ORIGINAL ARTICLE

Discontinuation of Beta-Blocker Therapy after Myocardial Infarction

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ABSTRACT

BACKGROUND

The role of long-term beta-blocker therapy after a myocardial infarction in patients without left ventricular systolic dysfunction or heart failure is unclear in the era of contemporary coronary-artery reperfusion and secondary prevention interventions.

METHODS

We conducted an open-label, randomized, noninferiority trial at 25 centers in South Korea. Patients whose condition remained stable after a myocardial infarction, who had a left ventricular ejection fraction of at least 40% and no heart failure, and who had received beta-blocker therapy for at least 1 year after the myocardial infarction were randomly assigned in a 1:1 ratio to discontinue or to continue beta-blocker therapy. The primary end point was a composite of death from any cause, recurrent myocardial infarction, or hospitalization for heart failure. The prespecified noninferiority margin was an upper limit of the 95% confidence interval for the hazard ratio of 1.4.

RESULTS

A total of 2540 patients underwent randomization; 1246 were assigned to beta-blocker discontinuation and 1294 to beta-blocker continuation. The mean age of the patients was 63.2 years, and 12.8% were women. At a median follow-up of 3.1 years (interquartile range, 2.5 to 3.5), a primary end-point event had occurred in 58 patients (4-year Kaplan–Meier estimate, 7.2%) in the discontinuation group and in 74 patients (4-year Kaplan–Meier estimate, 9.0%) in the continuation group (hazard ratio, 0.80; 95% confidence interval, 0.57 to 1.13; P=0.001 for noninferiority). The incidence of serious adverse events was similar in the two groups.

CONCLUSIONS

Among patients who received beta-blocker therapy beyond the first year after a myocardial infarction, discontinuation of beta-blocker therapy was noninferior to continuation with respect to a composite of death from any cause, recurrent myocardial infarction, or hospitalization for heart failure. (Funded by Patient-Centered Clinical Research Coordinating Center in the Ministry of Health and Welfare, South Korea; SMART-DECISION ClinicalTrials.gov number, NCT04769362.)

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CME

The role of beta-blockers after an acute myocardial infarction is being redefined in the contemporary era of early revascularization and comprehensive secondary prevention.[1] In patients with heart failure or a reduced left ventricular ejection fraction (<40%), beta-blockers remain a cornerstone therapy.[2-6] In contrast, several contemporary randomized trials and two meta-analyses have consistently shown no clinical benefit of beta-blockers in patients with preserved ejection fraction (≥50%) after a myocardial infarction[7-11]; a potential benefit of beta-blocker therapy has been observed in patients with a mildly reduced ejection fraction (40 to 49%),[12] which suggests that treatment effects may vary across the spectrum of left ventricular function.

Despite the evolving evidence, the limited support for prolonged beta-blocker therapy in patients without heart failure or left ventricular systolic dysfunction, and the potential adverse effects, many patients continue to receive beta-blockers for years solely because of a previous myocardial infarction.[13,14] The unresolved clinical question is whether survivors of myocardial infarction who are in stable condition and who have remained event-free should receive beta-blocker treatment over the long term. Observational studies evaluating continuation beyond the first year have shown inconsistent associations and remain susceptible to confounding by indication and treatment-selection bias.[14-17] The ABYSS trial (Assessment of Beta-Blocker Interruption 1 Year after an Uncomplicated Myocardial Infarction on Safety and Symptomatic Cardiac Events Requiring Hospitalization), which directly compared interruption with continuation of long-term beta-blocker therapy after a myocardial infarction, did not show noninferiority of beta-blocker interruption.[18] However, the ABYSS trial used a composite primary end point that included hospitalization for cardiovascular causes, a component that may be susceptible to clinical decision making in an open-label design. Therefore, the SMART-DECISION trial (Smart Angioplasty Research Team: Decision on Medical Therapy in Patients with Coronary Artery Disease or Structural Heart Disease Undergoing Intervention) was designed to determine whether discontinuation of long-term beta-blocker therapy in patients who were in stable condition after a myocardial infarction and did not have heart failure or left ventricular systolic dysfunction would be noninferior to the continuation of beta-blockers with respect to major clinical outcomes.

Methods

Trial Design

The trial design was reported previously.[19] In brief, the trial was an open-label, multicenter, randomized, noninferiority trial conducted at 25 sites in South Korea. The trial protocol, including the statistical analysis plan, is available with the full text of this article at NEJM.org; additional details regarding participating centers and trial organization are provided in the Supplementary Appendix, also available at NEJM.org. The protocol was approved by the institutional review board at each participating center, and all the patients provided written informed consent before randomization. This investigator-initiated trial was supported by the Patient-Centered Clinical Research Coordinating Center in the Ministry of Health and Welfare in South Korea. There were no confidentiality agreements regarding the data between the sponsor and the authors. An independent data and safety monitoring board monitored the trial, and an independent clinical event adjudication committee, whose members were unaware of the trial-group assignments, adjudicated all clinical events. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The first two authors and the last author designed the trial, collected and analyzed the data, wrote the manuscript, and made the decision to submit the manuscript for publication.



A Quick Take is available at NEJM.org



Population

Patients in stable condition who had had a myocardial infarction, had been receiving beta-blocker therapy for at least 1 year, and were event-free from the time of the index myocardial infarction to screening were candidates for enrollment. No restrictions on the beta-blocker type or dose were applied, and no upper limit was imposed on the interval from the index myocardial infarction diagnosis to enrollment. Key exclusion criteria were ongoing treatment for heart failure, a reduced ejection fraction (<40%), contraindications to beta-blocker therapy, and atrial fibrillation. Additional details regarding the inclusion and exclusion criteria are provided in the Supplementary Appendix.

RANDOMIZATION AND PROCEDURES

Patients were randomly assigned in a 1:1 ratio with the use of a Web-based randomization system (Internet-based Clinical Research and Trial Management System, version 2, National Institute of Health, South Korea) to discontinue or to continue beta-blocker therapy. In the discontinuation group, beta-blocker therapy was stopped immediately after randomization, whereas patients in the continuation group continued to receive beta-blocker treatment with the same agent at the same dose. Randomization was stratified according to type of myocardial infarction (ST-segment elevation or non–ST-segment elevation), beta-blocker received (carvedilol, bisoprolol, nebivolol, or other), and participating center. Clinical follow-up was performed at 6, 12, 24, and 30 months and annually thereafter.

END POINTS

The primary end point was a composite of death from any cause, recurrent myocardial infarction, or hospitalization for heart failure. The vital status of all patients was cross-checked with information in the South Korean National Health Insurance Service system. Myocardial infarction was defined according to the fourth universal definition.[20] Key secondary end points were the individual components of the primary end point, as well as death from a cardiovascular cause, any hospitalization, hospitalization for a cardiovascular cause, stroke, change in left ventricular ejection fraction, change in the N-terminal pro–B-type natriuretic peptide (NT-proBNP) level, occurrence of atrial fibrillation, the 29-item Patient-Reported Outcomes Measurement Information System (PROMIS-29) measuring quality of life in seven domains, and adverse effects related to beta-blockers. In exploratory analyses, we evaluated the composite end point that was used in the ABYSS trial (a composite of death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for cardiovascular reasons). All primary and secondary end points and definitions are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

We calculated that enrollment of 2540 patients would provide the trial with at least 80% power, at a one-sided alpha level of 2.5%, to test for noninferiority with respect to the primary end point, assuming a 3-year accrual period, 2 years of follow-up after enrollment of the last patient, and attrition of approximately 2%. With uniform accrual, the expected median duration of follow-up was 3.5 years. On the basis of previous studies, we expected the annual incidence of primary end-point events to be approximately 3% in the beta-blocker continuation group.[14,21] The prespecified noninferiority margin was an upper limit of the 95% confidence interval for the hazard ratio of 1.4, because relative-effect margins in the range of 1.3 to 1.5 are commonly used in cardiovascular noninferiority trials with low baseline event rates.[22] We assumed that allowing a hazard that was up to 1.4 times higher with discontinuation than with continuation would still be acceptable given the potential benefits of stopping long-term beta-blocker therapy, including fewer drug-related adverse effects and a reduced medication burden. However, the enrollment rate exceeded initial expectations, and the planned sample size was reached within approximately 2 years. To preserve the originally planned statistical power and median duration of follow-up, we extended follow-up to 2.5 years after enrollment of the last patient and expected the follow-up to range from 2.5 to 4.5 years. This modification was independent of treatment-effect estimates and was not accompanied by an interim analysis or an adaptive sample-size recalculation based on between-group comparisons.

All primary and secondary analyses were performed according to the intention-to-treat principle. Data from patients who did not have a primary end-point event during follow-up were censored at the time of the last known contact or at 4 years, whichever came first. The cumulative incidence of primary and secondary end-point events was estimated with the Kaplan–Meier method and compared between groups with log-rank tests. Hazard ratios and corresponding 95% confidence intervals were estimated with Cox proportional-hazards models. The proportional-hazards assumption for the primary end point was assessed by plotting Schoenfeld residuals. All the models were adjusted for the prespecified stratification factors, including type of myocardial infarction, beta-blocker that was used, and participating center. For the primary end point, hazard ratios were estimated on the log scale, on which the two-sided 95% confidence interval is symmetric. The upper bound of the two-sided 95% confidence interval is equivalent to the up-

per bound of a one-sided 97.5% confidence interval. Accordingly, the noninferiority of beta-blocker discontinuation would be concluded if the upper bound of the one-sided 97.5% confidence interval for the hazard ratio was less than the prespecified noninferiority margin of 1.4. Statistical inference for the primary end point focused on effect estimates, and a P value was reported only for the primary end-point analysis.

Secondary end points were analyzed with time-to-event methods and were interpreted as exploratory. For analyses of individual nonfatal components, subdistribution hazard ratios were estimated with Fine–Gray models, with death treated as a competing risk.[23] For death from cardiovascular causes, the competing risk was death from noncardiovascular causes. For continuous end points, linear mixed-effects models were used with fixed effects for visit, treatment group, and their interaction, with adjustment for baseline measurements and with random intercepts to account for within-patient correlation. A cluster-robust (sandwich) estimator was used to estimate standard errors and confidence intervals.

Prespecified subgroup analyses of the primary end point were performed with Cox proportional-hazards models with treatment-by-subgroup interaction terms. A per-protocol analysis was also performed. The per-protocol population, which included patients without major protocol violations, specifically excluded patients assigned to the beta-blocker discontinuation group who continued beta-blocker therapy and patients assigned to the beta-blocker continuation group who discontinued beta-blocker therapy. No imputation methods were used to infer missing values of variables. No adjustments for multiplicity were performed, and the widths of the confidence intervals should not be used to infer treatment effects. Statistical analyses were performed with R, version 4.1.2 (R Foundation for Statistical Computing).

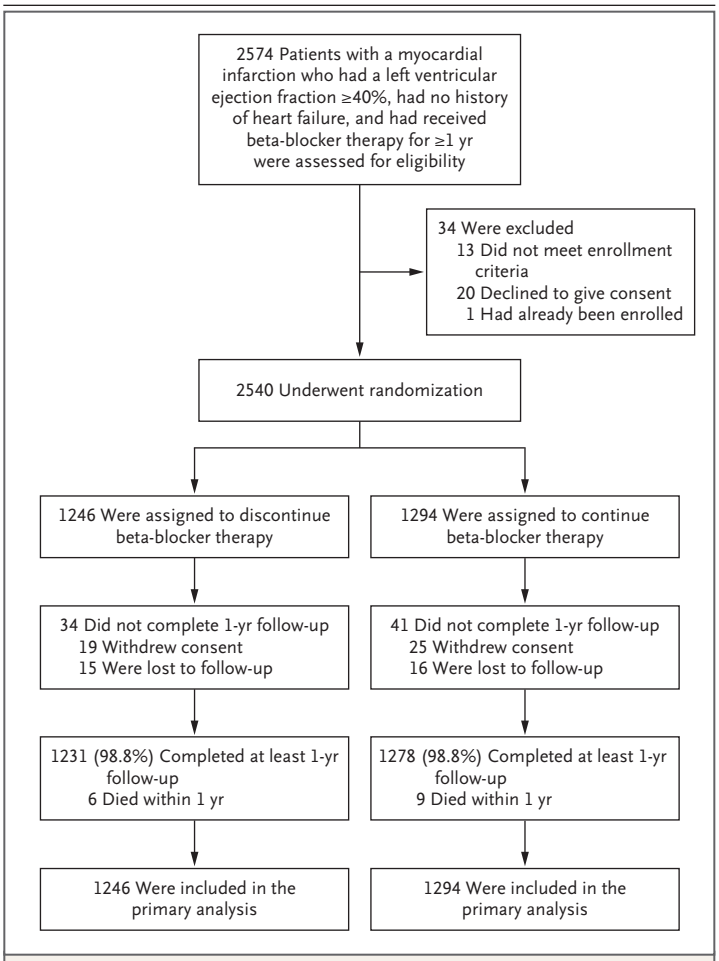

Figure 1. Randomization and Follow-up.

Patients who withdrew consent for continued participation in the trial or who did not adhere to their assigned strategy still allowed follow-up and outcome ascertainment and were included in the intention-to-treat population.

RESULTS

POPULATION

Between April 27, 2021, and April 7, 2023, a total of 14,696 patients who were potentially eligible to enroll in the trial were identified at participating centers (Fig. S1 in the Supplementary Appendix). Of these patients, 2574 were screened and 2540 underwent randomization; 1246 patients were assigned to discontinue beta-blocker therapy, and 1294 to continue beta-blocker therapy (Fig. 1). The database was locked on December 31, 2025. A total of 62 patients (2.4%) had protocol deviations during follow-up (Table S1).

The mean age of the patients was 63.2±10.1 years, and 12.8% were women. The baseline clinical characteristics of the patients appeared to be well balanced between the two groups (Table 1 and Table S2). A total of 1443 patients (56.8%) had an ST-segment elevation myocardial infarction, and 2488 patients (98.0%) underwent coronary revascularization at the time of the index myocardial infarction.

The median time from the index myocardial infarction to randomization was 4.7 years (inter-

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Discontinuation of Beta-Blocker (N = 1246)	Continuation of Beta-Blocker (N = 1294)
Age — yr	63.4±9.9	63.0±10.3
Sex — no. (%)		
Male	1088 (87.3)	1126 (87.0)
Female	158 (12.7)	168 (13.0)
Median body-mass index (IQR)†	25.2 (23.3–27.2)	25.0 (23.3–27.1)
Characteristics of index myocardial infarction		
Type — no. (%)		
STEMI	714 (57.3)	729 (56.3)
NSTEMI	532 (42.7)	565 (43.7)
Multivessel disease — no./total no. (%)	752/1239 (60.7)	758/1293 (58.6)
Revascularization strategy		
Percutaneous coronary intervention — no. (%)	1214 (97.4)	1262 (97.5)
Coronary-artery bypass grafting — no. (%)	2 (0.2)	6 (0.5)
Complete revascularization — no./total no. (%)	879/1203 (73.1)	970/1266 (76.6)
Combined revascularization procedure — no. (%)	1 (0.1)	3 (0.2)
Medical treatment only — no. (%)	29 (2.3)	23 (1.8)
Fibrinolysis — no. (%)	1 (0.1)	2 (0.2)
Median time from index myocardial infarction to randomization (IQR) — yr	4.6 (2.4–8.5)	4.8 (2.3–8.4)
Cardiovascular risk factors — no. (%)		
Hypertension	754 (60.5)	766 (59.2)
Diabetes mellitus	501 (40.2)	468 (36.2)
Dyslipidemia	785 (63.0)	788 (60.9)
Current smoking	366 (29.4)	352 (27.2)
Chronic kidney disease‡	106 (8.5)	122 (9.4)
Previous myocardial infarction before the index myocardial infarction	85 (6.8)	102 (7.9)
Previous stroke	30 (2.4)	37 (2.9)
Peripheral vascular disease	11 (0.9)	12 (0.9)
Health status at randomization		
Left ventricular ejection fraction by echocardiography (IQR) — %§	59.0 (53.7–64.6)	59.0 (53.0–65.0)
Median systolic blood pressure (IQR) — mm Hg	127 (118–136)	126 (117–136)
Median diastolic blood pressure (IQR) — mm Hg	73 (65–79)	73 (66–80)
Median heart rate (IQR) — beats/min	72 (65–80)	72 (65–80)
Beta-blocker received — no. (%)		
Carvedilol	596 (47.8)	614 (47.4)
Bisoprolol	404 (32.4)	417 (32.2)
Nebivolol	245 (19.7)	261 (20.2)
Other	1 (0.1)	2 (0.2)

* Plus–minus values are means ±SD. IQR denotes interquartile range, NSTEMI non–ST-segment elevation myocardial infarction, and STEMI ST-segment elevation myocardial infarction.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Chronic kidney disease was defined by kidney damage (pathologic abnormalities or markers of damage, including abnormalities on blood or urine testing or imaging) or an estimated glomerular filtration rate of less than 60 ml per minute per 1.73 m^2 of body-surface area.
§ The data shown are for the left ventricular ejection fraction measured at the most recent echocardiographic assessment performed after the index myocardial infarction and before randomization.

quartile range, 2.4 to 8.4). At baseline, the most commonly prescribed beta-blockers were carvedilol (in 47.6% of the patients), bisoprolol (in 32.3%), and nebivolol (in 19.9%). The distribution of the beta-blockers appeared to be similar in the two groups (Table S3). Concomitant cardiovascular medications received during follow-up are summarized in Table S4.

END POINTS

All percentages are 4-year Kaplan–Meier estimates. During the median follow-up of 3.1 years (interquartile range, 2.5 to 3.5), death from any cause, recurrent myocardial infarction, or hospitalization for heart failure (the primary end point) occurred in 58 patients (7.2%) in the discontinuation group and in 74 patients (9.0%) in the continuation group (risk difference, –1.8 percentage points; 95% confidence interval [CI], –5.5 to 1.9; hazard ratio, 0.80; 95% CI, 0.57 to 1.13; P=0.001 for noninferiority) (Fig. 2, Fig. S2, and Table 2). Death from any cause occurred in 27 patients (2.4%) in the discontinuation group and in 39 patients (3.4%) in the continuation group (hazard ratio, 0.71; 95% CI, 0.43 to 1.16); recurrent myocardial infarction occurred in 25 patients (2.3%) and 23 patients (2.6%), respectively (hazard ratio, 1.11; 95% CI, 0.63 to 1.96); and hospitalization for heart failure occurred in 16 patients (2.2%) and 20 patients (2.1%), respectively (hazard ratio, 0.82; 95% CI, 0.42 to 1.57) (Fig. S3 and Table 2). Results for other secondary end points are shown in Table 2.

A total of 143 patients (11.5%) in the discontinuation group and 174 patients (13.4%) in the continuation group had at least one serious adverse event during follow-up; serious cardiac events occurred in 71 patients (5.7%) and 79 patients (6.1%), respectively. Other serious adverse events are shown in Table S5. The specific causes of hospitalization are shown in Table S6.

The results of the per-protocol analysis of the primary end point were consistent with those in the intention-to-treat population; the hazard ratio for death from any cause, recurrent myocardial infarction, or hospitalization for heart failure in the per-protocol population was 0.79 (95% CI, 0.56 to 1.12) (Fig. S4 and Table S7). The results were also consistent across the prespecified subgroups in the intention-to-treat population (Fig. 3). Competing-risk analyses to account for the risk of death showed consistent results for the secondary end points (Table S8). Side effects of the beta-blockers reported by the patients in the continuation group during follow-up are listed in Table S9.

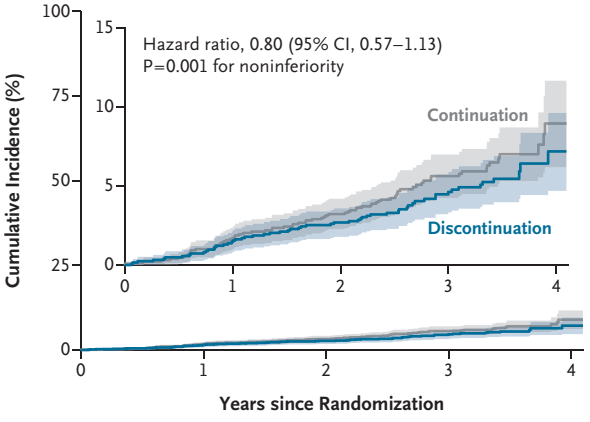

Figure 2. Death from Any Cause, Recurrent Myocardial Infarction, or Hospitalization for Heart Failure.

Shown are the Kaplan–Meier estimates of the cumulative incidence of death from any cause, recurrent myocardial infarction, or hospitalization for heart failure (the primary composite end point), with 95% confidence intervals indicated by the shaded regions. The inset shows the same data on an expanded y axis.

QUALITY OF LIFE

A total of 2522 patients (99.3%) completed the baseline PROMIS-29 questionnaire, and 2411 patients (95.6%) completed at least one follow-up PROMIS-29 questionnaire. Baseline scores appeared to be similar in the two groups. The estimated mean changes in quality-of-life scores during follow-up are shown in Table S10. Domain-specific results are provided in Tables S11 through S18.

CARDIAC FUNCTION, BIOMARKERS, AND HEMODYNAMICS

Results of longitudinal analyses of changes from baseline in left ventricular ejection fraction and in NT-proBNP levels are shown in Figures S5 and S6, respectively. Blood pressure and heart rate during follow-up are shown in Figure S7. The prevalence of uncontrolled tachycardia and uncontrolled hypertension is shown in Table S19.

Table 2. Primary and Secondary End Points.*

End Point	Discontinuation of Beta-Blocker (N = 1246)		Continuation of Beta-Blocker (N = 1294)		Risk Difference (95% CI)	Hazard Ratio (95% CI)
	no. (%)	*events/100 person-yr*	*no. (%)*	*events/100 person-yr*	*percentage points*	
Primary end point						
Composite of death from any cause, recurrent myocardial infarction, or hospitalization for heart failure†	58 (7.2)	1.57	74 (9.0)	1.95	−1.8 (−5.5 to 1.9)	0.80 (0.57 to 1.13)
Secondary end points						
Death from any cause	27 (2.4)	0.60	39 (3.4)	0.85	−1.0 (−2.4 to 0.5)	0.71 (0.43 to 1.16)
Recurrent myocardial infarction‡	25 (2.3)	0.67	23 (2.6)	0.60	−0.3 (−2.2 to 1.5)	1.11 (0.63 to 1.96)
Hospitalization for heart failure	16 (2.2)	0.43	20 (2.1)	0.52	0.0 (−2.0 to 2.0)	0.82 (0.42 to 1.57)
Death from cardiovascular cause	17 (1.6)	0.38	23 (1.9)	0.50	−0.3 (−1.4 to 0.8)	0.76 (0.40 to 1.42)
Any hospitalization	129 (13.1)	3.65	154 (18.2)	4.25	−5.1 (−10.0 to −0.2)	0.86 (0.68 to 1.09)
Hospitalization for cardiovascular cause	78 (7.8)	2.15	87 (11.0)	2.34	−3.2 (−7.2 to 0.8)	0.92 (0.68 to 1.25)
Hospitalization for acute coronary syndrome	33 (3.8)	0.89	35 (4.8)	0.92	−1.1 (−4.2 to 2.1)	0.96 (0.60 to 1.55)
Death from any cause or recurrent myocardial infarction	50 (5.8)	1.35	59 (7.2)	1.55	−1.4 (−4.7 to 1.8)	0.86 (0.59 to 1.26)
Death from cardiovascular cause or recurrent myocardial infarction	41 (4.8)	1.10	43 (4.5)	1.13	0.3 (−2.3 to 2.8)	0.97 (0.63 to 1.49)
Recurrent myocardial infarction or hospitalization for heart failure	36 (4.0)	0.97	38 (4.3)	1.00	−0.4 (−3.0 to 2.3)	0.97 (0.61 to 1.53)
Any revascularization	38 (4.3)	1.03	45 (6.7)	1.19	−2.4 (−6.1 to 1.3)	0.86 (0.56 to 1.33)
Recurrent myocardial infarction or any revascularization	39 (4.4)	1.06	48 (7.0)	1.27	−2.6 (−6.2 to 1.1)	0.83 (0.54 to 1.26)
Composite of death from cardiovascular cause, recurrent myocardial infarction, or hospitalization for heart failure	49 (6.2)	1.33	58 (6.2)	1.53	−0.0 (−3.2 to 3.1)	0.86 (0.59 to 1.26)
Composite of death from cardiovascular cause, recurrent myocardial infarction, or any revascularization	55 (6.9)	1.49	67 (8.7)	1.78	−1.8 (−5.8 to 2.2)	0.84 (0.58 to 1.19)
Atrial fibrillation occurrence	14 (1.5)	0.37	20 (1.8)	0.53	−0.3 (−1.5 to 0.9)	0.72 (0.36 to 1.43)
Stroke	8 (0.7)	0.21	19 (1.8)	0.50	−1.1 (−2.1 to −0.1)	0.43 (0.19 to 0.99)
Exploratory end point						
Composite of death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for cardiovascular reasons	100 (11.0)	2.76	116 (14.5)	3.12	−3.5 (−8.1 to 1.1)	0.89 (0.68 to 1.16)

* All percentages are 4-year Kaplan–Meier estimates. The database for the analysis was locked on December 31, 2025. Clinical end points were evaluated in the intention-to-treat population during the overall trial period (i.e., from the time of randomization to the day of the first occurrence of a primary end-point event, the day of the last known contact, or the day of death during follow-up).

† P=0.001. Noninferiority was met because the upper limit of the two-sided 95% confidence interval for the hazard ratio was less than 1.4.

‡ Myocardial infarction was defined according to the fourth universal definition.

DISCUSSION

In this randomized trial involving patients in stable condition after a myocardial infarction who did not have heart failure or left ventricular systolic dysfunction, discontinuation of beta-blocker therapy after at least 1 year of maintenance therapy was noninferior to continued therapy with respect to death from any cause, recurrent myocardial infarction, or hospitalization for heart failure (the composite primary end point). No apparent differences between the groups were observed with respect to unfavorable changes in left ventricular ejection fraction or quality of life, although we cannot exclude differences in the change in blood pressure or heart rate.

Routine use of beta-blockers in patients who did not have a reduced left ventricular ejection fraction after a myocardial infarction was questioned in recent randomized trials. In the REBOOT (Treatment with Beta-Blockers after Myocardial Infarction without Reduced Ejection Fraction) and REDUCE-AMI (Randomized Evaluation of Decreased Usage of Beta-Blockers after Acute Myocardial Infarction) trials, beta-blocker therapy that was initiated in the early phase after myocardial infarction was not associated with better major clinical outcomes than no beta-blocker use, findings that supported a reconsideration of their use in patients receiving current guideline-directed secondary prevention.[7,8] Nevertheless, many patients who are in stable condition after myocardial infarction and do not have compelling indications for beta-blockers continue to receive them in clinical practice. Whether beta-blocker therapy can be safely discontinued in this population therefore remains an important unanswered question. The ABYSS trial compared continuation of long-term beta-blocker therapy with interruption of therapy after myocardial infarction but the results for interruption of therapy did not meet the prespecified criterion for noninferiority.[18] In contrast, the SMART-DECISION randomized trial showed that discontinuation of beta-blocker therapy after prolonged maintenance was noninferior to continuation in patients who were in stable condition after a myocardial infarction and did not have heart failure or left ventricular systolic dysfunction.

The apparent discrepancy in results between the ABYSS and SMART-DECISION trials may be explained by key differences in trial design and clinical context. First, the primary end point in the ABYSS trial included hospitalization for cardiovascular causes, which may be less suitable for an open-label trial design and more susceptible to clinical decision making than hard clinical end points such as death and myocardial infarction. Of note, the differences in event counts in the ABYSS trial were driven largely by hospitalizations for a broad range of events, such as angina-related admissions and diagnostic coronary angiography without revascularization. In contrast, the SMART-DECISION trial prespecified the primary end point to be composed exclusively of objective clinical outcomes. It is important to note that in the ABYSS trial the risk of death from any cause, of myocardial infarction, and of hospitalization for heart failure was similar in the beta-blocker interruption and continuation groups. Second, background secondary prevention appeared to be more intensive in the SMART-DECISION trial, with more frequent use of ezetimibe and greater use of P2Y12 inhibitor monotherapy rather than aspirin, and lower low-density lipoprotein cholesterol levels were achieved; these factors may have contributed to the lower overall incidence of events observed in the present trial.[24-27] Third, the timing of beta-blocker discontinuation differed substantially between the two trials. Our trial required at least 1 year of beta-blocker therapy before enrollment and included patients who underwent randomization a median of 4.7 years after the index myocardial infarction, which reflected a population in highly stabilized condition. In contrast, the ABYSS trial enrolled patients after a minimum of 6 months of beta-blocker therapy, with randomization occurring a median of 2.9 years after the myocardial infarction. Finally, baseline risk profiles differed across the trials — the SMART-DECISION trial had higher percentages of patients with hypertension and diabetes and lower percentages of patients with peripheral vascular disease and included fewer women than the ABYSS trial. These differences may reflect regional and ethnic variation in cardiovascular risk profiles. Of note, in our trial, mean beta-blocker doses were lower than those reported in the ABYSS trial. Nonetheless, several analyses involving patients who had had a myocardial infarction have suggested that higher beta-blocker doses do not consistently confer additional outcome benefit as compared with lower doses in contemporary

Subgroup	Total No. of Patients	Discontinuation of Beta-Blocker	Continuation of Beta-Blocker	Hazard Ratio (95% CI)
		no. of patients with event/no. of patients (4-year Kaplan–Meier estimate, %)		
All patients	2540	58/1246 (7.2)	74/1294 (9.0)	0.80 (0.57–1.13)
Age				
<65 yr	1416	14/678 (2.4)	21/738 (5.5)	0.72 (0.36–1.41)
≥65 yr	1124	44/568 (13.6)	53/556 (13.9)	0.78 (0.52–1.16)
Sex				
Male	2214	49/1088 (6.3)	69/1126 (9.1)	0.72 (0.50–1.05)
Female	326	9/158 (17.1)	5/168 (10.0)	1.95 (0.65–5.82)
Body-mass index				
<25	1175	31/558 (10.6)	47/617 (12.3)	0.72 (0.46–1.14)
≥25	1254	23/632 (4.4)	25/622 (6.1)	0.89 (0.51–1.57)
Hypertension				
No	1020	26/492 (9.8)	28/528 (8.7)	1.00 (0.59–1.70)
Yes	1520	32/754 (6.0)	46/766 (9.2)	0.68 (0.43–1.07)
Diabetes mellitus				
No	1571	31/745 (6.2)	49/826 (8.6)	0.67 (0.43–1.05)
Yes	969	27/501 (8.7)	25/468 (9.3)	1.02 (0.59–1.76)
Chronic kidney disease				
No	2312	50/1140 (6.9)	57/1172 (7.6)	0.89 (0.61–1.30)
Yes	228	8/106 (11.3)	17/122 (23.2)	0.53 (0.23–1.23)
Left ventricular ejection fraction				
40–50%	2144	51/1063 (7.0)	62/1081 (9.0)	0.82 (0.57–1.19)
>50%	396	7/183 (9.9)	12/213 (7.8)	0.64 (0.25–1.63)
Systolic blood pressure				
<140 mm Hg	2073	49/1021 (7.6)	55/1052 (8.5)	0.91 (0.62–1.33)
≥140 mm Hg	451	9/214 (5.5)	19/237 (10.6)	0.50 (0.22–1.10)
Heart rate				
<60 beats/min	238	6/117 (5.8)	1/121 (0.8)	5.94 (0.71–49.49)
≥60 beats/min	2279	52/1112 (7.4)	73/1167 (9.8)	0.73 (0.51–1.05)
Type of myocardial infarction				
STEMI	1443	31/714 (6.4)	40/729 (9.8)	0.78 (0.49–1.25)
NSTEMI	1097	27/532 (8.3)	34/565 (7.8)	0.81 (0.49–1.35)
Beta-blocker received				
Carvedilol	1210	24/596 (8.5)	33/614 (7.9)	0.74 (0.44–1.26)
Bisoprolol	821	17/404 (5.0)	22/417 (8.2)	0.78 (0.41–1.47)
Nebivolol	506	17/245 (9.8)	19/261 (14.0)	0.91 (0.48–1.76)
Other	3	0/1 (0)	0/2 (0)	—
Time since index myocardial infarction				
<4.7 yr	1275	24/636 (5.6)	35/639 (8.0)	0.67 (0.40–1.13)
≥4.7 yr	1265	34/610 (8.8)	39/655 (9.8)	0.93 (0.58–1.47)
Complete revascularization				
No	620	18/324 (9.5)	22/296 (11.1)	0.75 (0.40–1.41)
Yes	1849	39/879 (6.5)	52/970 (8.5)	0.80 (0.53–1.21)

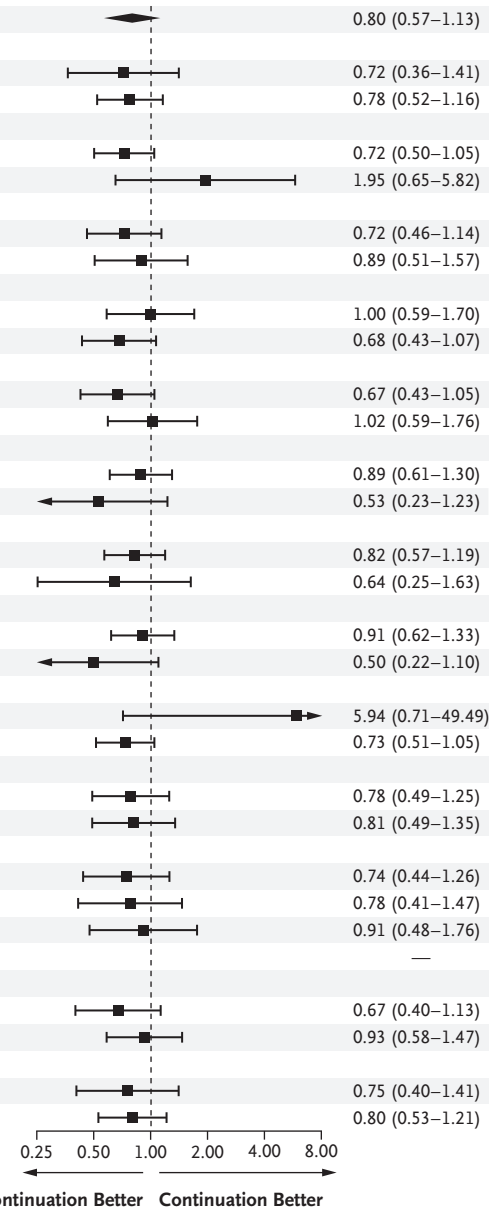

Figure 3. Analysis of the Primary End Point in Prespecified Subgroups (Intention-to-Treat Population).

The body-mass index is the weight in kilograms divided by the square of the height in meters. Chronic kidney disease was defined as kidney damage (pathologic abnormalities or markers of damage, including abnormalities on blood or urine testing or imaging) or an estimated glomerular filtration rate of less than 60 ml per minute per 1.73 m^2 of body-surface area. The median time since the index myocardial infarction was 4.7 years. NSTEMI denotes non–ST-segment elevation myocardial infarction, and STEMI ST-segment elevation myocardial infarction.

practice.[13,28,29] In addition, carvedilol, bisoprolol, and nebivolol, which have favorable pharmacologic profiles (e.g., beta-1–receptor selectivity or vasodilatory properties) were used more frequently in the SMART-DECISION trial than in the ABYSS trial, which indicated that differences in dose or agent alone are unlikely to explain the observed results.

Beyond clinical outcomes, this trial provides objective cardiac measures of the effects of beta-blocker discontinuation, including serial assessments of left ventricular ejection fraction and the NT-proBNP level. We also used the PROMIS-29 questionnaire to assess patient-reported quality of life, which has not been evaluated routinely in previous beta-blocker discontinuation trials. Together, these measures offer potential mechanistic and patient-centered insights beyond event rates alone. Blood pressure appeared to increase after beta-blocker discontinuation, although the baseline mean systolic blood pressure was below 130 mm Hg and lower than that observed in the ABYSS trial. Heart rate also appeared to increase after discontinuation. However, collectively, our findings provide reassurance that discontinuation of long-term beta-blocker therapy in some appropriately selected patients who are in clinically stable condition does not appear to compromise hemodynamic control. In the context of contemporary secondary prevention, the results of the SMART-DECISION trial show that discontinuation of beta-blocker therapy beyond the first year after myocardial infarction may be a reasonable strategy in selected patients who are in stable condition without heart failure or left ventricular systolic dysfunction and that routine long-term continuation may not be required in this population.

Our trial has several limitations. First, this trial was open-label; however, the primary end point comprised largely objective events, and all events that were considered possible or probable were adjudicated by an independent committee whose members were unaware of the group assignments. Second, all the patients involved in the trial were enrolled in South Korea, and the results cannot be fully generalized to health care systems with different patient characteristics, revascularization practices, or patterns of background medical therapy (Table S20). Furthermore, the trial enrolled a selected population of patients in stable condition, with a low prevalence of peripheral artery disease and no atrial fibrillation. Because patients underwent randomization at a late phase after the index myocardial infarction, the trial did not define a time point earlier after myocardial infarction when beta-blocker discontinuation would be safe. Accordingly, the findings may not be generalizable to higher-risk patients early after myocardial infarction or to populations with a greater burden of coexisting conditions. Third, the noninferiority margin was relatively wide, and the observed incidence of events was lower than expected, which reduced precision and limited the ability to exclude a clinically important increase in risk. Fourth, women and patients with a mildly reduced left ventricular ejection fraction comprised a small proportion of the trial population. Therefore, analyses in these subgroups should be considered exploratory and hypothesis generating, and firm conclusions regarding the safety of beta-blocker discontinuation in these subgroups should be avoided. Finally, because left ventricular ejection fraction was based on the most recent clinically obtained prerandomization echocardiogram, the possibility that there may have been changes in left ventricular systolic function between imaging and randomization cannot be fully excluded.

Among patients in stable condition who were receiving beta-blocker therapy beyond the first year after a myocardial infarction, discontinuation of beta-blocker therapy was noninferior to continuation with respect to a composite of death from any cause, recurrent myocardial infarction, or hospitalization for heart failure.

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