ORIGINAL ARTICLE

Beta-Blockers after Myocardial Infarction without Reduced Ejection Fraction

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ABSTRACT

BACKGROUND

Current guideline recommendations for the use of beta-blockers after myocardial infarction without reduced ejection fraction are based on trials conducted before routine reperfusion, invasive care, complete revascularization, and contemporary pharmacologic therapies became standard practice.

METHODS

We conducted an open-label, randomized trial in Spain and Italy to evaluate the effect of beta-blocker therapy, as compared with no beta-blocker therapy, in patients with acute myocardial infarction (with or without ST-segment elevation) and a left ventricular ejection fraction above 40%. The primary outcome was a composite of death from any cause, reinfarction, or hospitalization for heart failure.

RESULTS

In total, 4243 patients were randomly assigned to receive beta-blocker therapy and 4262 to receive no beta-blocker therapy; after exclusions, 8438 patients were included in the main analysis. During a median follow-up of 3.7 years, a primary-outcome event occurred in 316 patients (22.5 events per 1000 patient-years) in the beta-blocker group and in 307 patients (21.7 events per 1000 patient-years) in the no-beta-blocker group (hazard ratio, 1.04; 95% confidence interval [CI], 0.89 to 1.22; P=0.63). Death from any cause occurred in 161 patients and 153 patients, respectively (11.2 vs. 10.5 events per 1000 patient-years; hazard ratio, 1.06; 95% CI, 0.85 to 1.33); reinfarction in 143 patients and 143 patients (10.2 vs. 10.1 events per 1000 patient-years; hazard ratio, 1.01; 95% CI, 0.80 to 1.27); and hospitalization for heart failure in 39 patients and 44 patients (2.7 vs. 3.0 events per 1000 patient-years; hazard ratio, 0.89; 95% CI, 0.58 to 1.38). No apparent between-group differences in safety outcomes were noted.

CONCLUSIONS

Among patients discharged after invasive care for a myocardial infarction with a left ventricular ejection fraction above 40%, beta-blocker therapy appeared to have no effect on the incidence of death from any cause, reinfarction, or hospitalization for heart failure. (Funded by Centro Nacional de Investigaciones Cardiovasculares Carlos III and others; ClinicalTrials.gov number, NCT03596385; EudraCT number, 2017-002485-40.)

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*A complete list of the investigators in this trial is provided in the Supplementary Appendix, available at NEJM.org.

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Beta-blockers have long been a foundational treatment after acute myocardial infarction; their use was initially supported by the results of early randomized trials, which showed a 23% lower risk of death among patients who received beta-blockers than among those in control groups at 2 years.[1] However, these trials were conducted in an era that predates what is now modern standard care — routine reperfusion, invasive management, complete revascularization, and potent adjunctive therapies such as dual antiplatelet therapy and statins.[2] Reexamining the role of beta-blockers is warranted,[3] particularly in patients with uncomplicated myocardial infarction and a preserved or mildly reduced left ventricular ejection fraction (>40%). By contrast, in patients with a reduced left ventricular ejection fraction (≤40%), the benefit of beta-blockers has been well established in contemporary clinical trials.[4,5]

In the past decade, there has been renewed interest in the role of beta-blockers in the contemporary management of myocardial infarction, particularly in patients without a reduced left ventricular ejection fraction.[6,7] Although findings from observational studies and meta-analyses have been heterogeneous,[8-13] the overall weight of evidence shows no clear benefit of beta-blockers in this patient population.[8,9,11,13,14] Some studies have indicated a possible benefit during the first year after a myocardial infarction[7,9] but not beyond. However, the nonrandomized designs of these studies have inherent limitations, including imbalances in patient characteristics at baseline and confounding by indication.[3]

The results of the Randomized Evaluation of Decreased Usage of Beta-Blockers after Acute Myocardial Infarction (REDUCE-AMI) trial, which involved 5020 patients with a left ventricular ejection fraction of at least 50%, showed no evidence of benefit from beta-blocker therapy.[15] However, the trial excluded patients with a mildly reduced left ventricular ejection fraction, and clinical events were not centrally adjudicated. Given these limitations, the 2025 guidelines of the American College of Cardiology, the American Heart Association, the American College of Emergency Physicians, the National Association of Emergency Medical Service Physicians, and the Society for Cardiovascular Angiography and Interventions continue to give a class I recommendation for beta-blockers for all patients after a myocardial infarction.[16] Similarly, the 2023 European Society of Cardiology guidelines endorse the use of beta-blockers in such patients.[17] We conducted the Treatment with Beta-Blockers after Myocardial Infarction without Reduced Ejection Fraction (REBOOT) trial to determine whether oral beta-blocker therapy initiated at hospital discharge in patients with acute myocardial infarction and a preserved or mildly reduced left ventricular ejection fraction would lead to a lower risk of a composite of death from any cause, reinfarction, or hospitalization for heart failure than no beta-blocker therapy.

METHODS

TRIAL OVERSIGHT

The REBOOT trial was a pragmatic, controlled trial that was conducted at 109 centers across Spain and Italy according to a PROBE (prospective, randomized, open-label, with blinded outcome evaluation) design. The PROBE design implies that the trial-group assignments were not concealed, but clinical outcomes were centrally adjudicated by a committee whose members were unaware of the trial-group assignments. Details of the trial design have been described previously,[18] and the protocol and statistical analysis plan are available with the full text of this article at NEJM.org. This investigator-initiated trial was financed by Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC). Patient data were recorded in accordance with national laws regarding personal data. The protocol was approved by the relevant ethics committees in Spain and Italy. The trial was conducted in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guidelines. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The first author, who had unrestricted access to the data, wrote the first draft of the manuscript, which was then revised by all the authors. All the authors made the decision to submit the manuscript.

PATIENTS

Patients with type 1 or 2 myocardial infarction (with or without ST-segment elevation) were eligible for enrollment if they had received invasive care (defined as coronary angiography, regardless

of the final therapeutic strategy) during the index hospitalization and had had a left ventricular ejection fraction of more than 40% before discharge. Patients were excluded if they had a history of heart failure (including Killip class ≥II during the index hospitalization), if they had a contraindication to beta-blocker therapy, or if they had an indication for beta-blocker therapy that was unrelated to myocardial infarction as determined by the treating physician. A complete list of inclusion and exclusion criteria is provided in the Supplementary Appendix, available at NEJM .org. All the patients provided written informed consent.

PROCEDURES

Patients were randomly assigned in a 1:1 ratio to receive either beta-blocker therapy (the intervention) or no beta-blocker therapy (the control), with the use of a secure Web-based system. In the beta-blocker group, the type and dose of beta-blocker were determined by the managing physician. All the patients received standard care. Randomization was performed at the time of hospital discharge or within 14 days after discharge. Treatment began at the time of randomization. Follow-up assessments of clinical outcomes and treatment adherence were performed at 3 months after randomization (with a window of ±1 month), at 15 months (with a window of ±3 months), at 36 months (with a window of ±3 months), and at 48 months (with a window of ±6 months). These data were obtained through telephone interviews and a review of medical records and national vital-status registries. All the hospital admission reports, in which data were deidentified and the trial-group assignments were concealed, were screened centrally to determine whether the cause of hospitalization was cardiovascular or the outcome was death. If either of these factors was present, the report was submitted to an adjudication panel whose members were unaware of the trial-group assignments.

OUTCOMES

The primary outcome was a composite of death from any cause, reinfarction, or hospitalization for heart failure. Secondary outcomes were individual components of the primary outcome, death from cardiac causes, sustained ventricular tachycardia, ventricular fibrillation, and resuscitated cardiac arrest. Tertiary outcomes were unplanned revascularization and a composite of death from cardiac causes, stroke, or myocardial infarction. Safety outcomes were hospitalization for symptomatic advanced atrioventricular block (Mobitz type II second degree or third degree) and hospitalization for stroke. The data and safety monitoring board met twice during the course of the trial to evaluate the results of interim analyses and to make recommendations to the steering committee.

STATISTICAL ANALYSIS

The sample size was set at 8468 patients with the expectation that a primary-outcome event would occur in 728 patients on the basis of the following assumptions: a median follow-up of 2.75 years (minimum of 2 years and maximum of 3 years) with a 3-year incidence of a primary-outcome event of 10% in the no-beta-blocker group and a 5% overall incidence of withdrawal from the trial. The assumption of a hazard ratio (beta-blocker vs. no beta-blocker) for a primary-outcome event of 0.80 provided the trial with 85% power at a two-sided alpha level of 0.05. Two interim analyses were performed with the use of the Haybittle–Peto approach for superiority. At the second interim analysis, the overall incidence of a primary-outcome event was lower than we had expected, and therefore, it was agreed to extend follow-up for an additional year and to reduce the minimum follow-up to 1 year.

The main analyses were performed according to the intention-to-treat principle with the use of proportional-hazards models to generate unadjusted hazard ratios and 95% confidence intervals, along with a log-rank test of significance for the primary outcome. A per-protocol analysis, in which patient follow-up data were censored at the point of known crossover (i.e., the point at which a patient in the beta-blocker group stopped taking beta-blocker therapy or a patient in the no-beta-blocker group started taking beta-blocker therapy), was also performed. Subgroup analyses of the primary outcome were performed in 12 prespecified subgroups that were defined according to patient characteristics at baseline, with hazard ratios and 95% confidence intervals shown for each subgroup category in a forest plot. The results for the secondary and tertiary outcomes are presented without formal adjustment for multiplicity. Thus, all the secondary, tertiary, and subgroup analyses are considered to be explor-

atory; the widths of the confidence intervals have not been adjusted for multiple comparisons. Given that no formal inference was intended for the nonfatal outcomes (i.e., all these findings were considered to be exploratory), we did not prespecify a sensitivity analysis with adjustment for the competing risk of death. All analyses were performed with the use of Stata software, version 18.5 (StataCorp).

RESULTS

PATIENTS AND FOLLOW-UP

From October 2018 through April 2024, a total of 8505 patients underwent randomization; 4243 were assigned to the beta-blocker group and 4262 to the no-beta-blocker group at 109 centers in Spain and Italy (Table S1 in the Supplementary Appendix). The mean (±SD) time from the index myocardial infarction to randomization was 3.8±2.6 days in the beta-blocker group and 3.8±2.6 days in the no-beta-blocker group. After the exclusion of patients who had withdrawn consent, had not provided written informed consent, had not met eligibility criteria, or had undergone randomization twice in error, 4207 patients assigned to the beta-blocker group and 4231 assigned to the no-beta-blocker group remained; these patients were included in the intention-to-treat analysis (Fig. S1).

The characteristics of the patients at baseline are shown in Table 1 and Table S2. The mean age of the patients was 61.3±11.1 years, and 19.3% of the patients were women. A total of 51.9% of the patients had hypertension, 21.4% had diabetes mellitus, 51.4% had dyslipidemia, 44.8% were active smokers, 9.5% had had a previous myocardial infarction, and 12.1% had been receiving treatment with beta-blockers before the index hospitalization. Details of the index hospitalization are shown in Table 1 and Table S3. At discharge, 97.9% of the patients were receiving dual antiplatelet therapy, 98.4% were receiving statins, and 75.0% were receiving angiotensin-converting–enzyme inhibitors or angiotensin-receptor blockers. A total of 50.9% of the patients had ST-segment elevation myocardial infarction (STEMI), and 49.1% had non-STEMI (NSTEMI). A total of 25.9% of the patients had multivessel disease. The most common revascularization procedure was percutaneous coronary intervention with stent implantation (in 92.1% of the patients). Complete revascularization was achieved in 88.2% of the patients. Details of the medications that patients were receiving at the time of discharge and the results of laboratory tests obtained before or at the time of discharge are provided in Tables S4, S5, and S6.

Among the patients in the beta-blocker group, the type of beta-blocker prescribed by the treating physicians was bisoprolol in 85.9% of the patients, metoprolol in 7.5%, carvedilol in 3.1%, nebivolol in 2.8%, and atenolol in 0.6%. The median starting doses for each agent are provided in the Supplementary Appendix.

The median follow-up was 3.7 years. A total of 71 patients (0.8%) were lost to follow-up; the time points of loss to follow-up or censoring are shown in Tables S7 and S8.

The frequency of crossovers at each trial visit is shown in Table S9 and Figure S2. Among the patients in the beta-blocker group with available data, the percentage who were still taking beta-blockers was 94.9% (3742 of 3942) at 3 months, 87.1% (3563 of 4089) at 15 months, 81.9% (2633 of 3215) at 36 months, and 77.9% (1815 of 2330) at 48 months; the denominators indicate the number of patients who completed the visit or in whom crossover was reported at that visit. Among the patients in the no-beta-blocker group with available data, the percentage who were taking beta-blockers was 9.3% (370 of 3964) at 3 months, 17.6% (727 of 4127) at 15 months, 22.9% (741 of 3239) at 36 months, and 27.9% (656 of 2350) at 48 months. Table S10 provides a summary of the complete list of medications recorded at each follow-up visit.

EFFICACY OUTCOMES

Death from any cause, reinfarction, or hospitalization for heart failure (primary outcome) occurred in 316 patients (22.5 events per 1000 patient-years) in the beta-blocker group and in 307 patients (21.7 events per 1000 patient-years) in the no-beta-blocker group (hazard ratio, 1.04; 95% confidence interval [CI], 0.89 to 1.22; P=0.63) (Table 2 and Fig. 1A). Death from any cause occurred in 161 patients (11.2 events per 1000 patient-years) in the beta-blocker group and in 153 patients (10.5 events per 1000 patient-years) in the no-beta-blocker group (hazard ratio, 1.06; 95% CI, 0.85 to 1.33) (Fig. 1B). Rein-

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Beta-Blocker (N=4207)	No Beta-Blocker (N=4231)
Age — yr	61.4±11.2	61.3±11.1
Female sex — no. (%)	816 (19.4)	811 (19.2)
Left ventricular ejection fraction		
Value — %	57.0±7.1	57.2±7.1
<50% — no. (%)	515 (12.2)	464 (11.0)
Country of enrollment — no. (%)		
Spain	3260 (77.5)	3283 (77.6)
Italy	947 (22.5)	948 (22.4)
Medical history — no./total no. (%)		
Arterial hypertension	2182/4200 (52.0)	2185/4214 (51.9)
Diabetes mellitus	901/4191 (21.5)	893/4200 (21.3)
Dyslipidemia	2158/4199 (51.4)	2166/4214 (51.4)
Current smoker	1851/4095 (45.2)	1824/4115 (44.3)
Previous myocardial infarction	408/4200 (9.7)	394/4218 (9.3)
Previous stroke	86/4203 (2.0)	67/4215 (1.6)
Chronic obstructive pulmonary disease	145/4204 (3.4)	133/4218 (3.2)
Previous atrial fibrillation	91/4205 (2.2)	102/4215 (2.4)
Details of index hospitalization — no./total no. (%)		
Infarction type		
STEMI	2146/4207 (51.0)	2150/4231 (50.8)
NSTEMI	2061/4207 (49.0)	2081/4231 (49.2)
Multivessel disease	1073/4194 (25.6)	1104/4215 (26.2)
Type of revascularization		
None	207/4177 (5.0)	190/4190 (4.5)
Percutaneous coronary intervention	3906/4177 (93.5)	3925/4190 (93.7)
Coronary-artery bypass grafting	6/4177 (0.1)	10/4190 (0.2)
Complete revascularization achieved	3464/3935 (88.0)	3484/3940 (88.4)
Medication at discharge — no./total no. (%)		
Type of beta-blocker		
Atenolol	26/4131 (0.6)	—
Bisoprolol	3549/4131 (85.9)	—
Carvedilol	128/4131 (3.1)	—
Metoprolol	309/4131 (7.5)	—
Nebivolol	114/4131 (2.8)	—
Other	5/4131 (0.1)	—
Aspirin	4136/4201 (98.5)	4165/4226 (98.6)
P2Y12 inhibitor	4120/4203 (98.0)	4129/4225 (97.7)
Angiotensin-converting–enzyme inhibitor or angiotensin-receptor blocker	3040/4193 (72.5)	3269/4223 (77.4)
Statin	4130/4202 (98.3)	4161/4224 (98.5)
Aldosterone-receptor antagonist	93/4193 (2.2)	84/4215 (2.0)
Oral anticoagulant	170/4198 (4.0)	164/4219 (3.9)
Ivabradine	20/4194 (0.5)	243/4221 (5.8)
Diuretic agent	366/4194 (8.7)	410/4220 (9.7)
Calcium-channel blocker	431/4194 (10.3)	515/4218 (12.2)

* Plus–minus values are means ±SD. Percentages may not sum to 100 because of rounding. NSTEMI denotes non–ST-segment elevation myocardial infarction, and STEMI ST-segment elevation myocardial infarction.

Table 2. Primary, Secondary, and Other Outcomes.

Outcome	Beta-Blocker	No Beta-Blocker	Rate Difference (95% CI)	Hazard Ratio (95% CI)*
	no. of patients (event rate per 1000 patient-yr)			
Primary outcome				
Death from any cause, reinfarction, or hospitalization for heart failure	316 (22.5)	307 (21.7)	0.84 (–2.63 to 4.32)	1.04 (0.89 to 1.22)†
Secondary outcomes				
Death from any cause	161 (11.2)	153 (10.5)	0.66 (–1.75 to 3.07)	1.06 (0.85 to 1.33)
Reinfarction	143 (10.2)	143 (10.1)	0.09 (–2.26 to 2.43)	1.01 (0.80 to 1.27)
Hospitalization for heart failure	39 (2.7)	44 (3.0)	–0.32 (–1.56 to 0.92)	0.89 (0.58 to 1.38)
Death from cardiac causes	65 (4.5)	57 (3.9)	0.60 (–0.90 to 2.10)	1.15 (0.81 to 1.64)
Sustained ventricular tachycardia	3 (0.2)	2 (0.1)	0.07 (–0.23 to 0.38)	1.52 (0.25 to 9.08)
Ventricular fibrillation	3 (0.2)	5 (0.3)	–0.14 (–0.52 to 0.25)	0.61 (0.14 to 2.53)
Resuscitated cardiac arrest	4 (0.3)	4 (0.3)	0.00 (–0.38 to 0.39)	1.01 (0.25 to 4.05)
Tertiary outcomes				
Death from cardiac causes, stroke, or myocardial infarction	235 (16.8)	216 (15.3)	1.51 (–1.45 to 4.47)	1.10 (0.91 to 1.32)
Unplanned revascularization	170 (12.1)	171 (12.1)	0.02 (–2.55 to 2.59)	1.00 (0.81 to 1.24)
Safety outcomes				
Hospitalization for symptomatic advanced atrioventricular block	7 (0.5)	6 (0.4)	0.07 (–0.42 to 0.56)	1.18 (0.40 to 3.50)
Hospitalization for stroke	37 (2.6)	25 (1.7)	0.86 (–0.21 to 1.93)	1.50 (0.90 to 2.49)

* Hazard ratios were estimated with the use of Cox proportional-hazards models to compare the effect of beta-blocker therapy with that of no beta-blocker therapy. No adjustment for multiplicity was made for the analyses of the secondary and tertiary outcomes. The widths of the confidence intervals should not be used to infer a treatment effect.

† P=0.63 for the comparison of the beta-blocker group with the no-beta-blocker group. The P value was calculated with the use of a log-rank test.

farction occurred in 143 patients (10.2 events per 1000 patient-years) in the beta-blocker group and in 143 patients (10.1 events per 1000 patient-years) in the no-beta-blocker group (hazard ratio, 1.01; 95% CI, 0.80 to 1.27) (Fig. 1C). Hospitalization for heart failure occurred in 39 patients (2.7 events per 1000 patient-years) in the beta-blocker group and in 44 patients (3.0 events per 1000 patient-years) in the no-beta-blocker group (hazard ratio, 0.89; 95% CI, 0.58 to 1.38) (Fig. 1D). Death from cardiac causes occurred in 65 patients (4.5 events per 1000 patient-years) in the beta-blocker group and in 57 patients (3.9 events per 1000 patient-years) in the no-beta-blocker group (hazard ratio, 1.15; 95% CI, 0.81 to 1.64) (Table 2 and Fig. S3). Results of additional secondary and tertiary outcomes are shown in Table 2 and Figures S4 and S5. The total numbers of events are provided in Table S11.

Results of the primary-outcome analysis in prespecified subgroups are shown in Figure 2. Potential heterogeneity in the treatment effect was observed in the subgroups defined according to sex and type of myocardial infarction.

The results of the per-protocol analyses of all the outcomes appeared to be consistent with those of the main intention-to-treat analyses (Table S12). The results of a post hoc analysis of the primary outcome according to the type of beta-blocker and the dose at discharge are provided in Table S6.

SAFETY OUTCOMES

Hospitalization for symptomatic advanced atrioventricular block occurred in 7 patients (0.5 events per 1000 patient-years) in the beta-blocker group and in 6 patients (0.4 events per 1000 patient-years) in the no-beta-blocker group (hazard ratio, 1.18; 95% CI, 0.40 to 3.50). Hospitalization for stroke occurred in 37 patients (2.6 events per 1000 pa-

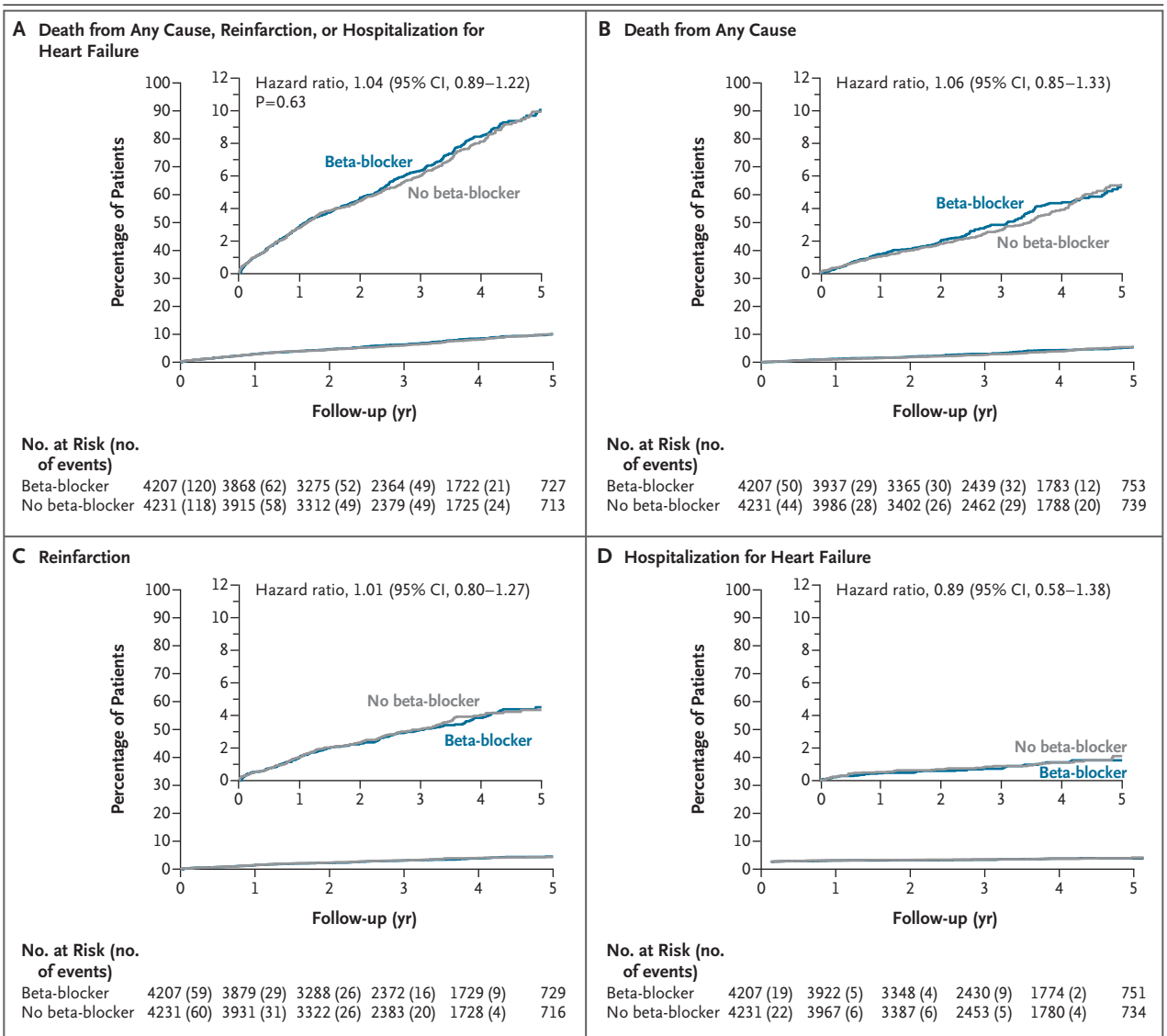

Figure 1. Kaplan–Meier Curves for the Primary Outcome and Its Components.

Panel A shows the incidence of death from any cause, reinfarction, or hospitalization for heart failure (primary composite outcome). Panels B, C, and D show the incidence of the individual components of the primary outcome. The insets show the same data on an expanded y axis. Hazard ratios and 95% confidence intervals were estimated with the use of Cox proportional-hazards models. The widths of the confidence intervals in Panels B, C, and D have not been adjusted for multiple comparisons and should not be interpreted as formal tests of significance.

tient-years) and 25 patients (1.7 events per 1000 patient-years) in the respective groups (hazard ratio, 1.50; 95% CI, 0.90 to 2.49) (Table 2).

DISCUSSION

Among patients who had been discharged after invasive care for a myocardial infarction (either with or without ST-segment elevation) and had had a left ventricular ejection fraction of more than 40%, treatment with beta-blockers showed no evidence of an effect on the incidence of death from any cause, reinfarction, or hospitalization for heart failure (primary composite outcome) during a median follow-up of 3.7 years. In addition, no apparent between-group differences were observed for any of the secondary or tertiary efficacy outcomes. Although the lack of benefit of beta-blocker therapy was seen across all prespecified subgroups, the results of the subgroup analy-

Subgroup	Beta-Blocker	No Beta-Blocker	Hazard Ratio (95% CI)
	no. of patients with event/ total no. (event rate per 1000 patient-yr)		
Overall	316/4207 (22.5)	307/4231 (21.7)	1.04 (0.89–1.22)
Sex			
Male	233/3391 (20.6)	250/3420 (21.8)	0.94 (0.79–1.13)
Female	83/816 (30.4)	57/811 (21.0)	1.45 (1.04–2.03)
Age			
<75 yr	213/3629 (17.4)	218/3664 (17.5)	1.00 (0.83–1.20)
≥75 yr	103/578 (57.3)	89/567 (53.2)	1.08 (0.81–1.44)
Country			
Spain	238/3260 (21.6)	235/3283 (21.1)	1.03 (0.86–1.23)
Italy	78/947 (25.8)	72/948 (23.9)	1.08 (0.79–1.49)
Infarction type during index hospitalization			
STEMI	149/2146 (20.8)	119/2150 (16.3)	1.27 (1.00–1.62)
NSTEMI	167/2061 (24.3)	188/2081 (27.4)	0.89 (0.72–1.10)
Revascularization			
Incomplete	47/471 (28.2)	51/456 (31.5)	0.90 (0.61–1.34)
Complete	242/3464 (21.3)	225/3484 (19.7)	1.08 (0.90–1.30)
AMI lesions			
MINOCA	6/101 (19.0)	10/112 (28.8)	0.66 (0.24–1.81)
Obstructive lesions	306/4093 (22.4)	297/4103 (21.6)	1.04 (0.88–1.22)
Left ventricular ejection fraction			
≥50%	277/3692 (22.3)	259/3767 (20.4)	1.09 (0.92–1.29)
<50%	39/515 (24.4)	48/464 (32.6)	0.75 (0.49–1.14)
Rhythm at discharge			
Sinus	258/3577 (21.8)	240/3568 (20.4)	1.07 (0.90–1.28)
Atrial fibrillation	10/36 (93.8)	7/28 (92.0)	1.03 (0.39–2.72)
Previous therapy with beta-blocker			
No	244/3682 (19.9)	237/3700 (19.2)	1.04 (0.87–1.24)
Yes	71/510 (40.9)	68/509 (39.3)	1.04 (0.74–1.45)
Arterial hypertension			
No	110/2018 (16.3)	101/2029 (14.5)	1.12 (0.85–1.47)
Yes	206/2182 (28.4)	205/2185 (28.7)	0.99 (0.82–1.20)
Diabetes mellitus			
No	211/3290 (19.2)	192/3307 (17.2)	1.11 (0.92–1.35)
Yes	103/901 (34.8)	113/893 (39.0)	0.89 (0.68–1.16)
COPD			
No	288/4059 (21.2)	287/4085 (20.9)	1.01 (0.86–1.19)
Yes	28/145 (66.3)	20/133 (49.0)	1.35 (0.76–2.40)

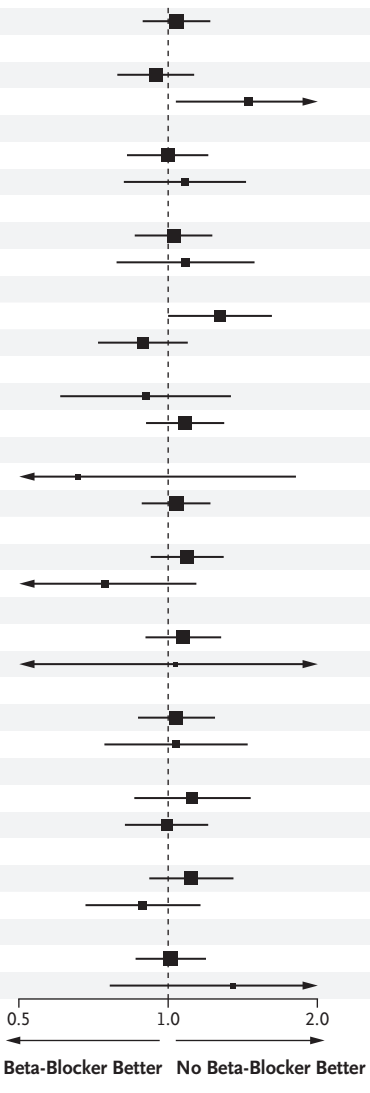

Figure 2. Subgroup Analysis of the Primary Outcome.

The primary outcome was a composite of death from any cause, reinfarction, or hospitalization for heart failure. For the analysis of revascularization, data were missing for 272 patients in the beta-blocker group and 291 patients in the no-beta-blocker group. For the analysis of acute myocardial infarction (AMI) lesions, data were missing for 13 patients and 16 patients, respectively. For the analysis of rhythm at discharge, data were missing for 578 patients and 619 patients. For the analysis of previous therapy with a beta-blocker, data were missing for 15 patients and 22 patients. For the analysis of arterial hypertension, data were missing for 7 patients and 17 patients. For the analysis of diabetes mellitus, data were missing for 16 patients and 31 patients. For the analysis of chronic obstructive pulmonary disease (COPD), data were missing for 3 patients and 13 patients. The size of the boxes is proportional to the number of patients in the subgroup, and arrows on the confidence interval bars indicate that the upper or lower boundary of the confidence interval is off the scale. MINOCA denotes myocardial infarction with nonobstructive coronary arteries, NSTEMI non–ST-segment elevation myocardial infarction, and STEMI ST-segment elevation myocardial infarction.

sis suggested the possibility that beta-blockers were associated with more primary-outcome events in women than in men and in patients with STEMI than in those with NSTEMI. The characteristics of the patients at baseline showed that the trial population was representative of the overall population of patients with myocardial infarction and without a reduced ejection fraction (Table S13) and that patients were treated according to current evidence-based strategies.[16,17]

The results of the present trial are in line with those of the REDUCE-AMI trial,[15] as well as those of the smaller CAPITAL-RCT (Carvedilol Post-Intervention Long-Term Administration in Large-Scale) trial[19] and those of several observational studies and meta-analyses.[8,9,11,13] The REDUCE-AMI trial involved 5020 patients with myocardial infarction and a left ventricular ejection fraction of more than 50%. During a median of 3.5 years of follow-up in that trial, the overall incidence of death from any cause was 3.9% in the beta-blocker group and 4.1% in the no-beta-blocker group (as compared with 3.8% and 3.6%, respectively, in the current trial), the incidence of death from cardiovascular causes was 1.5% and 1.3% (incidence of death from cardiac causes, 1.5% and 1.3% in the current trial), and the incidence of reinfarction was 4.5% and 4.7% (3.4% and 3.4% in the current trial).

Minimizing potential bias in open-label trials necessitates blinded central adjudication of primary-outcome events.[20] The current trial incorporated blinded adjudication, as did the CAPITAL-RCT[19] and ABYSS (Assessment of Beta-Blocker Interruption 1 Year after an Uncomplicated Myocardial Infarction on Safety and Symptomatic Cardiac Events Requiring Hospitalization)[21] trials. By contrast, blinded central adjudication was not performed in the REDUCE-AMI[15] trial despite its open-label design. This difference in methodologic approach may account for variations in the reported incidence of reinfarction between the REDUCE-AMI trial and the current trial.

The question of whether treatment with beta-blockers has an effect on clinical outcomes can also be considered from the opposite perspective: how does a policy of no beta-blocker therapy compare with one that includes beta-blockers? When viewed in this way, the hazard ratio inverts to 0.96 (95% CI, 0.82 to 1.12). On the basis of the upper limit of the confidence interval, one can infer that this trial provides evidence to rule out an increase in the risk of a primary-outcome event of 12% or more when no beta-blocker therapy is used. As additional data emerge from ongoing trials, it may be possible to further narrow this estimate.

The results of one observational study suggested that the clinical benefit of beta-blockers may be limited to the first year after myocardial infarction.[9] In the current trial, the event rates for the primary outcome were consistent throughout the follow-up period, including the first year after the index event, when the risk of adverse outcomes (particularly reinfarction) is typically highest.

In line with clinical practice guidelines that recommend beta-blockers without preference for a specific agent, the choice of beta-blocker and the dose was left to the discretion of the treating physician. Unlike the approach used in the REDUCE-AMI trial, in which the type of agent (metoprolol or bisoprolol) and the target dose (100 mg for metoprolol and 5 mg for bisoprolol) were specified, we used a more pragmatic approach by allowing for any beta-blocker and dose. In any case, the starting daily doses of bisoprolol (2.5 mg) and metoprolol (50 mg) were identical to those used in the REDUCE-AMI trial. Therefore, the lack of a target dose is unlikely to have had any effect on the beta-blocker strategy followed by the physicians in both trials. The most commonly prescribed beta-blocker was bisoprolol. The frequent selection of this medication is consistent with that of trials conducted in southern Europe, including the ABYSS trial (which was conducted in France), in which 71.5% of the patients received bisoprolol.[21] Similarly, in the REDUCE-AMI trial,[15] more than 40% of the patients were treated with bisoprolol and no benefit of beta-blocker therapy was observed. A post hoc analysis in our trial showed no substantial differences in the primary outcome according to the type or dose of beta-blocker used.

The incidence of crossover in the current trial was not negligible: at 15 months, 12.9% of the patients in the beta-blocker group and 17.6% of those in the no-beta-blocker group were no lon-

ger following their assigned trial regimen. Other trials have shown a similar incidence of crossover; in the REDUCE-AMI trial,[15] 18.1% of the patients who had been assigned to receive beta-blockers were not taking them at 1 year, and 14.3% of those who had been assigned to no–beta-blocker therapy were receiving treatment. Crossover was monitored at all trial visits, a particularly relevant feature in an open-label design. The occurrence of crossover did not affect the conclusions of the trial, given that a per-protocol analysis in which patient follow-up data were censored at the point of crossover and were adjusted for key baseline prognostic factors yielded results that were consistent with those of the intention-to-treat analysis.

In the prespecified subgroup analyses, no apparent difference was noted on the basis of the subgroups defined according to left ventricular ejection fraction (<50% vs. ≥50%). The potential benefit of beta-blockers in patients with a left ventricular ejection fraction between 41% and 49% was suggested by a meta-analysis of clinical trials involving patients with a mildly reduced ejection fraction[22] and also by a large registry study.[23] In the current trial, among the patients with a mildly reduced ejection fraction, fewer events occurred in the beta-blocker group than in the no-beta-blocker group; however, the number of patients in this subgroup (<1000) limits interpretability. A pooled analysis may provide further insight.

In our trial, a higher rate of primary-outcome events was observed among women who had been assigned to the beta-blocker group than among women who had been assigned to the no-beta-blocker group. This finding was not seen in the REDUCE-AMI trial[15] or in observational studies. The results of a large Canadian cohort study involving approximately 34,000 patients who had had a myocardial infarction and had been identified through administrative databases also showed an event rate that appeared to be higher among women who had received beta-blockers than among women who had not received beta-blockers.[14] In our trial, we also observed a higher rate of primary-outcome events among patients with STEMI who had been assigned to the beta-blocker group than among patients with STEMI who had been assigned to the no-beta-blocker group. Similarly, the results of a cohort study involving approximately 43,000 patients who had had a myocardial infarction showed that, among patients with STEMI, the occurrence of primary-outcome events was higher among those who had been treated with beta-blockers than among those who had not been treated with beta-blockers.[24] These possible signals of harm should be interpreted with caution and considered to be hypothesis-generating.

Recent guidelines regarding acute coronary syndrome continue to recommend beta-blocker therapy in patients without a reduced left ventricular ejection fraction — with a class I recommendation in the U.S. guidelines[16] and a class IIa recommendation in the European guidelines.[17] Both sets of guidelines note that results from ongoing trials should be considered before revising this long-standing recommendation.

Our trial has limitations. First, REBOOT was an open-label trial. However, the blinded central adjudication of events partially mitigates this limitation. Second, the enrollment period was longer than expected, but all the patients were treated according to current clinical best practice, which had not changed over the course of the trial. Third, although the planned sample size was reached,[18] the overall event rate was lower than anticipated; a primary-outcome event occurred in 623 patients, but events were expected to have occurred in 728 patients.[18] Because the number of patients with primary-outcome events was slightly higher in the beta-blocker group than in the no-beta-blocker group (316 vs. 307), the risk of a type II error is considered to be negligible. Fourth, owing to its pragmatic design, the trial protocol did not mandate beta-blocker dose adjustments, which were left to clinical discretion. Fifth, heart-rate monitoring was not required during follow-up.

In this trial involving patients who had been discharged after an uncomplicated myocardial infarction and had had a left ventricular ejection fraction of more than 40%, beta-blocker therapy was not associated with a lower cumulative incidence of death from any cause, reinfarction, or hospitalization for heart failure than no beta-blocker therapy.

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