zealand•	2485 (28.1)	2482 (27.7)
Norway	1207 (13.7)	1234 (13.8)
Denmark	1126 (12.8)	1151 (12.8)
Italy	759 (8.6)	769 (8.7)
Japan	321 (3.6)	336 (3.7)
Medical history - no./total no. (%)		
Current smoker	2762 / 8279 (33.4)	2794 / 8375 (33.4)
Hypertension	4194 / 8822 (47.5)	4261 / 8951 (47.6)
Diabetes mellitus	1483 / 8813 (16.8)	1523 / 8938 (17.0)
Dyslipidaemia	2650 / 6334 (41.8)	2726 / 6471 (42.1)
Previous MI†*	583 / 7292 (8.0)	603 / 7384 (8.2)
Stroke□*	188 / 8504 (2.2)	179 / 8615 (2.1)
Index MI		
STEMI - no./total no. (%)	4022 / 8830 (45.5)	4108 / 8970 (45.8)
In hospital treatment - no./total no. (%)		
Percutaneous coronary intervention	8306 / 8784 (94.6)	8399 / 8909 (94.3)
Coronary-artery bypass grafting	169 / 8283 (2.0)	199 / 8399 (2.4)
No revascularization	350 / 8481 (4.1)	366 / 8954 (4.1)
Beta-blocker therapy - no./total no. (%)		
Beta-blocker therapy prior to randomization*	923 / 8551 (10.8)	931 / 8572 (10.9)
Type of beta-blocker therapy after randomization		
Bisoprolol	4136 / 8742 (47.3)	
Metoprolol	4000 / 8742 (45.7)	
Carvedilol	446 / 8742 (5.1)	
Others	164 / 8742 (1.9)	

§ No missing data on age

• A total of 198 patients were included from New Zealand, and 32 patients from Estonia.

□Not available in REDUCE-AMI, †Not available in BETAMI, *Not available in CAPITAL-RCT

IQR denotes interquartile range, LVEF left ventricular ejection fraction, MI myocardial infarction, and STEMI ST-segment elevation myocardial infarction.

Table 2. Effect Estimates for the Primary, Secondary, and Safety End Points

	Beta-blockers No./Total Number (%)	No Beta-blockers No./Total Number (%)	Hazard Ratio‡ (95% confidence intervals)	P-value
Primary end point				
A composite of all-cause mortality, new myocardial infarction, or heart failure	717 / 8831 (8.1)	748 / 8970 (8.3)	0.97 (0.87 – 1.07)	0.54
Key secondary end points				
All-cause mortality	335 / 8831 (3.8)	326 / 8970 (3.6)	1.04 (0.89 – 1.21)	
Myocardial infarction	360 / 8831 (4.1)	407 / 8970 (4.5)	0.89 (0.77 – 1.03)	
Heart failure	75 / 8831 (0.9)	87 / 8970 (1.0)	0.87 (0.64 – 1.19)	
Other secondary end points				
Cardiac death†	97 / 7624 (1.3)	78 / 7736 (1.0)	1.26 (0.94 – 1.70)	
Unplanned coronary revascularization□	315 / 6346 (5.0)	315 / 6488 (4.9)	1.03 (0.88 – 1.20)	
Malignant ventricular arrhythmias□*	16 / 6025 (0.3)	23 / 6152 (0.4)	0.71 (0.37 – 1.34)	
Safety end points				
Ischemic stroke§	115 / 8831 (1.3)	94 / 8970 (1.1)	2.6 days (-0.73 – 4.4)	
Advanced atrioventricular block*	69 / 8510 (0.8)	68 / 8634 (0.8)	1.03 (0.73 – 1.44)	

The median follow-up time was 3.6 years (interquartile range, 2.3 to 4.6 years).

The widths of the confidence intervals for the secondary end points have not been adjusted for multiplicity and should not be used in place of hypothesis testing.

‡ Hazard ratio for all end points except ischemic stroke. For this end point, the between-group difference in restricted mean event-free survival time from baseline until three years follow-up was estimated.

□ Not available in REDUCE-AMI, † Not available in BETAMI, * Not available in CAPITAL-RCT

§ Difference (beta-blockers - no beta-blockers) in restricted mean event-free survival time (95% confidence interval) from baseline until 3 years follow-up.

Figures

Figure 1. Kaplan–Meier Curves Illustrating the Cumulative Incidence of the Primary End Point and Its Individual Components

The widths of the confidence intervals for the secondary end points have not been adjusted for multiplicity and should not be used in place of hypothesis testing.

Figure 2. Effect Estimates from the Individual Patient-Level Meta-analysis and Its Corresponding Sensitivity Analyses

The between-trial variance was estimated to be 0.005 (95% CI 0.000 to 0.10) and the amount of variance due to heterogeneity was estimated as I^2=20.0% The widths of the confidence intervals for the secondary end points have not been adjusted for multiplicity and should not be used in place of hypothesis testing.

Figure 3. Prespecified Subgroup Analyses of the Primary End Point

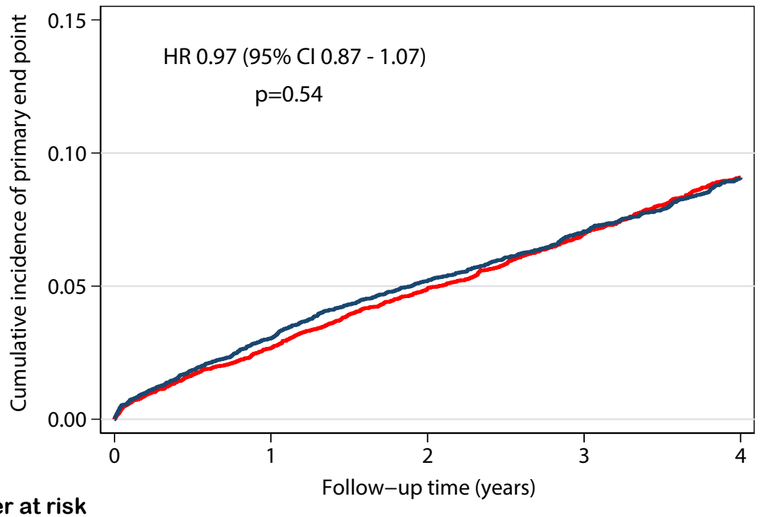
Atrial fibrillation was not available in REDUCE-AMI, prior beta-blocker therapy was not available for subgroup analyses in DANBLOCK.

The widths of the confidence intervals for the secondary end points have not been adjusted for multiplicity and should not be used in place of hypothesis testing.

HR denotes hazard ratio, MI myocardial infarction, NSTEMI non-ST-elevation myocardial infarction, STEMI ST-elevation myocardial infarction and yo, years old.

A

Primary end point

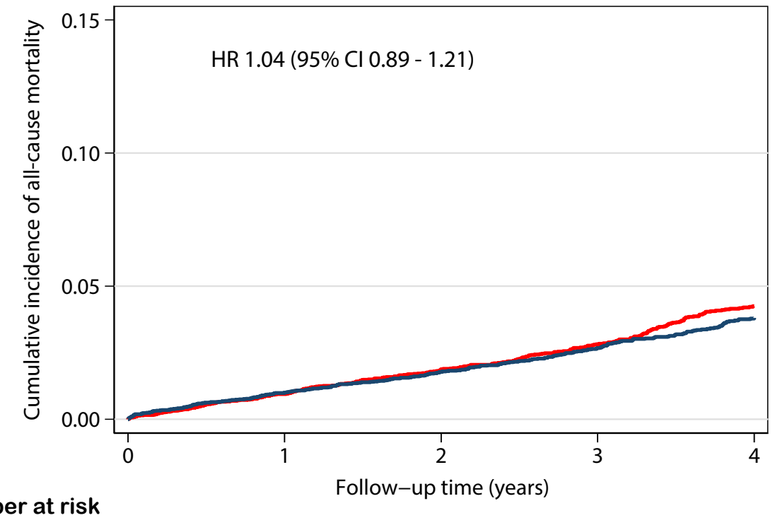


Number at risk

Beta−blocker	8831	8272	7037	5253	3642
No beta−blocker	8970	8382	7098	5286	3641

B

All-cause mortality

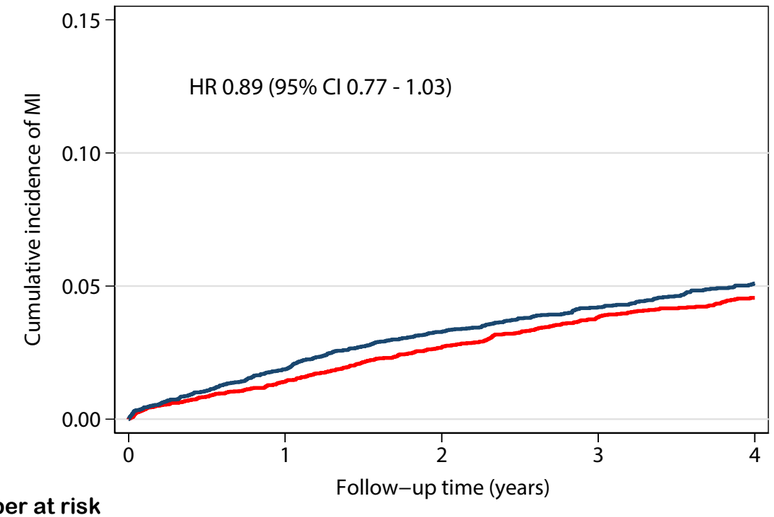


Number at risk

Beta−blocker	8831	8424	7268	5494	3839
No beta−blocker	8970	8555	7359	5541	3853

C

Myocardial infarction

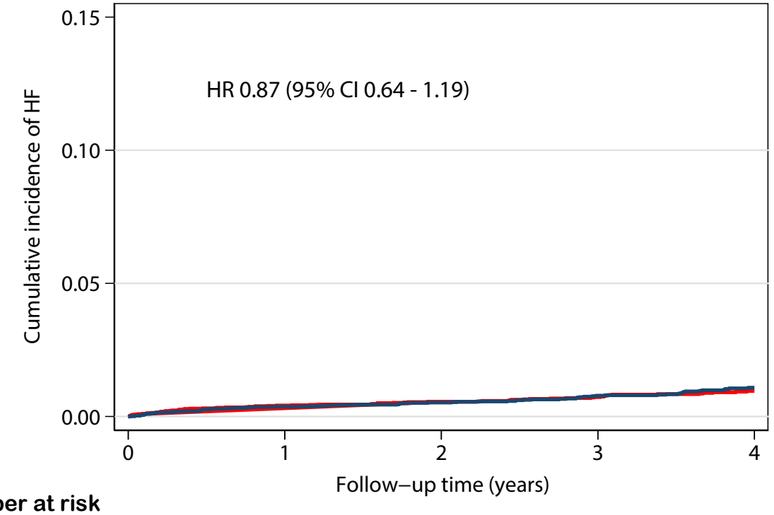


Number at risk

Beta−blocker	8831	8301	7073	5286	3672
No beta−blocker	8970	8405	7127	5312	3669

D

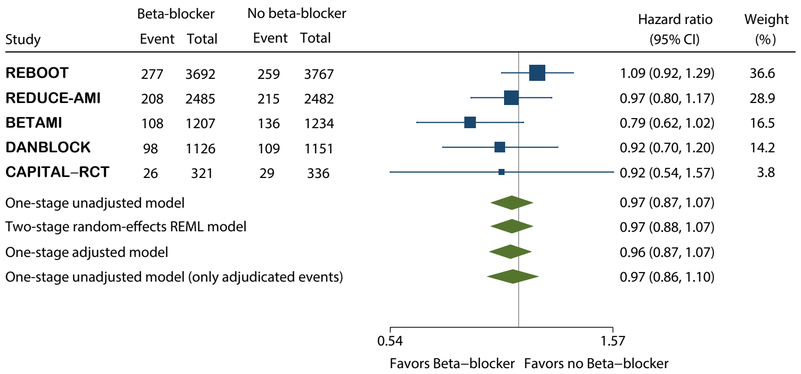
Heart failure

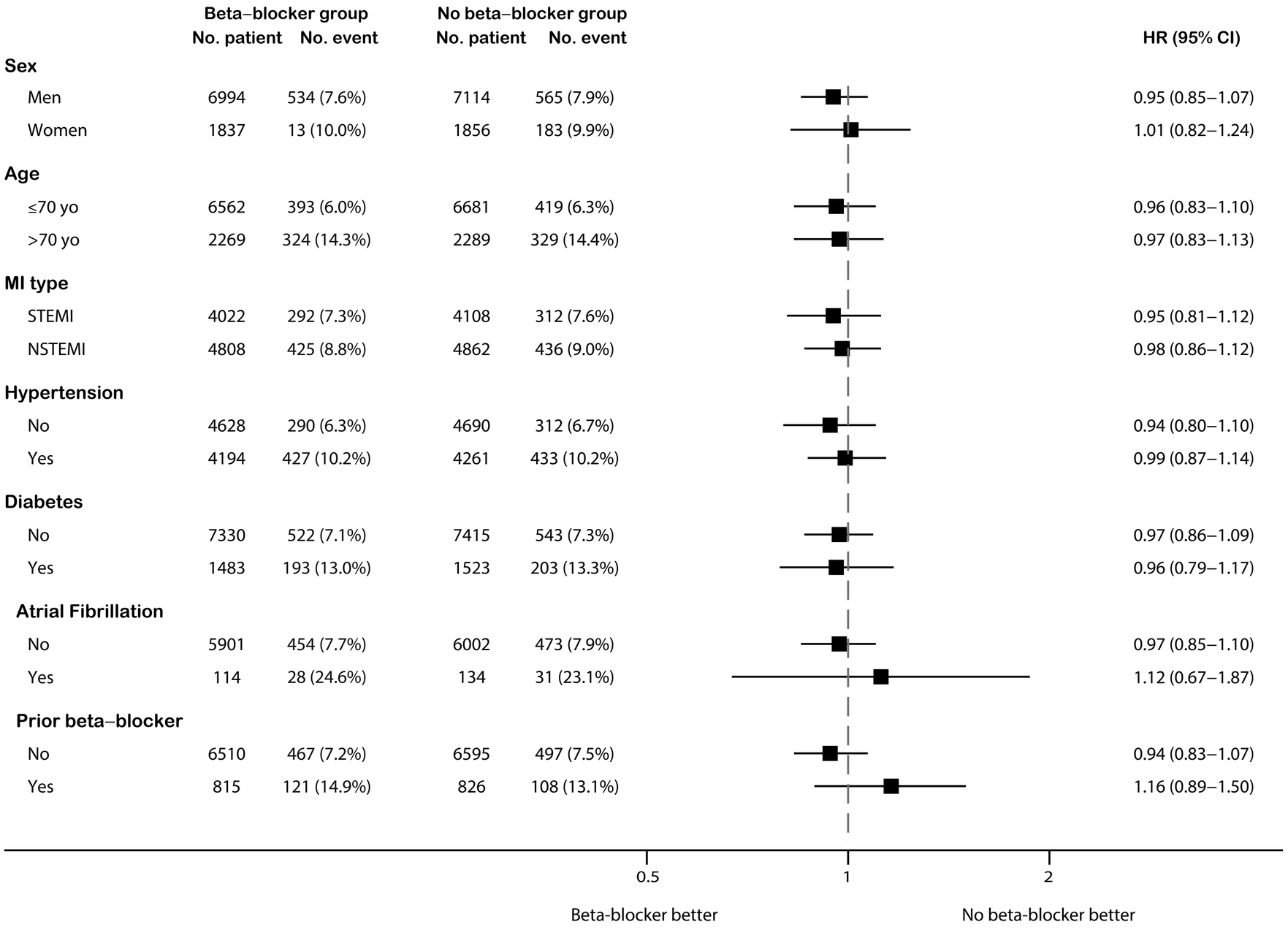


Number at risk

Beta−blocker	8831	8392	7230	5459	3809
No beta−blocker	8970	8529	7332	5512	3823

Beta−blocker Control


Study
Beta-blocker
Event
Total
No beta-blocker
Event
Total
Hazard ratio
(95% CI)
Weight
(%)
REBOOT 277 3692 259 3767 1.09 (0.92, 1.29) 36.6
REDUCE-AMI 208 2485 215 2482 0.97 (0.80, 1.17) 28.9
BETAMI 108 1207 136 1234 0.79 (0.62, 1.02) 16.5
DANBLOCK 98 1126 109 1151 0.92 (0.70, 1.20) 14.2
CAPITAL–RCT 26 321 29 336 0.92 (0.54, 1.57) 3.8
One-stage unadjusted model 0.97 (0.87, 1.07)
Two-stage random-effects REML model 0.97 (0.88, 1.07)
One-stage adjusted model 0.96 (0.87, 1.07)
One-stage unadjusted model (only adjudicated events) 0.97 (0.86, 1.10)
0.54
1.57
Favors Beta–blocker
Favors no Beta–blocker


Beta–blocker group
No. patient
No. event
No beta–blocker group
No. patient
No. event
HR (95% CI)
Sex
Men 6994 534 (7.6%) 7114 565 (7.9%) 0.95 (0.85–1.07)
Women 1837 13 (10.0%) 1856 183 (9.9%) 1.01 (0.82–1.24)
Age
≤70 yo 6562 393 (6.0%) 6681 419 (6.3%) 0.96 (0.83–1.10)
>70 yo 2269 324 (14.3%) 2289 329 (14.4%) 0.97 (0.83–1.13)
MI type
STEMI 4022 292 (7.3%) 4108 312 (7.6%) 0.95 (0.81–1.12)
NSTEMI 4808 425 (8.8%) 4862 436 (9.0%) 0.98 (0.86–1.12)
Hypertension
No 4628 290 (6.3%) 4690 312 (6.7%) 0.94 (0.80–1.10)
Yes 4194 427 (10.2%) 4261 433 (10.2%) 0.99 (0.87–1.14)
Diabetes
No 7330 522 (7.1%) 7415 543 (7.3%) 0.97 (0.86–1.09)
Yes 1483 193 (13.0%) 1523 203 (13.3%) 0.96 (0.79–1.17)
Atrial Fibrillation
No 5901 454 (7.7%) 6002 473 (7.9%) 0.97 (0.85–1.10)
Yes 114 28 (24.6%) 134 31 (23.1%) 1.12 (0.67–1.87)
Prior beta–blocker
No 6510 467 (7.2%) 6595 497 (7.5%) 0.94 (0.83–1.07)
Yes 815 121 (14.9%) 826 108 (13.1%) 1.16 (0.89–1.50)
0.5
1
2
Beta-blocker better
No beta-blocker better