The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 10, 2024 VOL. 391 NO. 14

Beta-Blocker Interruption or Continuation after Myocardial Infarction

J. Silvain, G. Cayla, E. Ferrari, G. Range, E. Puymirat, N. Delarche, P. Guedeney, T. Cuisset, F. Ivanes, T. Lhermusier, T. Petroni, G. Lemesle, F. Bresoles, J.-N. Labeque, T. Pommier, J.-G. Dillinger, F. Leclercq, F. Boccara, P. Lim, T. Besseyre des Horts, T. Fourme, F. Jourda, A. Furber, B. Lattuca, N. Redjimi, C. Thuaire, P. Deharo, N. Procopi, R. Dumaine, M. Slama, L. Payot, M. El Kasty, K. Aacha, A. Diallo, E. Vicaut, and G. Montalescot, for the ABYSS Investigators of the ACTION Study Group*

ABSTRACT

BACKGROUND

The appropriate duration of treatment with beta-blocker drugs after a myocardial infarction is unknown. Data are needed on the safety and efficacy of the interruption of long-term beta-blocker treatment to reduce side effects and improve quality of life in patients with a history of uncomplicated myocardial infarction.

METHODS

In a multicenter, open label, randomized, noninferiority trial conducted at 49 sites in France, we randomly assigned patients with a history of myocardial infarction, in a 1:1 ratio, to interruption or continuation of beta-blocker treatment. All the patients had a left ventricular ejection fraction of at least 40% while receiving long-term beta-blocker treatment and had no history of a cardiovascular event in the previous 6 months. The primary end point was a composite of death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for cardiovascular reasons at the longest follow-up (minimum, 1 year), according to an analysis of noninferiority (defined as a between-group difference of <3 percentage points for the upper boundary of the two-sided 95% confidence interval). The main secondary end point was the change in quality of life as measured by the European Quality of Life–5 Dimensions questionnaire.

RESULTS

A total of 3698 patients underwent randomization: 1846 to the interruption group and 1852 to the continuation group. The median time between the last myocardial infarction and randomization was 2.9 years (interquartile range, 1.2 to 6.4), and the median follow-up was 3.0 years (interquartile range, 2.0 to 4.0). A primary-outcome event occurred in 432 of 1812 patients (23.8%) in the interruption group and in 384 of 1821 patients (21.1%) in the continuation group (risk difference, 2.8 percentage points; 95% confidence interval [CI], <0.1 to 5.5), for a hazard ratio of 1.16 (95% CI, 1.01 to 1.33; P=0.44 for noninferiority). Beta-blocker interruption did not seem to improve the patients' quality of life.

CONCLUSIONS

In patients with a history of myocardial infarction, interruption of long-term beta-blocker treatment was not found to be noninferior to a strategy of beta-blocker continuation. (Funded by the French Ministry of Health and ACTION Study Group; ABYSS ClinicalTrials.gov number, NCT03498066; EudraCT number, 2017-003903-23.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Silvain can be contacted at johanne.silvain@aphp.fr or at ACTION Group, Sorbonne Université, Pitié–Salpêtrière Hospital, Paris Institut de Cardiologie, 83 Boulevard de l'Hôpital, 75013 Paris, France.

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

This article was published on August 30, 2024, at NEJM.org.

N Engl J Med 2024;391:1277-86.
DOI: 10.1056/NEJMoa2404204
Copyright © 2024 Massachusetts Medical Society.

CME

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society.
Downloaded from nejm.org at Chinese Academy of Medical Sciences (CAMS) on March 29, 2025. For personal use only.
No other uses without permission. Copyright © 2024 Massachusetts Medical Society. All rights reserved.

It is estimated that 2 million persons every year in the United States and Europe have an acute myocardial infarction.[1,2] The lack of contemporary large-scale randomized trials and of consensus recommendation[3,4] on the duration of beta-blocker therapy after myocardial infarction has resulted in lifelong therapy in many patients, making this class of drugs one of the most prescribed worldwide. Beta-blocker therapy is not only a standard of care for patients after myocardial infarction but also a quality indicator of secondary prevention, with a prescription rate that has reached over 90% in most Western registries.

A Quick Take is available at NEJM.org

The benefit of beta-blocker therapy in patients with myocardial infarction is derived from trials carried out before the modern era of myocardial reperfusion and pharmacotherapy.[5] Early coronary reperfusion therapy has led to a sharp decrease in the risks of heart failure and death after myocardial infarction and has led to questions about the add-on benefits of lifelong beta-blocker treatment in patients with a preserved left ventricular ejection fraction and no other primary indication for beta-blocker therapy.[6] Contemporary large nationwide registries have often suggested an absence of long-term benefit of beta-blocker therapy in such patients,[7-10] although data have been inconsistent. Results from a randomized trial have been lacking to evaluate late discontinuation of beta-blockers in the absence of chronic heart failure or left ventricular dysfunction.

We conducted the ABYSS (Assessment of Beta-Blocker Interruption 1 Year after an Uncomplicated Myocardial Infarction on Safety and Symptomatic Cardiac Events Requiring Hospitalization) trial to evaluate beta-blocker continuation or interruption among patients with a history of myocardial infarction who had a left ventricular ejection fraction of at least 40%. We hypothesized that beta-blocker interruption would be clinically safe and that the patients' quality of life would improve.

Methods

Trial Design

The trial design has been published previously[11] (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). In brief, ABYSS was a multicenter noninferiority trial that was conducted at 49 clinical sites in France according to a PROBE (prospective, randomized, open-label, blinded end-point) design. Details regarding the trial organization are provided in the Supplementary Appendix, along with the trial protocol, which is also available at NEJM.org.

The ABYSS trial was led by the ACTION (Allies in Cardiovascular Trials, Initiatives, and Organized Networks) Group at Pitié–Salpêtrière Hospital and was funded by a grant from the French Ministry of Health; administrative sponsorship was provided by Assistance Publique–Hôpitaux de Paris. National and institutional regulatory and ethics authorities approved the protocol, and all the patients provided written informed consent. The first and last authors designed the trial, wrote the first draft of the manuscript, and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Trial Population

Patients were eligible for enrollment if they had a history of myocardial infarction at least 6 months before enrollment and were being treated with a beta-blocker, regardless of the agent or the dose. Key exclusion criteria were chronic heart failure or a reduced left ventricular ejection fraction (<40%), any cardiac event during the 6 months before enrollment, or any other primary indication for beta-blocker therapy, such as arrythmia, migraine, or uncontrolled hypertension.[9]

Intervention and Management

Patients were randomly assigned in a 1:1 ratio to a strategy of either interruption or continuation of beta-blocker therapy with the same agent at the same dose. Randomization was performed with the use of a centralized system and stratification according to trial center. Beta-blocker interruption could be tapered if the patient was receiving a high dose of the drug, according to the physician's preference. All the patients were evaluated at 6 months and 12 months and then annually after randomization until the last trial entrant had completed the 1-year minimum follow-up.

End Points

The primary end point was a composite of death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for any other cardiovascular reason. The main secondary end point was the change in score from baseline to 6 months and

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society.
Downloaded from nejm.org at Chinese Academy of Medical Sciences (CAMS) on March 29, 2025. For personal use only.
No other uses without permission. Copyright © 2024 Massachusetts Medical Society. All rights reserved.

12 months on the European Quality of Life–5 Dimensions (EQ-5D) questionnaire (with scores ranging from 0 to 1, and higher scores indicating better health status; minimal clinically important difference, 0.05 points).

Other secondary end points were a composite of death, nonfatal myocardial infarction, or nonfatal stroke and a composite of death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure. Definitions for all secondary and adjudicated end points are provided in the Supplementary Appendix. Adjudication of all events was performed by an independent clinical end-point committee whose members were unaware of the trial-group assignments.

STATISTICAL ANALYSIS

We determined that the enrollment of 3700 patients would provide the trial with 80% power to show the noninferiority of the primary hypothesis, with noninferiority defined as a margin of less than 3.0 percentage points in the upper boundary of the two-sided 95% confidence interval for the difference in event rate (beta-blocker interruption minus beta-blocker continuation). This calculation was based on an estimated risk of 12% for the primary end point in the continuation group at a median follow-up of 3 years at an alpha level of 5%. The margin of 3 percentage points was chosen to correspond to a 25% difference in relative risk that is commonly used in cardiology trials.

Categorical data are presented as numbers and percentages. Continuous variables are presented as means with standard deviations and medians with interquartile ranges. The primary noninferiority analysis was performed in the intention-to-treat population, which included all the patients who had undergone randomization and provided written informed consent. The per-protocol population included all the patients who had received the assigned treatment and excluded patients with major protocol violations (i.e., missing data for the primary efficacy end point or crossover from the initial randomized strategy). The event rate was based on the observed outcome at the longest follow-up. Noninferiority was tested at a margin of less than 3.0 percentage points in both the intention-to-treat and per-protocol populations.

For the intention-to-treat analysis of the primary end point, we used the Markov chain Monte Carlo method for the imputation of missing values (PROC MI). A total of 50 imputed data sets were generated from the initial data set, and each complete data set was analyzed with the use of a generalized linear model with binomial distribution and identity link function (PROC GLIMMIX); the results from the multiple imputation analyses were combined into a single inference with the use of Rubin's rule. The variables that were included in the imputation models were trial group, demographic data, cardiovascular risk factors, and medical history at baseline. Trace plots and distribution plots were created to check the accuracy of the imputations. A complete-case analysis was performed as a sensitivity analysis. The confidence intervals of differences in the event rate were also calculated for the individual components of the primary end points and the prespecified secondary end points. The widths of the confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing.

In addition, we performed Kaplan–Meier analyses of all time-to-event data for the 4-year follow-up, with data censoring at the last assessment. Kaplan–Meier estimates at follow-up reviews that were performed at 12, 24, 36, and 48 months were reported in both groups, and hazard ratios and 95% confidence intervals were calculated with the use of a Cox survival model. We analyzed the main secondary end point in the intention-to-treat population with the use of the Markov chain Monte Carlo method for multiple imputation for missing values; the maximum value was used if the main secondary end point was evaluated at both 6 months and 12 months. The difference in means between groups and the 95% confidence interval was estimated by the means of the Wald method. The confidence intervals of event-rate differences were also calculated for the prespecified subgroups. All statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

POPULATION

The patients underwent randomization between August 28, 2018, and September 12, 2022; scheduled recruitment continued during the coronavirus disease 2019 pandemic and lockdown in France. A total of 3698 patients underwent randomiza-

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society. Downloaded from nejm.org at Chinese Academy of Medical Sciences (CAMS) on March 29, 2025. For personal use only. No other uses without permission. Copyright © 2024 Massachusetts Medical Society. All rights reserved.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Beta-Blocker Interruption (N=1846)	Beta-Blocker Continuation (N=1852)
Demographic and cardiovascular risk		
Age — yr	63.5±11.2	63.5±10.9
Male sex — no. (%)	1530 (82.9)	1531 (82.7)
Median body-mass index (IQR)†	26.3 (23.9–29.4)	26.5 (24.1–29.6)
Current smoker — no. (%)	385 (20.9)	342 (18.5)
Hypertension — no. (%)	786 (42.6)	805 (43.5)
Diabetes — no. (%)	372 (20.2)	375 (20.2)
Dyslipidemia — no. (%)	948 (51.4)	994 (53.7)
Medical history		
ST-segment elevation myocardial infarction — no. (%)	1168 (63.3)	1162 (62.7)
Non–ST-segment elevation myocardial infarction — no. (%)	678 (36.7)	690 (37.3)
Median time from index myocardial infarction to randomization (IQR) — yr	2.9 (1.2–6.2)	2.8 (1.1–6.6)
Multivessel disease — no. (%)	955 (51.7)	979 (52.9)
Revascularization for index myocardial infarction — no./total no. (%)	1755/1846 (95.1)	1757/1852 (94.9)
Completeness‡	1601/1753 (91.2)	1619/1755 (92.1)
Percutaneous coronary intervention	1709/1755 (97.4)	1693/1757 (96.4)
Fibrinolysis	29/1755 (1.7)	46/1757 (2.6)
Coronary-artery bypass grafting	62/1755 (3.5)	83/1757 (4.7)
Peripheral vascular disease — no. (%)	104 (5.6)	83 (4.5)
Stroke or transient ischemic attack — no. (%)	56 (3.0)	67 (3.6)
Episode of heart failure — no. (%)§	34 (1.8)	26 (1.4)
Arrhythmia — no. (%)	7 (0.4)	5 (0.3)
Health status		
Left ventricular ejection fraction		
Median (IQR) — %	60 (52–60)	60 (52–60)
Patients with value of 40 to 50% — no. (%)	430 (23.3)	435 (23.5)
Residual angina — no. (%)	21 (1.1)	30 (1.6)
Median blood pressure (IQR) — mm Hg		
Systolic	132 (121–144)	131 (121–144)
Diastolic	77 (70–83)	77 (70–83)
Median resting heart rate (IQR) — beats/min	63 (57–71)	63 (57–71)

* Plus–minus values are means ±SD. IQR denotes interquartile range.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Completeness was defined as successful revascularization of all coronary artery lesions.
§ Included in this category are episodes of heart failure that occurred more than 2 years before randomization.

tion: 1846 to the interruption group and 1852 to the continuation group (Fig. S2). The mean (±SD) age of the patients was 63.5±11 years, and 17.2% were women. At the time of randomization, the clinical characteristics of the two groups seemed to be well balanced in terms of risk factors and guideline-recommended drugs for secondary prevention (Table 1 and Table S1).

A total of 2330 patients (63.0%) had a previous ST-segment elevation myocardial infarction, and 287 patients (7.8%) had more than one previous myocardial infarction. The median time

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society.
Downloaded from nejm.org at Chinese Academy of Medical Sciences (CAMS) on March 29, 2025. For personal use only.
No other uses without permission. Copyright © 2024 Massachusetts Medical Society. All rights reserved.

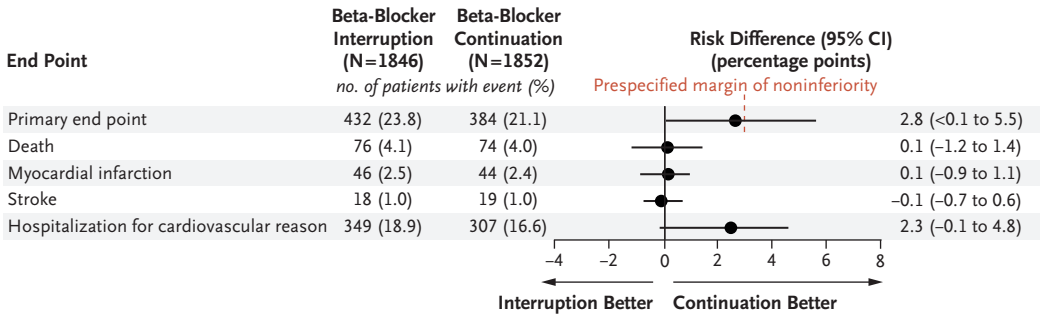

Figure 1. Primary End Point and Its Components.

With respect to the primary end point (a composite of death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for cardiovascular reasons), noninferiority of the interruption of beta-blocker therapy was defined as a between-group difference of less than 3 percentage points for the upper boundary of the two-sided 95% confidence interval for the event rate.

between the qualifying myocardial infarction and randomization was 2.9 years (interquartile range, 1.2 to 6.4). A total of 842 patients (22.8%) were receiving ticagrelor or prasugrel at the time of randomization; 95% of the population had undergone a coronary revascularization procedure (percutaneous coronary intervention in 96.9%) for the index myocardial infarction. The trial patients were representative of the French population and similar to those in other European nations (Tables S2 and S3).

At baseline, the most frequently prescribed beta-blockers were bisoprolol (in 71.5% of patients), acebutolol (in 10.8%), atenolol (in 8.7%), nebivolol (in 5.9%), metoprolol (in 1.2%), carvedilol (in 1.1%), and celiprolol, sotalol, celectol, betaxolol, propranolol, or nadolol (all in <1.0%). The distribution and the average dose of the beta-blocker between the two groups appeared to be similar (Table S4). The median resting heart rate during the randomization visit was 63 beats per minute (interquartile range, 57 to 71). Patients were followed for a median of 3.0 years (interquartile range, 2.0 to 4.0). Crossover from one strategy to the other occurred in 209 patients (5.7%) and was more frequent in the interruption group (158 patients [8.6%]) than in the continuation group (51 patients [2.8%]).

OUTCOMES

At the longest follow-up, data regarding the primary outcome were missing for 34 patients in the interruption group and for 31 patients in the continuation group. A primary-outcome event occurred in 432 of 1812 patients (23.8%) in the interruption group and 384 of 1821 patients (21.1%) in the continuation group (risk difference, 2.8 percentage points; 95% confidence interval [CI], <0.1 to 5.5), for a hazard ratio of 1.16 (95% CI, 1.01 to 1.33; P=0.44 for noninferiority) (Fig. 1 and Table 2).

Death occurred in 76 patients (4.1%) in the interruption group and 74 (4.0%) in the continuation group; myocardial infarction occurred in 46 patients (2.5%) and 44 patients (2.4%), respectively; stroke occurred in 18 patients (1.0%) and 19 patients (1.0%), respectively; and hospitalization for cardiovascular causes occurred in 349 patients (18.9%) and 307 patients (16.6%), respectively. Estimates of the event rate during follow-up are provided in Table S5. The results appeared to be consistent across the prespecified subgroups (Fig. S3). The results of the per-protocol analysis appeared to be similar to the findings of the intention-to-treat analysis (Table S6).

The composite end point of death, myocardial infarction, or stroke occurred in 132 patients (7.2%) in the interruption group and 126 patients (6.8%) in the continuation group. The composite end point of death, myocardial infarction, stroke, or hospitalization for heart failure occurred in 155 patients (8.4%) in the interruption group and 141 patients (7.6%) in the continuation group (Table 2).

The Kaplan–Meier event rates for the primary and secondary end points are shown in Figure 2. In this time-to-event analysis, the risk of the primary cardiovascular end point was 21.8% in

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society. Downloaded from nejm.org at Chinese Academy of Medical Sciences (CAMS) on March 29, 2025. For personal use only. No other uses without permission. Copyright © 2024 Massachusetts Medical Society. All rights reserved.

Table 2. Primary and Secondary End Points (Intention-to-Treat Population).

End Point	Beta-Blocker Interruption (N=1846)	Beta-Blocker Continuation (N=1852)	Risk Difference (95% CI)*	Hazard Ratio (95% CI)*	P Value††
Primary end point					
Composite of death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for cardiovascular reason — no./total no. (%)	432/1812 (23.8)	384/1821 (21.1)	2.8 (<0.1 to 5.5)	1.16 (1.01 to 1.33)	0.44
Secondary end points					
Composite of death, myocardial infarction, or stroke — no. (%)	132 (7.2)	126 (6.8)	0.4 (–1.3 to 2.0)	1.05 (0.82 to 1.34)	
Composite of death, myocardial infarction, stroke, or hospitalization for heart failure — no. (%)	155 (8.4)	141 (7.6)	0.8 (–1.0 to 2.5)	1.11 (0.88 to 1.39)	
Death — no. (%)	76 (4.1)	74 (4.0)			
Cardiovascular cause	28 (1.5)	21 (1.1)			
Noncardiovascular cause	44 (2.4)	48 (2.6)			
Undetermined cause	4 (0.2)	5 (0.3)			
Myocardial infarction — no. (%)	46 (2.5)	44 (2.4)			
Type 1: spontaneous	36 (2.0)	32 (1.7)			
Type 2: related to ischemic imbalance	1 (0.1)	0 (0.0)			
Type 4a: related to percutaneous coronary intervention	2 (0.1)	1 (0.1)			
Type 4b: related to stent thrombosis	8 (0.4)	11 (0.6)			
Stroke — no. (%)	18 (1.0)	19 (1.0)			
Ischemic	14 (0.8)	14 (0.8)			
Hemorrhagic	1 (0.1)	1 (0.1)			
Transient ischemic attack	3 (0.2)	4 (0.2)			
Hospitalization for cardiovascular reason — no. (%)	349 (18.9)	307 (16.6)			
Coronary-related reason	263 (14.2)	221 (11.9)			
Angina or ischemia	67 (3.6)	55 (3.0)			
Angiography	146 (7.9)	117 (6.3)			
Percutaneous coronary intervention	90 (4.9)	84 (4.5)			
Coronary-artery bypass grafting	4 (0.2)	4 (0.2)			
Heart failure	34 (1.8)	23 (1.2)			
Tachycardia					
Supraventricular	28 (1.5)	28 (1.5)			
Ventricular	6 (0.3)	7 (0.4)			
Syncope or dizziness	28 (1.5)	25 (1.3)			
Invasive procedure aside from pacemaker implantation	31 (1.7)	24 (1.3)			
Pacemaker or equivalent implantation	11 (0.6)	11 (0.6)			
Conduction disorder	2 (0.1)	2 (0.1)			
High blood pressure	5 (0.3)	3 (0.2)			
Peripheral artery disease or limb ischemia	34 (1.8)	23 (1.2)			
Aortic dissection or aneurysm	4 (0.2)	8 (0.4)			
Valvular reason	4 (0.2)	4 (0.2)			
Bleeding event	18 (1.0)	15 (0.8)			
Other cardiovascular event	18 (1.0)	11 (0.6)			

* Wald-type 95% confidence intervals are presented. Confidence intervals for secondary end points have not been adjusted for multiplicity and may not be used in place of hypothesis testing.

† Noninferiority was met if the upper limit of the two-sided 95% confidence interval for the risk difference was less than 3 percentage points. Shown is the P value for noninferiority after multiple imputation by the Markov chain Monte Carlo method. The P value for a sensitivity analysis on completed cases was similar to that for the primary end point (P=0.43).

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society. Downloaded from nejm.org at Chinese Academy of Medical Sciences (CAMS) on March 29, 2025. For personal use only. No other uses without permission. Copyright © 2024 Massachusetts Medical Society. All rights reserved.

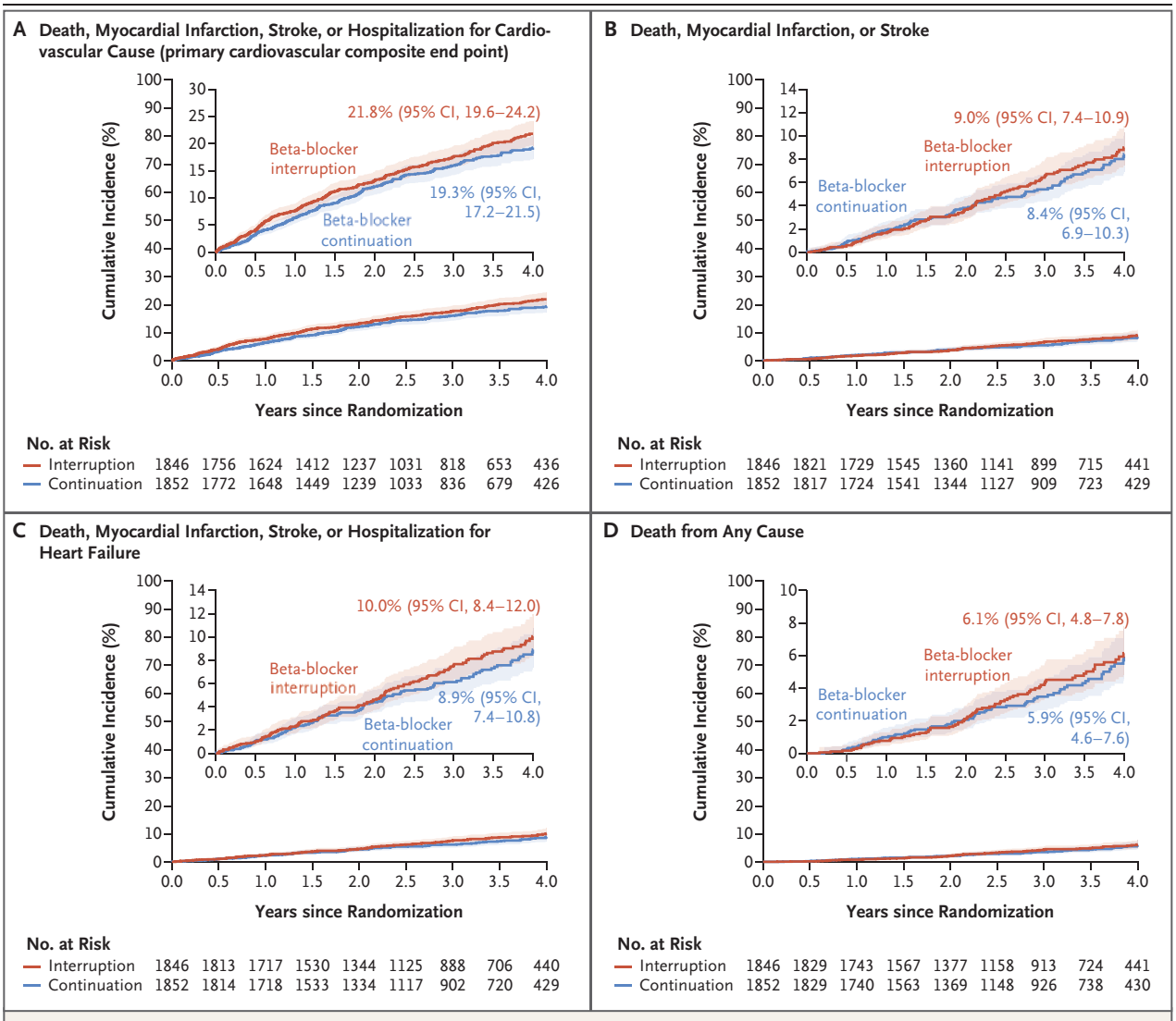

Figure 2. Time-to-Event Analysis of Primary and Confirmatory Secondary Efficacy End Points.

Shown are Kaplan–Meier estimates of the cumulative incidence of the primary cardiovascular composite end point (Panel A); the composite end point of death, nonfatal myocardial infarction, or nonfatal stroke (Panel B); the composite end point of death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure (Panel C); and death from any cause (Panel D). The definitions of all end points are provided in the Supplementary Appendix. Results for the secondary end points are reported as point estimates and 95% confidence intervals, which are shown for each curve. The widths of these confidence intervals have not been adjusted for multiplicity and therefore should not be used to infer definitive treatment effects for these secondary end points. In each panel, the inset shows the same data on an enlarged y axis.

the interruption group and 19.3% in the continuation group; the risk of death, myocardial infarction, or stroke was 9.0% and 8.4%, respectively; the risk of death, myocardial infarction, stroke, or hospitalization for heart failure was 10.0% and 8.9%, respectively; and the risk of death from any cause was 6.1% and 5.9%, respectively. Because the trial design was testing a drug-withdrawal strategy, safety events related to beta-blocker interruption are reported in Table 2.

QUALITY OF LIFE

Among the 3698 patients who underwent randomization, 3625 patients (98.0%), answered the baseline EQ-5D questionnaire and 3331 patients (90.1%) answered the follow-up questionnaire to evaluate the difference in quality of life. The ab-

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society.
Downloaded from nejm.org at Chinese Academy of Medical Sciences (CAMS) on March 29, 2025. For personal use only.
No other uses without permission. Copyright © 2024 Massachusetts Medical Society. All rights reserved.

Table 3. Scores on European Quality of Life–5 Dimensions (EQ-5D) Questionnaire.*

Variable	Beta-Blocker Interruption (N=1846)	Beta-Blocker Continuation (N=1852)	Difference (95% CI)
EQ-5D score at baseline			
No. of patients with data	1804	1821	
Mean score	0.866±0.181	0.866±0.182	
Median score (IQR)	0.910 (0.817–1.000)	0.910 (0.817–1.000)	
Peak EQ-5D score at 6 or 12 mo			
No. of patients with data	1674	1657	
Mean score	0.901±0.168	0.897±0.176	
Median score (IQR)	1.000 (0.872–1.000)	1.000 (0.872–1.000)	
Absolute change in EQ-5D score from baseline to last follow-up			
No. of patients with data	1639	1631	
Mean difference	0.033±0.150	0.032±0.164	0.002 (–0.008 to 0.012)†
Median difference (IQR)	0.000 (0.000–0.090)	0.000 (0.000–0.090)	

* Plus–minus values are means ±SD. Scores on the EQ-5D range from 0 to 1, with higher scores indicating better health status (minimal clinically important difference, 0.05 points).
† The mean between-group difference was calculated with the use of multivariate imputation by chained equations on the basis of imputed data sets. The width of the confidence interval has not been adjusted for multiplicity and may not be used in place of hypothesis testing.

solute change in the score between baseline and the last follow-up was 0.033±0.150 in the interruption group and 0.032±0.164 in the continuation group (mean difference, 0.002; 95% CI, −0.008 to 0.012) (Table 3). Patient-reported secondary outcomes are provided in Tables S7 through S12.

DISCUSSION

In our trial, we tested the hypothesis that the interruption of beta-blocker therapy would be noninferior to the continuation of such therapy over a 3-year follow-up period among patients with a history of myocardial infarction. However, the noninferiority of this strategy was not shown with respect to the risk of death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for cardiovascular reasons (the composite primary outcome). In addition, interruption of beta-blocker therapy did not result in an improvement in patient-reported quality of life. Beta-blocker interruption was associated with a numerical increase in the risk of recurrent angina and other coronary-related conditions leading to hospitalization and coronary procedures, although hypothesis testing was not performed for these end points.

Improvements in acute myocardial infarction care and prognosis have led physicians to believe that long-term beta-blocker treatment may not be useful unless patients have another primary indication for these agents, such as heart failure, left ventricular dysfunction, arrythmias, or residual angina. Current guidelines state that beta-blockers have no benefit after 1 year in certain patient groups and recommend their discontinuation[3] on the basis of expert opinion and results from large registries. We conducted the ABYSS trial to evaluate these recommendations, but our results did not show the noninferiority of interruption, as compared with continuation, with respect to cardiovascular events. There was no apparent difference between the groups regarding quality of life, despite the current belief among many physicians and patients that this class of drugs has a poor side-effect profile.

The differences between the groups with re-

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society.
Downloaded from nejm.org at Chinese Academy of Medical Sciences (CAMS) on March 29, 2025. For personal use only.
No other uses without permission. Copyright © 2024 Massachusetts Medical Society. All rights reserved.

spect to hospitalization for cardiovascular reasons associated with the interruption strategy and the absence of improvement in patient-reported quality of life question the rationale and current recommendations for the interruption of a class of drugs with an acceptable side-effect profile in patients with previous myocardial infarction. The numerical difference between the groups with respect to hospitalization for coronary-related reasons reminds us that Sir James Whyte Black revolutionized the medical management of angina pectoris in 1964 when he synthesized propranolol, the first beta-adrenoceptor antagonist to decrease hospitalization rates in patients with chronic coronary syndromes.

Our trial has several limitations. First, the trial was not blinded, which may have influenced several outcomes, including evaluation of quality of life. Second, we anticipated that in daily practice patients who have a history of myocardial infarction would be treated with less-than-effective doses of beta-blockers, as suggested in previous reports,[11,12] but the baseline heart rate of our patients seems to indicate appropriate use of beta-blockers. Third, the trial was conducted within a single country, so results may not be generalizable to other health care systems with different practices. Finally, the trial evaluated hard clinical end points but also hospitalization for cardiovascular events; the latter is subject to potential bias with a PROBE trial design, but all events were adjudicated in a blinded fashion.

Our results should be considered within the context of the recent results of the open-label REDUCE-AMI (Randomized Evaluation of Decreased Usage of Beta-Blockers after Acute Myocardial Infarction) registry-based trial,[13] which suggested that oral beta-blockers that were initiated during the acute phase of myocardial infarction did not lead to a lower risk of death or new myocardial infarction, a finding that is consistent with our own results regarding these end points. However, the main difference with our results is that we found an increase in hospitalization for cardiovascular reasons with beta-blocker interruption, an end point that was not evaluated in REDUCE-AMI. Other trials that are evaluating the superiority of beta-blockers after an uncomplicated myocardial infarction with preserved left ventricular ejection fraction are ongoing,[14-16] including the SMART-DECISION trial (ClinicalTrials.gov number, NCT04769362), in which investigators are also evaluating beta-blocker interruption in patients with stable chronic coronary artery disease who were considered to be at low risk late after the index event.[17]

Interruption of long-term beta-blocker treatment in patients with a history of myocardial infarction was not shown to be noninferior to a strategy of beta-blocker continuation with respect to a composite outcome of death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for cardiovascular reasons, nor did it seem to improve the patients' quality of life.

Supported by a grant (PHRC-2015) from the French Ministry of Health and the ACTION (Allies in Cardiovascular Trials, Initiatives, and Organized Networks) Study Group.

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.

APPENDIX

The authors' full names and academic degrees are as follows: Johanne Silvain, M.D., Ph.D., Guillaume Cayla, M.D., Ph.D., Emile Ferrari, M.D., Ph.D., Grégoire Range, M.D., Etienne Puymirat, M.D., Ph.D., Nicolas Delarche, M.D., Paul Guedeney, M.D., Ph.D., Thomas Cuisset, M.D., Ph.D., Fabrice Ivanes, M.D., Ph.D., Thibault Lhermusier, M.D., Ph.D., Thibault Petroni, M.D., Ph.D., Gilles Lemesle, M.D., Ph.D., François Bresoles, M.D., Jean-Noël Labeque, M.D., Thibaut Pommier, M.D., Jean-Guillaume Dillinger, M.D., Ph.D., Florence Leclercq, M.D., Ph.D., Franck Boccara, M.D., Ph.D., Pascal Lim, M.D., Ph.D., Timothée Besseyre des Horts, M.D., Thierry Fourme, M.D., François Jourda, M.D., Alain Furber, M.D., Ph.D., Benoit Lattuca, M.D., Ph.D., Nassim Redjimi, M.D., Ph.D., Christophe Thuaire, M.D., Pierre Deharo, M.D., Niki Procopi, M.D., Raphaelle Dumaine, M.D., Michel Slama, M.D., Ph.D., Laurent Payot, M.D., Mohamad El Kasty, M.D., Karim Aacha, M.D., Abdourahmane Diallo, Ph.D., Eric Vicaut, M.D., Ph.D., and Gilles Montalescot, M.D., Ph.D.

The authors' affiliations are as follows: Sorbonne Université, ACTION Group, INSERM Unité Mixte de Recherche (UMRS) 1166, Hôpital Pitié–Salpêtrière Assistance Publique–Hôpitaux de Paris (AP-HP) (J.S., P.G., N.P., K.A., G.M.), the Department of Cardiology, Hôpital Européen Georges Pompidou, AP-HP, Université Paris Cité (E.P.), FACT (French Alliance for Cardiovascular Trials) (G.L.), the Department of Cardiology, Université Paris Cité, Hôpital Lariboisière, AP-HP, INSERM Unité 942 (J.-G.D.), the Cardiology Department, Hôpital Saint-Antoine, ACTION Group, Sorbonne Université, INSERM UMRS 938 (F. Boccara), the Cardiology Department Hôpital Bichat, AP-HP (M.S.), Unité de Recherche Clinique, ACTION Group, Hôpital Fernand Widal (AP-HP) (A.D., E.V.), and SAMM (Statistique, Analyse et Modélisation Multidisciplinaire) EA 4543, Université Paris 1 Panthéon Sorbonne (A.D., E.V.), Paris, the Cardiology Department, Nimes University Hospital, Montpellier University, ACTION Group, Nimes (G.C., B.L.), the Cardiology Department, Pasteur University Hospital, Nice (E.F., N.R.), the Cardiology Department, Hôpitaux de Chartres, ACTION Group, Hôpital Louis Pasteur, Chartres (G.R., C.T.), Cardiology Department, Hôpital Centre François Mitterrand de Pau, Pau (N.D.), Département de Cardiologie, Centre Hospitalo–Universitaire (CHU) La Timone, ACTION Group, Marseille University, INSERM, Marseille (T.C., P.D.), the Cardiology

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society. Downloaded from nejm.org at Chinese Academy of Medical Sciences (CAMS) on March 29, 2025. For personal use only. No other uses without permission. Copyright © 2024 Massachusetts Medical Society. All rights reserved.

Department, CHU Tours, INSERM Unité 1327 ISCHEMIA, Université de Tours, Tours (F.I.), the Cardiology Department, CHU de Toulouse, Toulouse (T.L.), the Cardiology Department, Clinique du Pont de Chaume, Montauban (T. Petroni), the Heart and Lung Institute, University Hospital of Lille, and Institut Pasteur of Lille, INSERM Unité 1011-EGID, Lille (G.L.), the Cardiology Department, CHU d'Avignon, Avignon (F. Bresoles), the Cardiology Group of the Côte Basque, Bayonne (J.-N.L.), the Cardiology Department, CHU de Dijon Bourgogne, Dijon (T. Pommier), the Cardiology Department, CHU de Montpellier, Montpellier (F.L.), the Cardiology Department, CHU Henri Mondor, Créteil (P.L.), the Cardiology Department, Centre Hospitalier (CH) Métropole-Savoie (Hôpital Chambéry), Chambéry (T.B.H.), the Cardiology Department, Groupe Hospitalier Mutualiste (GHM) de Grenoble, Grenoble (T.F.), the Cardiology Department, CHU d'Auxerre, Auxerre (F.J.), Cardiology Department, CHU Angers et UMR Centre National de la Recherche Scientifique (CNRS) 6015, INSERM Unité 1083 Equipe Physiopathologie Cardiovasculaire, Unité de Formation et de Recherche (UFR) Santé, Angers (A.F.), Grands Prés Cardiac Rehabilitation Centre, St. Denis (R.D.), the Cardiology Department, General Hospital Yves Le Foll, Saint-Brieuc (L.P.), and the Cardiology Department, Grand Hôpital de l'Est Francilien Site Marne-La-Vallée, Jossigny (M.E.K.) — all in France.

REFERENCES

1. Martin SS, Aday AW, Almarzooq ZI, et al. 2024 Heart disease and stroke statistics: a report of us and global data from the American Heart Association. Circulation 2024;149(8):e347-e913.

2. Zuin M, Rigatelli G, Temporelli P, et al. Trends in acute myocardial infarction mortality in the European Union, 2012-2020. Eur J Prev Cardiol 2023;30:1758-71.

3. 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):e9-e119.

4. Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC guidelines for the management of acute coronary syndromes. Eur Heart J 2023;44:3720-826.

5. Zeitouni M, Kerneis M, Lattuca B, et al. Do patients need lifelong beta-blockers after an uncomplicated myocardial infarction? Am J Cardiovasc Drugs 2019; 19:431-8.

6. 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;136:1908-19.

7. Holt A, Blanche P, Zareini B, et al. Effect of long-term beta-blocker treatment following myocardial infarction among stable, optimally treated patients without heart failure in the reperfusion era: a Danish, nationwide cohort study. Eur Heart J 2021;42:907-14.

8. Park CS, Yang H-M, Ki Y-J, et al. Left ventricular ejection fraction 1 year after acute myocardial infarction identifies the benefits of the long-term use of beta-blockers: analysis of data from the KAMIR-NIH Registry. Circ Cardiovasc Interv 2021; 14(4):e010159.

9. Puymirat E, Riant E, Aissaoui N, et al. β Blockers and mortality after myocardial infarction in patients without heart failure: multicentre prospective cohort study. BMJ 2016;354:i4801.

10. Kim J, Kang D, Park H, et al. Long-term β-blocker therapy and clinical outcomes after acute myocardial infarction in patients without heart failure: nationwide cohort study. Eur Heart J 2020;41: 3521-9.

11. Silvain J, Cayla G, Ferrari E, et al. βeta Blocker interruption after uncomplicated myocardial infarction: rationale and design of the randomized ABYSS trial. Am Heart J 2023;258:168-76.

12. Komajda M, Cosentino F, Ferrari R, et al. Profile and treatment of chronic coronary syndromes in European Society of Cardiology member countries: the ESC EORP CICD-LT registry. Eur J Prev Cardiol 2021;28:432-45.

13. 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.

14. Kristensen AMD, Bovin A, Zwisler AD, et al. Design and rationale of the Danish trial of beta-blocker treatment after myocardial infarction without reduced ejection fraction: study protocol for a randomized controlled trial. Trials 2020;21: 415.

15. Munkhaugen J, Ruddox V, Halvorsen S, et al. BEtablocker Treatment After acute Myocardial Infarction in revascularized patients without reduced left ventricular ejection fraction (BETAMI): rationale and design of a prospective, randomized, open, blinded end point study. Am Heart J 2019;208:37-46.

16. Rossello X, Raposeiras-Roubin S, Latini R, et al. Rationale and design of the pragmatic clinical trial tREatment with Beta-blockers after myOcardial infarction with-Out reduced ejection fracTion (REBOOT). Eur Heart J Cardiovasc Pharmacother 2022; 8:291-301.

17. Suc G, Zeitouni M, Procopi N, et al. Beta-blocker prescription and outcomes in uncomplicated acute myocardial infarction: insight from the ePARIS registry. Arch Cardiovasc Dis 2023;116:25-32.

Copyright © 2024 Massachusetts Medical Society.

The New England Journal of Medicine is produced by NEJM Group, a division of the Massachusetts Medical Society. Downloaded from nejm.org at Chinese Academy of Medical Sciences (CAMS) on March 29, 2025. For personal use only. No other uses without permission. Copyright © 2024 Massachusetts Medical Society. All rights reserved.