This is the peer reviewed version of the following article:

- Kristensen AMD, Rossello X, Atar D, Yndigegn T, Kimura T, Latini R, Lindahl B, Halvorsen S, Olsen MH, Fuster V, Hofmann R, Vikenes K, Maeng M, Erlinge D, Pocock S, Karlström P, Bakken A, Lange T, Barrabés JA, Benatar J, Raposeiras-Roubin S, Held C, Piepoli M, Fagerland MW, Holmager T, Ozasa N, Prescott EIB, Munkhaugen J, Jernberg T, Ibanez B; Beta-Blocker Trialists' Collaboration Study Group. Beta-Blockers after Myocardial Infarction with Normal Ejection Fraction. ***N Engl J Med***. 2025 Nov 9. doi: 10.1056/NEJMoa2512686. Epub ahead of print. PMID: 41211954.

which has been published in final form at

https://doi.org/10.1056/NEJMoa2512686

Beta-Blockers after Myocardial Infarction with Normal Ejection Fraction

A.M.D. Kristensen,1 X. Rossello,2-5 D. Atar,6,7 T. Yndigegn,8 T. Kimura,9 R. Latini,10 B. Lindahl,11 S. Halvorsen,6,7 M.H. Olsen,12,13 V. Fuster,2,14 R. Hofmann,15

K. Vikenes,16,17 M. Maeng,18,19 D. Erlinge,8 S. Pocock,2,20 P. Karlström,21 A. Bakken,6

T. Lange,22 J.A. Barrabés,5,23 J. Benatar,24 S. Raposeiras-Roubin,2,25 C. Held,11

M. Piepoli,26,27 M.W. Fagerland,28 T. Holmager,1 N. Ozasa,29

E.I.B. Prescott,1 J. Munkhaugen,30,31 T. Jernberg,32 and B. Ibanez,2,5,33 for the Beta-Blocker Trialists' Collaboration Study Group.*

BACKGROUND

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

METHODS

We conducted a meta-analysis at the individual-patient level using data from five open-label trials that randomly assigned patients with recent myocardial infarction, no other indications for beta-blocker therapy, and an LVEF of at least 50% to receive beta-blocker therapy or no beta-blocker therapy. The primary end point was a composite of death from any cause, myocardial infarction, or heart failure. Event rates were analyzed with a one-stage fixed-effects Cox proportional-hazards model.

RESULTS

A total of 17,801 patients were included from the REBOOT (7459 patients), REDUCE-AMI (4967 patients), BETAMI (2441 patients), DANBLOCK (2277 patients), and CAPITAL-RCT (657 patients) trials. Of these 17,801 patients, 8831 (49.6%) were assigned to receive a beta-blocker and 8970 (50.4%) were assigned to receive no beta-blocker. During a median follow-up of 3.6 years (interquartile range, 2.3 to 4.6), a primary-end-point event 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% confidence interval [CI], 0.87 to 1.07; P = 0.54). Death from any cause occurred in 335 patients in the beta-blocker group and 326 patients in the no–betablocker group (hazard ratio, 1.04; 95% CI, 0.89 to 1.21); myocardial infarction occurred in 360 and 407 patients, respectively (hazard ratio, 0.89; 95% CI, 0.77 to 1.03); and heart failure occurred in 75 and 87 patients (hazard ratio, 0.87; 95% CI, 0.64 to 1.19).

CONCLUSIONS

In this meta-analysis including individual-patient data from five randomized trials, beta-blocker therapy did not reduce the incidence of death from any cause, myocardial infarction, or heart failure in patients with an LVEF of at least 50% after myocardial infarction without other indications for beta-blockers.

Beta-blocker therapy has been considered the standard of care after myocardial infarction on the basis of evidence from seminal trials performed in the early 1980s.14 Since then, advances in diagnostics, coronaryartery reperfusion, revascularization techniques, and pharmacologic treatments have markedly improved outcomes.5-7 These advances have led to uncertainty about the continued need for betablockers after myocardial infarction in patients without heart failure or a reduced left ventricular ejection fraction (LVEF <40%). Current guidelines provide divergent recommendations on the usefulness of beta-blockers in patients after myocardial infarction: the European Society of Cardiology designates a class IIA recommendation for patients without a reduced LVEF, whereas the American Heart Association and American College of Cardiology guidelines designate a class I recommendation for all patients with myocardial infarction regardless of LVEF.8,9

Five open-label, randomized trials that assessed the effects of beta-blockers in patients with recent myocardial infarction and a mildly reduced or preserved LVEF have yielded apparently conflicting results. Some of the trials reported no apparent benefit of beta-blockers when compared with placebo, whereas others suggested benefit.10-13 None of the trials were sufficiently powered for a definitive assessment of individual outcomes, such as death, myocardial infarction, or heart failure, and all the trials lacked sufficient data for robust subgroup analyses according to age, sex, type of myocardial infarction, or specific beta-blocker regimens. A recently published meta-analysis of these trials that focused on patients with mildly reduced LVEF (40 to 49%) suggested beneficial effects of beta-blockers on a composite of death from any cause, myocardial infarction, or heart failure.14 The current metaanalysis combined individual-patient data from five contemporary randomized trials to assess the effects of beta-blocker therapy on morbidity and mortality among patients with recent myocardial infarction and an LVEF of at least 50%.

Methods

- **Individual Trials, Search Strategy, and Selection Criteria**

This preplanned meta-analysis pooled individuallevel 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 PostIntervention Long-Term Administration in LargeScale Randomized Controlled Trial)13 trials. All these trials were investigator-initiated, open-label, randomized, superiority trials designed to evaluate the effect of beta-blockers after myocardial infarction. Patients with myocardial infarction within 14 days before randomization with a preserved or mildly reduced LVEF (≥40%) who met the eligibility criteria (shown for each trial in the Supplementary Appendix, available with the full text of this article at NEJM.org) were assigned to receive either oral beta-blocker therapy or no beta-blocker therapy. The type and dose of betablocker was determined by the treating physician in all trials, except for the CAPITAL-RCT trial, in which all patients received carvedilol. Key exclusion criteria were any indication for beta-blockers other than myocardial infarction, such as heart failure, and any contraindication to betablockers. All the patients received usual care. Key information on the trials including eligibility criteria and the primary and secondary end points is presented in Tables S1 through S3 in the Supplementary Appendix. All the patients

provided written informed consent, and all the trials received approval from the relevant authorities and ethics committees.10-13

We conducted a systematic review of Medline to confirm the inclusion of all relevant trials performed during the coronary-artery reperfusion era (published after January 1, 2000) that investigated the efficacy of long-term oral betablocker therapy (median follow-up of >1 year) in patients with recent myocardial infarction (within 14 days before randomization) and a preserved LVEF (≥50%). The preregistered search strategy performed on August 12, 2025, is presented in Table S4, and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart is shown in Figure S1. The titles, abstracts, and keywords of all retrieved records were screened, and full-text articles were reviewed for eligibility. No additional trials were identified from the search. The risk of bias was assessed with the use of the Cochrane Risk of Bias tool (additional information is provided in the Supplementary Appendix and Tables S5 through S9).15 Data were extracted and harmonized, analyzed, and replicated. The authors vouch for the completeness and accuracy of the data.

This meta-analysis of data at the individualpatient level is reported according to the PRISMA guidelines (see the Supplementary Appendix). A prespecified statistical analysis plan (available at NEJM.org) was developed before data analysis, at a time when the authors were aware of the individual trial results. The sponsors of the individual trials had no role in the design of the current study, data collection, analysis, interpretation, or writing of the manuscript.

- **End Points**

The prespecified primary end point was a composite of death from any cause, myocardial infarction, or heart failure. This end point was selected for its clinical relevance and to ensure consistency with our previous meta-analysis of individual-patient–level data on beta-blocker therapy in patients with mildly reduced LVEF.14 Each of the components of the primary end point was analyzed individually as a secondary end point. All myocardial infarction and heart-failure events underwent independent, blinded adjudication by a clinical-end-point adjudication committee in all trials except the REDUCE-AMI trial.11 Heart failure was diagnosed either during hospitalization (in all trials) or at an outpatient clinic (in the BETAMI and DANBLOCK trials). Definitions of end points in each trial are presented in the statistical analysis plan and summarized in Table S10.

Other secondary end points (for the 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 the availability of end-point data is presented in Table S11.

- **Statistical Analysis**

All end points were analyzed in accordance with the intention-to-treat principle and the prespecified statistical analysis plan. A fixed-effect model was used for a one-stage meta-analysis of individual-patient data. We used Poisson regression to estimate incidence rates and incidence rate ratios. Survival curves for the primary end point, assessed in a time-to-first-event analysis, were estimated with the Kaplan–Meier method and compared with the log-rank test. An unadjusted Cox proportional-hazards model with stratification according to trial was used to estimate the hazard ratio and 95% confidence interval for all end points. Between-trial heterogeneity was explored with a restricted maximum likelihood estimate of the between-trial variance of treatment effect. In addition, we examined the heterogeneity of treatment

according to trial with the Higgins and Thompson I2 statistic, which was calculated from a two-stage meta-analysis.

Three sensitivity analyses were performed: a multivariable Cox regression adjusted for age, sex, type of index myocardial infarction, LVEF, and trial; a two-stage meta-analysis with a random-effects model; and an analysis of adjudicated events only (excluding all data from the REDUCEAMI trial, because myocardial infarction and heart-failure events did not undergo independent, blinded adjudication by an 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.

In all the trials, the percentage of patients lost to follow-up (Table S12) and the percentage with missing data on subgroup-defining baseline characteristics were both less than 1%. Complete case analyses were performed for all end points and subgroups under the assumption that data were missing completely at random. Prespecified subgroup analyses were performed by adding an interaction term between treatment and subgroup in the model for the primary end point. Two stratified analyses of the primary end point were conducted, with stratification according to beta-blocker dose and type (more information on these analyses is provided in the Supplementary Appendix). Stratified analyses were adjusted for major potential confounders (sex, age, and index myocardial infarction type) because neither dose nor type of beta-blocker was randomized. The treatment effects were reported as hazard ratios and 95% confidence intervals in all strata. The proportional-hazards assumption was examined for all Cox regression models by evaluating plots of the log–log of survival by log of analysis time (Figs. S2 through S8). If the assumption was deemed not to be met, the between-group difference in restricted mean event-free survival time from baseline until 3 years of follow-up was estimated, as prespecified.

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. 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 (7459 patients in the REBOOT trial, 4967 in the REDUCE-AMI trial, 277 in the DANBLOCK trial, and 657 in the CAPITAL-RCT trial). Of these 17,801 patients, 8831 (49.6%) were randomly assigned receive to beta-blockers, and 8970 (50.4%) were assigned to receive no betablockers. Baseline characteristics of the study population appeared to be well balanced and similar to the overall population of persons with myocardial infarction and preserved LVEF (Table S13). The baseline characteristics of the patients are summarized in Table 1 and Table S14 according to study-regimen group and in Table S15 according to trial. The numbers of patients with missing data according to trial and study-regimen group are presented in Tables S16 through S20. The median age of the total study population was 62 years (interquartile range, 55 to 71), 20.7% were women, 8.1% had previously had myocardial infarction, and 2.0% had atrial fibrillation. A total of 45.7% had ST-segment elevation myocardial infarction, and 94.4% underwent a percutaneous coronary intervention.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Beta-Blockers (N = 8831)	No Beta-Blockers (N = 8970)
Median age (IQR) — yr†	62 (55–71)	62 (55–71)
Female sex — no. (%)	1837 (20.8)	1856 (20.7)
Country — no. (%)		
Spain	2933 (33.2)	2998 (33.4)
Sweden, Estonia, or 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 (8.6)
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)
Dyslipidemia	2650/6334 (41.8)	2726/6471 (42.1)
Previous myocardial infarction§¶	583/7292 (8.0)	603/7384 (8.2)
Stroke‖¶	188/8504 (2.2)	179/8615 (2.1)
STEMI as index myocardial infarction — 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 before randomization¶	923/8551 (10.8)	931/8572 (10.9)
Type of beta-blocker therapy after randomization		
Bisoprolol	4136/8746 (47.3)	
Metoprolol	4000/8746 (45.7)	
Carvedilol	446/8746 (5.1)	
Other	164/8746 (1.9)	

* This meta-analysis included 17,801 patients from the REBOOT (7459 patients), REDUCE-AMI (4967 patients), BETAMI (2441 patients), DANBLOCK (2277patients), and CAPITAL-RCT (657 patients) trials. IQR denotes interquartile range, and STEMI ST-segment elevation myocardial infarction.

† N o trial was missing data on age.

‡ A total of 4737 patients from Sweden, 198 patients from New Zealand, and 32 patients from Estonia were included in the REDUCE-AMI trial.

§ D ata were not available in the BETAMI trial.

¶ Data were not available in the CAPITAL-RCT trial.

‖ Data were not available in the REDUCE-AMI trial.

- **End Points**

During a median follow-up period of 3.6 years (interquartile range, 2.3 to 4.6) in the total study population and in each of the study groups, death from any cause, myocardial infarction, or heart failure occurred in 717 of the 8831 patients (8.1%; 2.37 events per 100 patient-years) in the beta-blocker group and in 748 of the 8970 patients (8.3%; 2.45 events per 100 patient-years) in the no–beta-blocker group (hazard ratio, 0.97; 95% confidence interval [CI], 0.87 to 1.07; P=0.54) (Fig. 1A and Table 2). The incidence rate in the total population was 2.41 events per 100 personyears (95% CI, 2.29 to 2.54). No patients had missing end-point data for the primary analysis. Rate ratios and incidence rate ratios according to trial are provided in Table S21. The betweentrial variance was estimated to be 0.005 (95% CI, 0.000 to 0.104), and the amount of variance due to heterogeneity was estimated as 20.0%. Results 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) appeared to be con sistent with the primary analyses. The results remained similar when data from the REDUCEAMI trial were excluded (hazard ratio, 0.97; 95% CI, 0.86 to 1.10). Death from any cause occurred in 335 patients (1.07 events per 100 patient-years) in the betablocker group and in 326 patients (1.03 events per 100 patient-years) in the no–beta-blocker group (hazard ratio, 1.04; 95% CI, 0.89 to 1.21); myocardial infarction occurred in 360 patients (1.19 events per 100 patient-years) and 407 patients (1.33 events per 100 patient-years), respectively (hazard ratio, 0.89; 95% CI, 0.77 to 1.03); and heart failure occurred in 75 patients (0.24 events per 100 patient-years) and 87 patients (0.28 events per 100 patient-years), respectively (hazard ratio, 0.87; 95% CI, 0.64 to 1.19) (Fig. 1B, 1C, and 1D and Table 2). Cardiac death occurred in 97 patients (0.37 events per 100 patient-years) in the beta-blocker group and in 78 patients (0.29 events per 100 patient-years) in the no–beta blocker group (hazard ratio, 1.26; 95% CI, 0.94 to 1.70), and unplanned coronary revascularization occurred in 315 patients (1.45 events per 100 patient-years) and 315 patients (1.41 events per 100 patient-years), respectively (hazard ratio, 1.03; 95% CI, 0.88 to 1.20) (Table 2). All sensitivity analyses and treatment estimates for the individual trials and the estimates of the primary analysis are presented in Figure 2. Additional details on secondary end points are provided in Table 2. The event rates for secondary end points according to study-regimen group and trial are shown in Table S22. In a prespecified analysis restricted to 12 months of follow-up, a primary-end-point event occurred in 235 patients (2.73 events per 100 patient-years) in the beta-blocker group and in 271 patients (3.10 events per 100 patient-years) in the no–beta-blocker group (hazard ratio, 0.88; 95% CI, 0.74 to 1.05).

Figure 1. Kaplan–Meier Curves for the Primary End Point and Its Components.

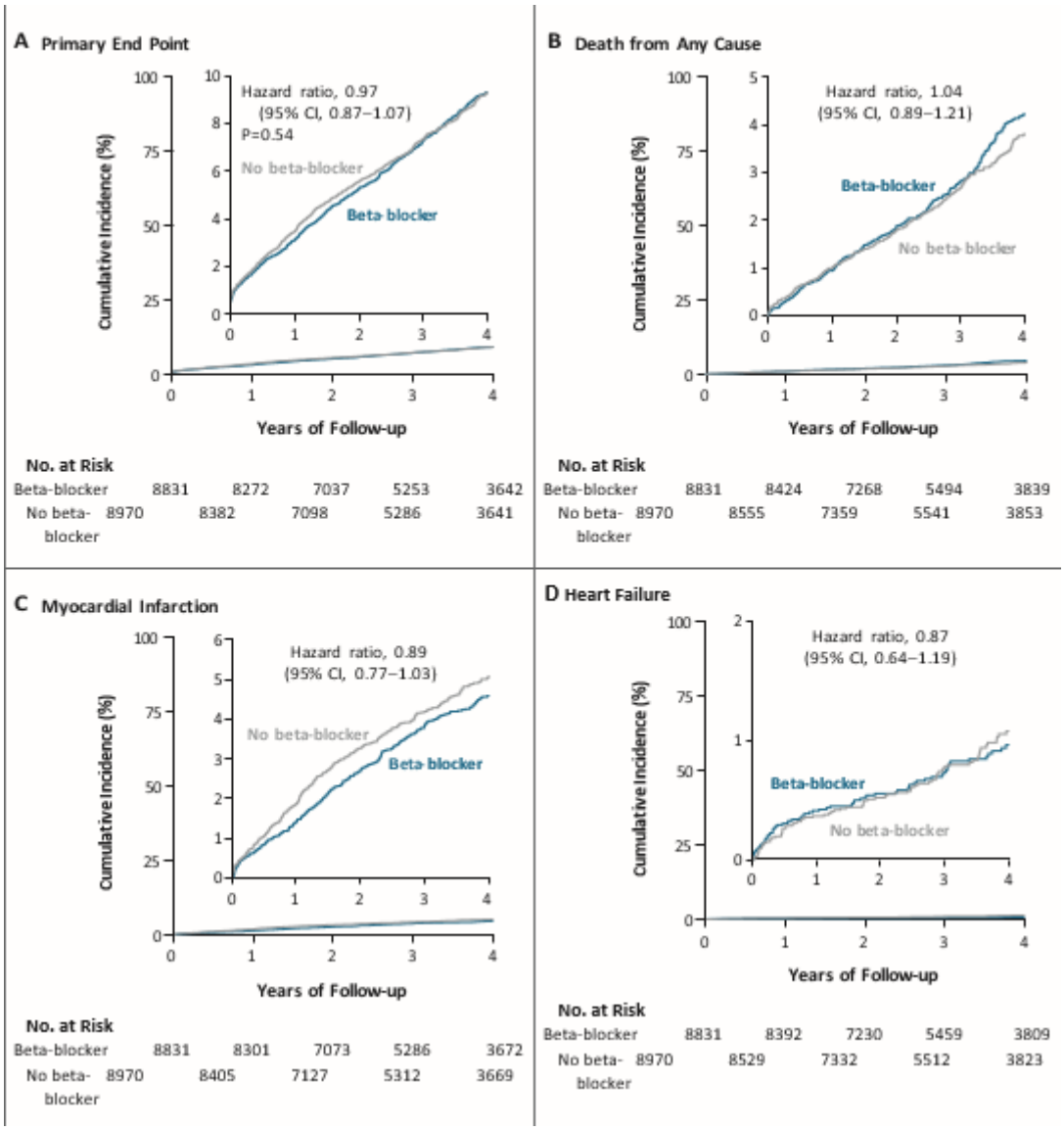

Figure 1. Kaplan–Meier Curves for the Primary End Point and Its Components. Shown are the Kaplan–Meier curves of the cumulative incidence of death from any cause, myocardial infarction, or heart failure (the composite primary end point) (Panel A) and of the individual components of the primary end point (the secondary end points) (Panels B, C, and D). 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. The insets show the same data on an expanded y axis.

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

End Point	Beta-Blockers (N = 8831)	No Beta-Blockers (N = 8970)	Hazard Ratio† (95% CI)
	number/total number (percent)		
Primary end point			
Composite of death from any cause, myocardial infarction, or heart failure	717/8831 (8.1)	748/8970 (8.3)	0.97 (0.87 to 1.07)‡
Key secondary end points			
Death from any cause	335/8831 (3.8)	326/8970 (3.6)	1.04 (0.89 to 1.21)
Myocardial infarction	360/8831 (4.1)	407/8970 (4.5)	0.89 (0.77 to 1.03)
Heart failure	75/8831 (0.8)	87/8970 (1.0)	0.87 (0.64 to 1.19)
Other secondary end points			
Cardiac death§	97/7624 (1.3)	78/7736 (1.0)	1.26 (0.94 to 1.70)
Unplanned coronary revascularization¶	315/6346 (5.0)	315/6488 (4.9)	1.03 (0.88 to 1.20)
Malignant ventricular arrhythmias¶‖	16/6025 (0.3)	23/6152 (0.4)	0.71 (0.37 to 1.34)
Safety end points			
Ischemic stroke	115/8831 (1.3)	94/8970 (1.0)	2.6 (−0.73 to 4.4)
Advanced atrioventricular block‖	69/8510 (0.8)	68/8634 (0.8)	1.03 (0.73 to 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.

† V alues are the hazard ratio for all end points except for ischemic stroke. For the ischemic stroke end point, the value is the estimated between-group difference in restricted mean event-free survival time (in days) from baseline until 3-year follow-up.

‡ P = 0.54.

§ D ata were not available in the BETAMI trial.

¶ Data were not available in the REDUCE-AMI trial. ‖ Data were not available in the CAPITAL-RCT trial.

- **Safety**

Ischemic stroke occurred in 115 patients (0.37 events per 100 patient-years) in the beta-blocker group and in 94 patients (0.30 events per 100 patient-years) in the no–beta-blocker group (betweengroup difference in restricted mean event-free survival time at 3-year follow-up, 2.6 days; 95% CI, −0.73 to 4.4). Advanced atrioventricular block occurred in 69 patients (0.23 events per 100 patient-years) in the beta-blocker group and in 68 patients (0.23 events per 100 patient-years) in the no–beta-blocker group (hazard ratio, 1.03; 95% CI, 0.73 to 1.44) (Table 2).

- **Subgroup Analyses and Stratified Analyses**

Results of the prespecified subgroup analyses of the primary end point are shown in Figure 3. The treatment effects appeared to be generally consistent on the basis of the subgroups included. Results of analyses with stratification according to the dose and type of beta-blockers are reported in Table S23.

Discussion

In this meta-analysis of individual-patient data from five contemporary randomized trials, treatment with beta-blocker therapy was not associated with a lower incidence of death from any cause, myocardial infarction, or heart failure (the composite primary end point) than no treatment with beta-blocker therapy in patients with recent myocardial infarction and a preserved LVEF (≥50%). The results appeared to be consistent for each individual component of the primary end point, other secondary end points, and safety end points, as well as across prespecified subgroups. Beta-blockers remain a cornerstone of therapy for patients with heart failure or reduced LVEF (<40%) after myocardial infarction. 8, 16, 18

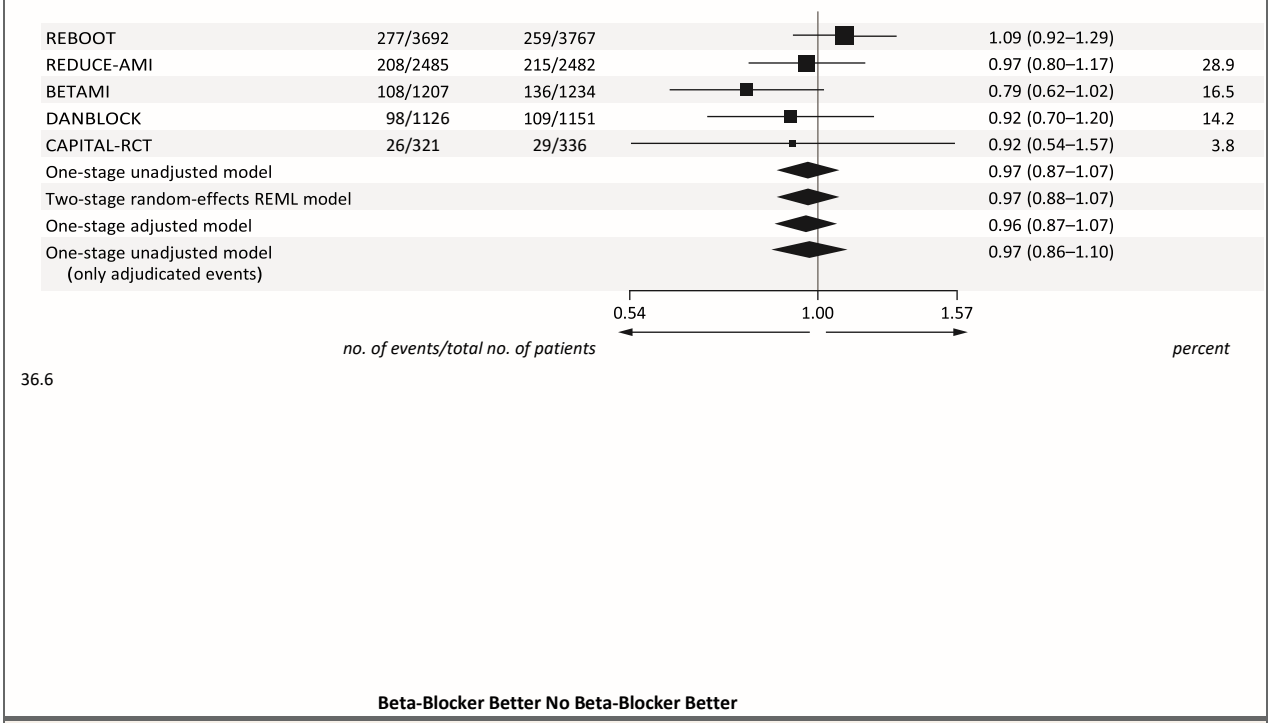

Figure 2. Treatment Estimates and Sensitivity Analyses.

Shown are the treatment estimates for each trial included in the meta-analysis of individual-patient data and the sensitivity analyses of the study. The between-trial variance was estimated to be 0.005 (95% CI, 0.000 to 0.104), and the amount of variance due to heterogeneity was estimated as 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. Squares indicate hazard ratios, horizontal lines indicate 95% confidence intervals, and diamonds indicate the overall pooled effect size and its 95% confidence interval. In the two-stage fixed-effects model, trials were weighted as the inverse of the variance.

The REBOOT,10 BETAMI,12 DANBLOCK,12 and CAPITAL-RCT13 trials investigated the efficacy of beta-blockers in patients with an LVEF of at least 40%, whereas the REDUCE-AMI trial11 exclusively enrolled patients with an LVEF of at least 50%. The individual trials differed in their primary end points and their results. The REBOOT trial10 showed no effect of beta-blockers on the composite of death from any cause, myocardial infarction, or heart failure (hazard ratio, 1.04; 95% CI, 0.89 to 1.22; P=0.63). Similarly, the REDUCE-AMI trial11 showed no effect on the composite of death from any cause or myocardial infarction (hazard ratio, 0.96; 95% CI, 0.79 to 1.16; P=0.64). In contrast, the BETAMI and DANBLOCK trials (with a pooled analysis in a single published article)12 showed that beta-blockers reduced the composite of death from any cause

or major adverse cardiovascular events (hazard ratio, 0.85; 95% CI, 0.75 to 0.98; P=0.03). The CAPITAL-RCT trial13 showed no significant effect on a composite of death from any cause, myocardial infarction, heart failure, or acute coronary syndromes (hazard ratio, 0.75; 95% CI, 0.47 to 1.16; P=0.20). Recently, a meta-analysis of data of individual patients with mildly reduced LVEF (40 to 49%) across the REBOOT,10 BETAMI,12 DANBLOCK,12 and CAPITAL-RCT13 trials showed a 25% relative reduction (hazard ratio, 0.75; 95% CI, 0.58 to 0.97) in the composite of death from any cause, myocardial infarction, or heart failure.14 In contrast, among patients with a preserved LVEF, we found no effect of beta-blockers on the composite primary end point (hazard ratio, 0.97; 95% CI, 0.87 to 1.07). In line with this result, the ABYSS (Assessment of Beta-Blocker Interruption 1 Year after an Uncomplicated Myocardial Infarction on Safety and Symptomatic Cardiac Events Requiring Hospitalization) trial19 — a noninferiority trial that randomly assigned patients with an LVEF of at least 40% to continuation or discontinuation

of beta-blockers at a median of 2.9 years after myocardial infarction — showed no effect on a composite of death from any cause, myocardial infarction, heart failure, or stroke. These findings are not unexpected given that LVEF is a strong prognostic factor both in patients with myocardial infarction and in those with heart failure.20,21 Patients with a preserved LVEF without other indications or contraindications for beta-blockers generally have fewer coexisting diseases and a better prognosis than patients with reduced or mildly reduced LVEF.22 This difference is reflected in the low event rates, with an incidence rate of 2.41 primary-end-point events per 100 person-years (95% CI, 2.29 to 2.54) in the overall population included in our meta-analysis, as compared with 3.76 events per 100 person-years (95% CI, 3.31 to 4.27) in the overall population included in the meta-analysis of patients with a mildly reduced LVEF.14 Patients with myocardial infarction and a preserved LVEF have probably experienced smaller infarctions with less myocardial scarring than patients with a reduced LVEF, which decreases the vulnerability of patients with a preserved LVEF to ventricular arrhythmias and sudden cardiac death. Consequently, the pharmacologic effects of beta-blockers after myocardial infarction may be less relevant in this population.23

A substantial proportion of patients were excluded from enrollment in the trials included in this meta-analysis. In the BETAMI and DANBLOCK trials, approximately half the persons screened for eligibility were ineligible despite having an LVEF of more than 40%, primarily because of 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 a preserved LVEF after myocardial infarction in our study does not apply to all patients with myocardial infarction and a preserved LVEF. We observed generally consistent findings in all subgroups, including women and older patients, who have been underrepresented in previous trials. The significant interaction between sex and beta-blocker effect found in the REBOOT trial24 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,2,25-27 whereas similar evidence for bisoprolol is lacking despite its common use in patients with myocardial infarction.28,29 We did not observe any apparent differences across type of beta-blocker. However, few patients were prescribed nonselective beta-blockers (e.g., carvedilol and propranolol), and patients were not randomly assigned to a type or dose of beta-blocker therapy. Although higher beta-blocker doses were associated with a higher incidence of events, this finding may relate to a greater burden of coexisting diseases or baseline risk of events among patients receiving higher doses than those receiving lower doses. Observational studies have shown no association between beta-blocker dose and outcomes.30-32 Beta-blocker doses were generally low in all trials, which reflects current clinical practice.30-32

Our meta-analysis has limitations. First, all included trials were open-label trials, with 6- and 12-month crossover occurring in 11 to 18% of the patients. These factors could potentially bias the result toward equipoise. However, the per-protocol analyses in the REBOOT trial showed findings consistent with those of the main analyses,10 and most of the trials included in this metaanalysis used adjudicated end points. In addition, the results appeared to be consistent across all trials, individual end points, countries, and betablocker classes. Second, we applied the end points as defined in each trial, and some definitions, such as those for heart failure, differed among the trials. Nonetheless, they were partially harmonized to ensure consistency where possible, and a sensitivity analysis was performed in which data from the REDUCE-AMI trial, which used nonadjudicated end points, were excluded. Some end points and some baseline characteristics used to define subgroups (Table 1) were not available in all datasets, which limited the generalizability of the findings for these analyses. Third, the included population was predominantly European and Japanese, and only a minority of patients were women, which may affect generalizability.

In this meta-analysis of individual-patient data, which consolidated the totality of evidence from five contemporary randomized trials, beta-blocker therapy did not decrease the incidence of death from any cause, myocardial infarction, or heart failure in patients with a preserved LVEF (≥50%) after recent myocardial infarction without other indications for beta-blocker therapy

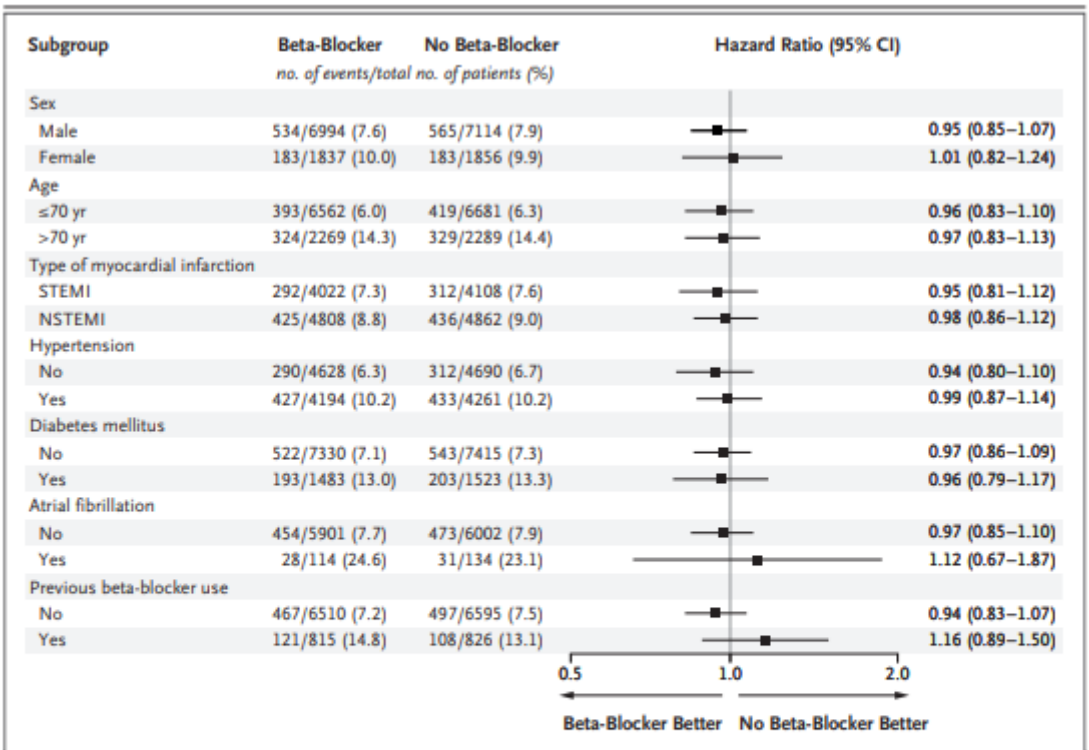

Figure 3. Prespecified Subgroup Analyses of the Primary End Point.

Shown are the analyses of the primary end point with stratification according to prespecified subgroups. Data on atrial fibrillation were not available in the REDUCE-AMI trial, and data on previous beta-blocker therapy were not available in the DANBLOCK trial. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing. NSTEMI denotes non–ST-segment elevation myocardial infarction, and STEMI ST-segment elevation myocardial infarction.

Supported by the Centro Nacional de Investigaciones Cardiovasculares Carlos III (the REBOOT trial); the Swedish Research Council, the Swedish Heart and Lung Association, and the Region of Stockholm (the REDUCE-AMI trial); the South-Eastern Norway Regional Health Authority and the Research Council of Norway (the BETAMI trial); the Danish Heart Foundation and the Novo Nordisk Foundation (the DANBLOCK trial); and the Research Institute for Production Development (Kyoto, Japan) (the CAPITAL-RCT trial). Disclosure forms provided by the authors are available with the full text of this article at NEJM.org. A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

Author Information

Anna Meta Dyrvig Kristensen, M.D.,1 Xavier Rossello, M.D., Ph.D.,2-5 Dan Atar, M.D., D.M.Sc.,6,7 Troels Yndigegn, M.D., Ph.D.,8

Takeshi Kimura, M.D., Ph.D.,9 Roberto Latini, M.D., Ph.D.,10 Bertil Lindahl, M.D., Ph.D.,11 Sigrun Halvorsen, M.D., D.M.Sc.,6,7 Michael Hecht Olsen, M.D., D.M.Sc.,12,13 Valentin Fuster, M.D., Ph.D.,2,14 Robin Hofmann, M.D., Ph.D.,15 Kjell Vikenes, M.D.,

D.M.Sc.,16,17 Michael Maeng, M.D., Ph.D.,18,19 David Erlinge, M.D., Ph.D.,8 Stuart Pocock, Ph.D.,2,20 Patric Karlström, M.D., Ph.D.,21 Arnhild Bakken, P.T., Ph.D.,6 Theis Lange, Ph.D.,22

Jose A. Barrabés, M.D., Ph.D.,5,23 Jocelyne Benatar, M.D.,24 Sergio

Raposeiras-Roubin, M.D., Ph.D.,2,25 Claes Held, M.D., Ph.D.,11 Massimo Piepoli, M.D., Ph.D.,26,27 Morten Wang Fagerland, Ph.D.,28 Therese Holmager, Ph.D.,1 Neiko Ozasa, M.D., Ph.D.,29 Eva Irene Bossano Prescott, M.D., D.M.Sc.,1 John Munkhaugen, M.D., Ph.D.,30,31 Tomas Jernberg, M.D., Ph.D.,32 and Borja Ibanez, M.D., Ph.D.2,5,33

1 Department of Cardiology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Copenhagen; 2 Centro Nacional de Investigaciones Cardiovasculares Carlos III, Madrid; 3 Department of Cardiology, University Hospital Son Espases, Instituto de Investigación Sanitaria Islas Baleares, Palma de Mallorca, Spain; 4 Facultad de Medicina, Universitat de les Illes Balears, Palma de Mallorca, Spain; 5 Centro de Investigación Biomédica en Red en Enfermedades Cardiovasculares, Madrid; 6 Department of Cardiology, Oslo University Hospital, Ullevål, Oslo; 7 Institute of Clinical Medicine, University of Oslo, Oslo; 8 Department of Cardiology, Clinical Sciences, Lund University, Lund, Sweden; 9 Department of Cardiology, Hirakata Kohsai Hospital, Osaka, Japan; 10 Department of Acute Brain and Cardiovascular Injury, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan; 11 Department of Medical Sciences, Uppsala University, Uppsala, Sweden; 12 Department of Clinical Medicine, University of Copenhagen, Copenhagen; 13 Department of Internal Medicine, Holbæk Hospital, Copenhagen; 14 Mount Sinai Fuster Heart Hospital, New York; 15 Department of Clinical Science and Education, Division of Cardiology, Södersjukhuset, Stockholm; 16 Department of Heart Disease, Haukeland University Hospital, Bergen, Norway; 17 University of Bergen, Bergen, Norway; 18 Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark; 19 Department of Clinical Medicine, Aarhus University, Aarhus, Denmark; 20 Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London; 21 Department of Internal Medicine, Ryhov County Hospital, Jönköping, Sweden; 22 Section of Biostatistics, Department of Public Health, University of Copenhagen, Copenhagen; 23 Department of Cardiology, Hospital Universitari Vall d'Hebron, Barcelona; 24 Department of Cardiology, Auckland City Hospital, Auckland, New Zealand; 25

Department of Cardiology, Hospital Universitario Álvaro Cunqueiro, Vigo, Spain; 26 University Cardiology, IRCCS Policlinico San Donato Milanese, Milan; 27 Dipartimento Scienze Biomediche Della Salute, Universita' degli Studi, Milan; 28 Oslo Center for Biostatistics and Epidemiology, Research Support Services, Oslo University Hospital, Oslo; 29 Department of Cardiology, Kansai Heart Center, Takanohara Central Hospital, Nara, Japan; 30 Department of Medicine, Drammen Hospital, Vestre Viken Trust, Drammen, Norway; 31 Department of Behavioral Medicine, Faculty of Medicine, University of Oslo, Oslo; 32 Department of Clinical Sciences, Danderyd Hospital, Karolinska Institutet, Stockholm; 33 Department of Cardiology, University Hospital Fundación Jiménez Díaz–Universidad Autónoma de Madrid, Instituto de Investigación Sanitaria-Fundación Jiménez Díaz, Madrid.

References

1. National Heart, Lung, and Blood Institute. A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. JAMA 1982; 247: 1707-14.

2. Hjalmarson A, Herlitz J, Holmberg S, et al. The Göteborg metoprolol trial: effects on mortality and morbidity in acute myocardial infarction. Circulation 1983; 67:I 26-32.

3. First International Study of Infarct Survival Collaborative Group. Randomised trial of intravenous atenolol among 16 027 cases of suspected acute myocardial infarction: ISIS-1. Lancet 1986; 2: 57-66. 4. Norwegian Multicenter Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. N Engl J Med 1981; 304:8 01-7.

5. Puymirat E, Simon T, Steg PG, et al. Association of changes in clinical characteristics and management with improvement in survival among patients with ST-elevation myocardial infarction. JAMA 2012; 308:9 98-1006.

6. Mannsverk J, Wilsgaard T, Mathiesen EB, et al. Trends in modifiable risk factors are associated with declining incidence of hospitalized and nonhospitalized acute coronary heart disease in a population. Circulation 2016; 133: 74-81.

7. Puymirat E, Simon T, Cayla G, et al. Acute myocardial infarction: changes in patient characteristics, management, and 6-month outcomes over a period of 20 years in the FAST-MI program (French registry of acute ST-elevation or non-ST-elevation myocardial infarction) 1995 to 2015. Circulation 2017; 136:1 908-19.

8. Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC guidelines for the management of acute coronary syndromes. Eur Heart J 2023; 44:3 720-826.

9. Rao SV, O'Donoghue ML, Ruel M, et al. 2025 ACC/AHA/ACEP/NAEMSP/SCAI guideline for the management of patients with acute coronary syndromes: a report of the American College of Cardiology/ American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2025; 151(13): e771-e862.

10. Ibanez B, Latini R, Rossello X, et al. Beta-blockers after myocardial infarction without reduced ejection fraction. N Engl J Med. DOI: 10.1056/NEJMoa2504735.

11. Yndigegn T, Lindahl B, Mars K, et al. Beta-blockers after myocardial infarction and preserved ejection fraction. N Engl J Med 2024; 390: 1372-81.

12. Munkhaugen J, Kristensen AMD, Halvorsen S, et al. Beta-blockers after myocardial infarction in patients without heart failure. N Engl J Med. DOI: 10.1056/ NEJMoa2505985.

13. Watanabe H, Ozasa N, Morimoto T, et al. Long-term use of carvedilol in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. PLoS One 2018; 13(8):e 0199347.

14. Rossello X, Prescott EIB, Kristensen AMD, et al. β Blockers after myocardial infarction with mildly reduced ejection fraction: an individual patient data metaanalysis of randomised controlled trials. Lancet 2025; 406: 1128-37.

15. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019; 366: l4898. 16. Virani SS, Newby LK, Arnold SV, et al.

2023 AHA/ACC/ACCP/ASPC/NLA/PCNA guideline for the management of patients with chronic coronary disease: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. Circulation 2023; 148(9):e 9-e119.

17. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2022; 145(18): e895-e1032. 18. McDonagh TA, Metra M, Adamo M, et al. 2023 focused update of the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure.

Eur Heart J 2023; 44: 3627-39.

19. Silvain J, Cayla G, Ferrari E, et al. Be-ta-blocker interruption or continuation after myocardial infarction. N Engl J Med 2024;3 91: 1277-86.

20. Liu Y, Song J, Wang W, et al. Associa-tion of ejection fraction with mortality and cardiovascular events in patients with coronary artery disease. ESC Heart Fail 2022; 9:3 461-8.

21. Solomon SD, Anavekar N, Skali H, et al. Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. Circulation 2005; 112: 3738-44.

22. Jortveit J, Myhre PL, Berge K, Halvors-en S. Survival after myocardial infarction according to left ventricular function and heart failure symptoms. ESC Heart Fail 2025;1 2: 2528-39.

23. López-Sendón J, Swedberg K, McMur-ray J, et al. Expert consensus document on beta-adrenergic receptor blockers. Eur Heart J 2004; 25:1 341-62.

24. Rossello X, Dominguez-Rodriguez A, Latini R, et al. Beta-blockers after myocardial infarction: effects according to sex in the REBOOT trial. Eur Heart J 2025 August 30 (Epub ahead of print).

25. Chen ZM, Pan HC, Chen YP, et al. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet 2005; 366: 1622-32. 26. The MIAMI Trial Research Group.

Metoprolol in acute myocardial infarction (MIAMI): a randomised placebo-controlled international trial. Eur Heart J 1985; 6: 199-226.

27. The CAPRICORN Investigators. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. Lancet 2001; 357: 1385-90.

28. CIBIS Investigators and Committees. A randomized trial of beta-blockade in heart failure: the Cardiac Insufficiency Bisoprolol Study (CIBIS). Circulation 1994; 90: 1765-73.

29. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet 1999; 353:9 -13.

30. Goldberger JJ, Bonow RO, Cuffe M, et al. Effect of beta-blocker dose on survival after acute myocardial infarction. J Am Coll Cardiol 2015; 66:1 431-41.

31. Mars K, Wallert J, Held C, et al. Asso-ciation between β-blocker dose and cardiovascular outcomes after myocardial infarction: insights from the SWEDEHEART registry. Eur Heart J Acute Cardiovasc Care 2021; 10: 372-9.

32. Pedersen SB, Nielsen JC, Bøtker HE, Udupi A, Goldberger JJ. Long-term follow-up after acute myocardial infarction according to beta-blocker dose. Am J Med 2023; 136(5): 458-465.e3.