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FULL RESEARCH PAPER
Coronary artery disease

Safety of beta-blocker discontinuation after acute coronary syndromes with preserved or mildly reduced left ventricular ejection fraction: a target trial emulation from a real-world cohort

Nicolas Johner [1], Mattia Branca [2], David Carballo [1], Stéphanie Baggio[3,4], David Nanchen[5], Elena Tessitore [1], Lorenz Räber [6], Thomas Felix Lüscher[7], Christian M. Matter[8], Stephan Windecker [6], Nicolas Rodondi [3,9], François Mach[1], and Baris Gencer [1,3,10]*

[1]Cardiology Division, Geneva University Hospitals, Rue Gabrielle-Perret-Gentil 4, 1205 Geneva, Switzerland; [2]CTU Bern, Department of Clinical Research, University of Bern, Bern, Switzerland; [3]Institute of Primary Healthcare (BIHAM), University of Bern, Mittelstrasse 43, 3012 Bern, Switzerland; [4]Laboratory of Population Health (#PopHealthLab), University of Fribourg, Fribourg, Switzerland; [5]Center for Primary Care and Public Health (Unisanté), University of Lausanne, Lausanne, Switzerland; [6]Department of Cardiology, Bern University Hospital, University of Bern, Bern, Switzerland; [7]Center for Molecular Cardiology, University of Zurich, Zurich, Switzerland; [8]Department of Cardiology, University Hospital Zurich, Zurich, Switzerland; [9]Department of General Internal Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; and [10]Department of Cardiology, Lausanne University Hospital, Rue du Bugnon 46, 1005 Lausanne, Switzerland

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Aims The benefit of long-term beta-blocker therapy after acute coronary syndromes (ACS) without heart failure in the reperfusion era is uncertain. Two recent randomized trials found conflicting results. The present study assessed the safety of beta-blocker discontinuation within 12 months following ACS with left ventricular ejection fraction (LVEF) ≥40%.

Methods and results In a multicentre prospective real-world cohort ($n = 3762$) of patients hospitalized for ACS, patients with LVEF ≥40% and beta-blockers at discharge were included. Patients who continued beta-blockers at 1 year were compared with those who discontinued beta-blockers within 12 months post-ACS using target trial emulation and inverse probability weighting over an additional 4-year follow-up. The primary endpoint was major adverse cardiovascular events (MACE), a composite of 4-year cardiovascular death, myocardial infarction, stroke, transient ischaemic attack, unplanned coronary revascularization, or unstable angina hospitalization. Of 2077 patients, 1758 (85%) continued beta-blockers and 319 (15%) had discontinued beta-blockers at 1 year. The risk of the primary endpoint was similar in both groups [14.1 vs. 14.3% with beta-blocker discontinuation vs. continuation; adjusted hazard ratio (aHR) = 0.98; 95% confidence interval, 0.72–1.34, $P = 0.91$]. Subgroup analysis suggested a higher risk of primary endpoint with beta-blocker discontinuation after STEMI [aHR = 1.46 (0.99–2.16)] compared with NSTEMI [aHR = 0.70 (0.40–1.22), $P_{interaction} = 0.033$], whereas there was no interaction with LVEF ($P_{interaction} = 0.68$).

Conclusion Beta-blocker discontinuation within 12 months following ACS with LVEF ≥40% was not associated with an increased risk of MACE compared with long-term beta-blocker therapy. Subgroup analysis suggested potential risk in STEMI patients. Discontinuing beta-blockers 12 months after ACS appears safe in patients with LVEF ≥40%, particularly after NSTEMI.

Lay summary

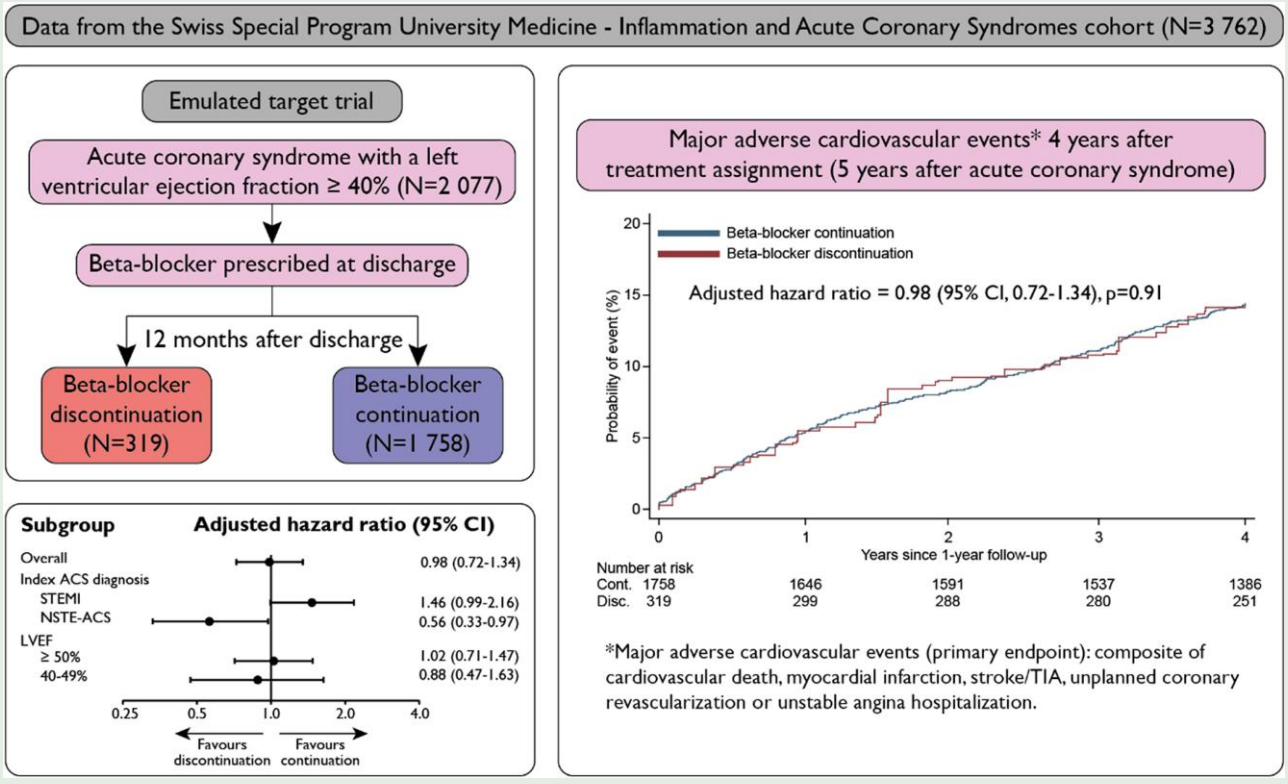
- Beta-blockers are part of the standard drug therapy prescribed to prevent adverse health events in patients who suffered from myocardial infarction. However, the studies that established their benefit were conducted before the advent of

* Corresponding author. Tel: +0041795565960, Email: baris.gencer@chuv.ch

modern therapies, which have since then dramatically changed the prognosis. The benefit of long-term beta-blockers in the contemporary era has therefore been questioned. The present study assessed the safety of beta-blocker discontinuation within 12 months after myocardial infarction in patients who did not have severely impaired heart function.

- Beta-blocker discontinuation within 12 months after myocardial infarction was safe, as it was not associated with a higher risk of major adverse cardiovascular events or death, compared with long-term beta-blocker continuation.
- Patients who presented with acute occlusion of a coronary artery—a severe type of myocardial infarction referred to as 'ST-elevation myocardial infarction'—may still benefit from long-term beta-blocker therapy based on subgroup analysis.

Graphical Abstract



Graphical summary of the emulated target trial (top left), using data form a real-world prospective cohort. Kaplan–Meier plot (right) of the cumulative probability of primary outcome during the 4-year follow-up. The primary outcome was major adverse cardiovascular events (the composite of cardiovascular death, myocardial infarction, stroke or transient ischaemic attack, unplanned coronary revascularization, or hospitalization for unstable angina). Subgroup analysis of the primary outcome (bottom left). CI denotes confidence interval; Cont., beta-blocker continuation; Disc., beta-blocker discontinuation; LVEF, left ventricular ejection fraction; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischaemic attack.

Keywords Beta-blocker • Acute coronary syndrome • Myocardial infarction • STEMI • NSTEMI • Preserved ejection fraction • Mildly reduced ejection fraction • Secondary prevention • Rehabilitation

Introduction

Beta-blockers have been shown to improve early and long-term cardiovascular outcomes following acute coronary syndromes (ACS), including in patients without heart failure.[1,2] However, most trials showing the efficacy of beta-blockers after ACS predate the advent of reperfusion therapy and modern secondary prevention treatments such as intensive lipid-lowering therapy and antiplatelet agents.[3] In a meta-analysis of 60 randomized trials that included 102 003 patients with ACS, beta-blocker therapy reduced 1-year mortality in the pre-reperfusion era, but not in the reperfusion era.[2] In addition, data regarding adequate duration of beta-blocker therapy following ACS, and safety of eventual discontinuation, is scarce. Most randomized trials reported follow-up periods up to 1 year and few extended beyond 2–3 years.[2,4] Likewise, several contemporary observational studies have failed to show the prognostic benefit of beta-blockers beyond 1–12 months after ACS.[5–13] Some evidence raises the question of potential harm, with one landmark analysis from randomized trials showing an increase in heart failure with beta-blocker use between 30 days and 1 year after ACS.[2] Most recently, the REDUCE-AMI randomized trial[14]

in patients with preserved ejection fraction (≥50%) after ACS showed no benefit of early beta-blockade on outcomes. In contrast, the ABYSS randomized trial[15] tested the non-inferiority of beta-blocker discontinuation compared with continuation, with randomization taking place a median 2.9 years after ACS in patients with a left ventricular ejection fraction (LVEF) ≥ 40%. The ABYSS trial did not meet its non-inferiority endpoint, and results in fact showed a higher rate of primary outcome (death, myocardial infarction, stroke, or cardiovascular hospitalization) with beta-blocker discontinuation. There is therefore an unmet need to determine the effects of long-term beta-blocker use after ACS with preserved or mildly reduced ejection fraction, and the safety of eventual beta-blocker discontinuation in this population. In addition, real-world data in a large well-characterized real-world prospective cohort are scarce.

We sought to evaluate the safety of beta-blocker discontinuation within 12 months following ACS in patients with an LVEF ≥40% at discharge, compared with continued long-term beta-blocker therapy, with respect to the incidence of major adverse cardiovascular events (MACE) at 5 years post-ACS. Secondary endpoints included all-cause death, the composite of cardiovascular death or myocardial infarction, and the negative control outcome of non-cardiovascular death. Exploratory subgroup analysis was performed by age, sex, body mass index (BMI), type of ACS, diabetes mellitus, LVEF, and beta-blocker use prior to index ACS.

Methods

Study design

Using observational prospective cohort data, a target trial emulation design was pursued to emulate a randomized controlled trial in which ACS patients who were prescribed beta-blocker therapy upon discharge of the index hospitalization would be randomized, at 1-year post-ACS, to continue or discontinue their beta-blocker, with subsequent follow-up for an additional 4 years (i.e. a total of 5 years after the index ACS).

Study population

Data were derived from the Swiss Special Program University Medicine—Inflammation and Acute Coronary Syndromes (SPUM-ACS) cohort (trial registration: NCT01000701). Details on patient inclusion and follow-up have been described previously.[16] Briefly, the SPUM-ACS cohort is a multicentre prospective cohort initiated in 2009 that studies patients hospitalized for ACS and referred for invasive management in four tertiary care centers in Switzerland (Bern, Geneva, Lausanne, Zurich). At the time of the present analysis, 5-year follow-up data were available for patients enrolled from 2009 to 2017.

We included ACS patients with an LVEF ≥40%[4,17] at the time of the index hospitalization, for whom beta-blockers were prescribed at discharge, and who had completed the 5-year follow-up (i.e. patients who were lost to follow-up or who withdrew from the 5-year visit, but not those who had died, had to be excluded from the analysis because no intermediate contacts between 1 and 5 years were available for this cohort). LVEF was determined based on transthoracic echocardiography (TTE) data from the index hospitalization. In the absence of available TTE, ventriculography data from index angiography were used. Patients without TTE or ventriculography data at index hospitalization were not included in the study.

Management and follow-up

Patients were managed following standard of care at the discretion of the physicians in charge, including invasive reperfusion in the acute setting, long-term secondary prevention with optimal medical therapy, and participation to a cardiac rehabilitation programme. Study follow-up visits took place at 1 and 5 years. Information on beta-blocker use was collected at discharge, at the 1-year follow-up, as well as the 5-year follow-up. In case of beta-blocker discontinuation, the date of discontinuation was collected at the next follow-up visit and the reason for discontinuation was self-reported by the patient. Likewise, we collected data on secondary prevention drugs, including antiplatelet therapy, oral anticoagulation, lipid-lowering therapy, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs).

Outcomes

The primary outcome was the 4-year (5 years post-ACS) risk of MACE, defined as the composite of cardiovascular death, myocardial infarction, stroke or transient ischaemic attack, unplanned coronary revascularization, or hospitalization for unstable angina. Secondary outcomes were all-cause death and a composite of cardiovascular death and myocardial infarction as done in a previous systematic review.[18] Non-cardiovascular death was used as a negative control outcome. The occurrence of MACE at the 5-year follow-up was adjudicated by a panel of independent clinicians. The causes of death were determined based on medical records.

Statistical analysis

We used a target trial emulation design.[19] Briefly, this is a method to emulate a target randomized controlled trial from observational data in an effort to answer a causal question, using similar principles as randomized trials while accounting for potential bias. Patients who continued beta-blockers at 1 year were compared with those who discontinued beta-blockers at any time throughout the first year after ACS. The time zero of the target trial was defined as the 1-year visit. A sensitivity analysis was performed with time zero defined as the date of beta-blocker discontinuation (occurring no later than 1 year post-ACS) to account for immortal time.

Continuous variables are described using mean with standard deviation or median with interquartile range. Categorical variables are summarized by absolute and relative frequencies. Comparisons between groups were performed using *t*-test or Mann–Whitney U-test for continuous variables, and Fisher's exact test or χ^2 test for categorical variables, as appropriate.

Inverse probability weighting (IPW), a method to adjust for confounding by indication, was used as an estimation method based on the following list of baseline characteristics: age, sex, index ACS diagnosis [ST-segment elevation myocardial infarction (STEMI) vs. non-ST-segment elevation ACS (NSTE-ACS)], LVEF, angina pectoris (none vs. CCS I vs. CCS II-IV), arterial hypertension, diabetes mellitus, prior myocardial infarction, antithrombotic therapy (any combination of single/dual antiplatelet therapy and/or oral anticoagulation), lipid-lowering therapy (any combination of statin and/or other lipid-lowering drugs), ACE inhibitor or ARB therapy, beta-blocker therapy prior to index ACS. Weights were obtained by modelling the probability of beta-blocker discontinuation given individual baseline characteristics (confounders listed above), and subsequently stabilized using the probability of beta-blocker discontinuation irrespective of baseline characteristics. Adjusted hazard ratios (aHR) were obtained with a Cox model, checking for post-estimation proportional-hazard assumptions. In case of clear violation of the proportionality assumption, survival parametric model was applied and compared with the Cox model. Primary analysis was conducted on an intention-to-treat (ITT) basis, i.e. based on beta-blocker status at the 1-year visit. A per-protocol analysis was performed secondarily by excluding patients whose beta-blocker status had changed between the 1-year and the 5-year visit (the date of beta-blocker discontinuation/resumption between years 1 and 5 was seldomly reported, precluding censoring at the date of cross-over). Post-hoc analysis of individual components of the primary endpoint was performed for descriptive purposes.

Exploratory subgroup analysis of the primary outcome was conducted based on LVEF category (≥50 vs. 40–49%), ACS type [STEMI, non-STEMI (NSTEMI) or unstable angina], age category (<70 vs. ≥70 years), sex, BMI category (≤25 vs. >25 kg/m^2), diabetes mellitus, and prior beta-blocker use. Subgroup analysis was performed in each subgroup separately, while

interaction was tested in whole-sample models, using bi- and multivariable Cox models as in the primary analysis. All models were weighted using IPW. Post-hoc analysis of the primary outcome by LVEF category (≥50 vs. 40–49%) within the STEMI subgroup was performed, as well as analysis of the secondary hard outcome of cardiovascular death or myocardial infarction. No adjustment was made for multiple hypothesis testing given the exploratory nature of subgroup analysis.

Missing data in the computation of the inverse probability weights were handled by a one-step imputation method: the mean and standard deviation of the derived weights were estimated, and the missing weights were randomly assigned a value from a normal distribution with the estimated mean and standard deviation. This simple imputation method was chosen based on a very small number of patients with missing data (see Results below) and on the distribution of the weights (very small number of extreme values). Additionally, sensitivity analysis was performed using complete cases only. Post-hoc sensitivity analysis with multiple imputation of the primary endpoint for patients who were lost to follow-up was performed. The primary endpoint was multiple imputed for missing values using logistic regressions. Variables included in the multiple imputation were: age, sex, diabetes mellitus, arterial hypertension, index ACS diagnosis, angina pectoris, single antiplatelet therapy, dual antiplatelet therapy, statin therapy, ACE inhibitor/ARB treatment, LVEF, and beta-blocker therapy at index ACS. Using the 20 imputed datasets, we conducted logistic regressions to compare the primary endpoint between the two groups (beta-blocker discontinuation vs. continuation) and the estimates on the 20 datasets were combined using Rubin's rule.

All analyses were conducted using Stata 17.0 (StataCorp. 2021. Stata Statistical Software: Release 17) and R version 4.3.1 [R Core Team (2023)] software.

Results

Study population

A total of 2077 patients with an LVEF ≥40% were included from the 3762 patients in the SPUM-ACS cohort [2374 (63%) met the inclusion criteria, of which 2077 (87%) completed follow-up]. The study flow chart is shown in *Figure 1*. At 1 year after index ACS, 1758 (85%) patients continued beta-blockers and 319 (15%) had discontinued beta-blocker therapy after a median 281 days (IQR 104–364 days). As per inclusion criteria, all patients included in the analysis completed the 5-year visit; as a result, the follow-up duration was 4 years for all patients. Missing data on variables used for IPW were present in 19 (0.9%) patients.

Baseline characteristics

Baseline characteristics (at time zero of the target trial, i.e. 1 year after index ACS) are shown in *Table 1*. Missing data are reported in Supplementary material online, *Table S1*. LVEF was assessed at index hospitalization by TTE in 1499 (72%) patients and by ventriculography in 578 (28%). TTE was performed a median 2 days (IQR 1–4 days) after index ACS. Age, sex, and LVEF did not differ significantly between the two groups. Of the 2077 patients, 1128 (54.3%) had a STEMI at index ACS, 882 (42.5%) had NSTEMI, and 66 (3.2%) had unstable angina. The proportion of STEMI at index ACS was lower in the beta-blocker discontinuation group compared with the continuation group [157 of 319 (49.2%) vs. 971 of 1758 (55.2%) patients, respectively, $P = 0.047$]. Coronary revascularization was performed with PCI in 1948 of 2077 (93.8%) patients and with CABG in 6 (0.3%) patients, whereas the treatment was conservative in 123 (5.9%) patients, without significant differences between both groups ($P = 0.30$). Baseline characteristics of the weighted groups are shown in *Table 1*. The distribution of inverse probability weights in each group is shown in Supplementary material online, *Figure S1*.

Outcomes

The primary outcome occurred in 45 of 319 (14.1%) patients in the beta-blocker discontinuation group and in 251 of 1758 (14.3%) patients in the continuation group (*Figure 2*). There was no significant difference between the two groups both before [HR, 0.99; 95% confidence interval (CI), 0.72–1.36; $P = 0.94$] and after weighting (aHR, 0.98; 95% CI, 0.72–1.34, $P = 0.91$) (*Table 2*).

Likewise, secondary outcomes did not differ between the two groups: all-cause death occurred in 17 (5.3%) and 82 (4.7%) patients in the beta-blocker discontinuation vs. continuation group, respectively (aHR, 1.08; 95% CI, 0.64–1.80; $P = 0.78$); the composite of cardiovascular death or myocardial infarction occurred in 23 (7.2%) and 121 (6.9%) patients in the beta-blocker discontinuation vs. continuation group, respectively (aHR, 0.97; 95% CI 0.62–1.52; $P = 0.89$).

The negative control outcome of non-cardiovascular death did not differ between the two groups: 9 (2.8%) and 47 (2.7%) patients died from non-cardiovascular causes in the beta-blocker discontinuation vs. continuation group, respectively (aHR, 0.82; 95% CI 0.39–1.76; $P = 0.62$).

Post-hoc analysis of components of the primary endpoint found consistent results: cardiovascular death occurred in 8 of 319 (2.5%) vs. 35 of 1758 (2.0%) patients (aHR, 1.42; 95% CI, 0.70–2.87; $P = 0.33$), myocardial infarction occurred in 17 of 319 (5.3%) vs. 89 of 1758 (5.1%) patients (aHR, 0.79; 95% CI 0.44–1.40; $P = 0.42$), stroke/transient ischaemic attack occurred in 5 of 319 (1.6%) vs. 26 of 1758 (1.5%) patients (aHR, 1.15; 95% CI, 0.47–2.82; $P = 0.76$), unplanned revascularization occurred in 28 of 319 (8.8%) vs. 182 of 1758 (10.4%) patients (aHR, 0.75; 95% CI, 0.50–1.14; $P = 0.18$), and unstable angina hospitalization occurred in 13 of 319 (4.1%) vs. 60 of 1758 (3.4%) patients (aHR, 1.38; 95% CI, 0.79–2.41; $P = 0.26$) in the discontinuation vs. continuation group, respectively.

Sensitivity analysis

In a sensitivity analysis in which time zero of the target trial was set at the date of beta-blocker discontinuation (no later than 1 year after index ACS) rather than at the 1-year visit, results were consistent with the primary analysis for the primary (aHR, 0.99; 95% CI, 0.72–1.35; $P = 0.93$) and secondary outcomes (see Supplementary material online, *Table S2*). Sensitivity analysis with IPW restricted to complete cases did not significantly change the results (see Supplementary material online, *Table S3*). Post-hoc sensitivity analysis with baseline low-density lipoprotein (LDL) cholesterol included as a covariate in IPW also did not significantly change the results (see Supplementary material online, *Table S4*). Post-hoc sensitivity analysis with multiple imputation of the primary endpoint for the 297 (12.5%) patients who were lost to follow-up found primary endpoint results to be robust, with a risk ratio of primary outcome of 0.99; 95% CI, 0.74–1.33, $P = 0.96$ with beta-blocker discontinuation compared with continuation.

Regarding cross-overs, there were 375 (21.3%) patients in the beta-blocker continuation group who had discontinued beta-blocker use at 5 years [of which 32 (8.5%) had a primary outcome event] and 45 (14.1%) patients in the beta-blocker discontinuation group who had resumed beta-blocker use at 5 years post-ACS [of which 16 (36%) had a primary outcome event]. In the per-protocol analysis (performed by excluding patients whose beta-blocker status changed from the 1-year to the 5-year visit), beta-blocker discontinuation was associated with a lower rate of primary outcome compared with beta-blocker continuation: 29 of 274 (10.8%) patients in the discontinuation group

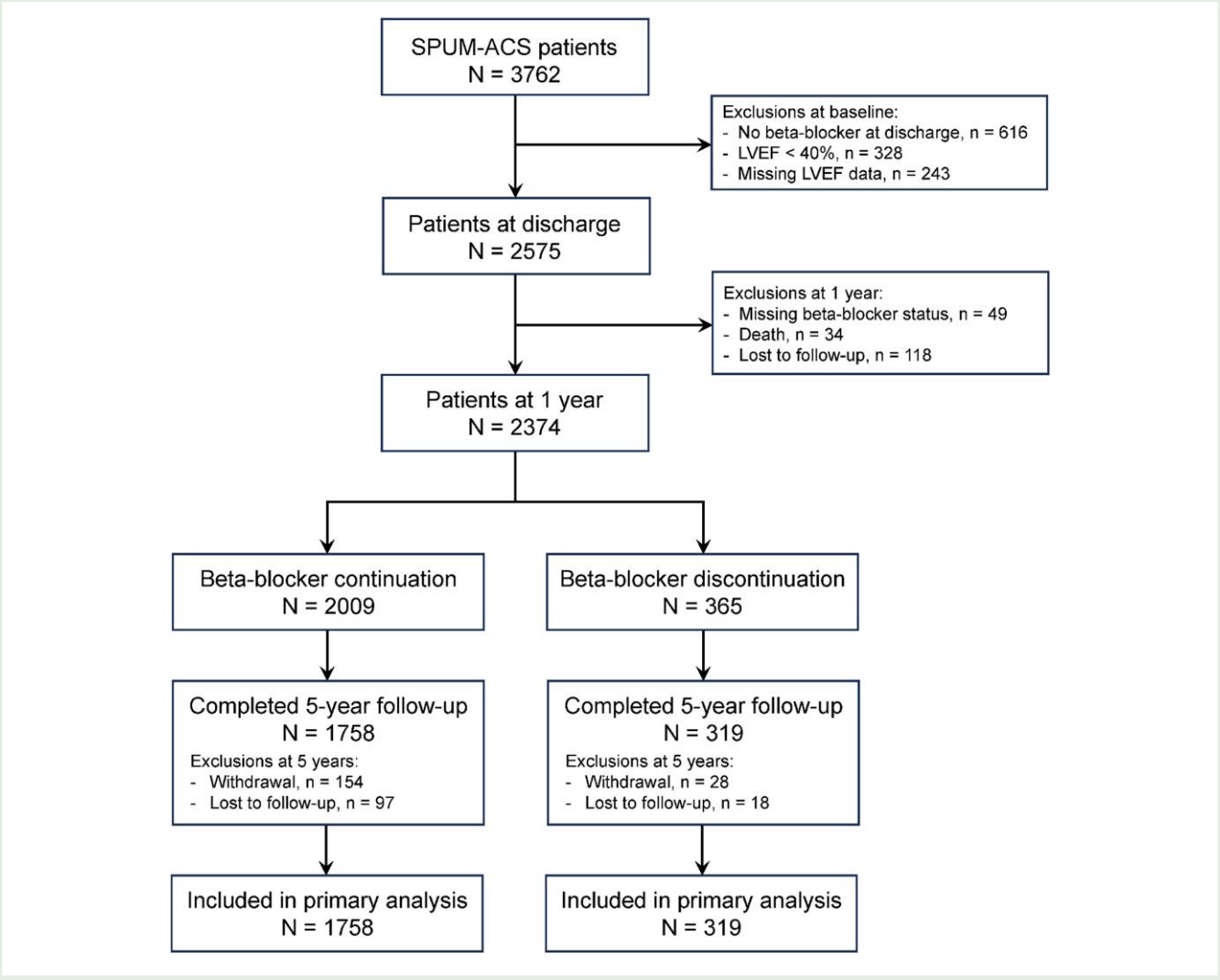


Figure 1 Study flow chart. LVEF, left ventricular ejection fraction.

vs. 219 of 1383 (16.1%) patients in the continuation group had a primary outcome event; aHR, 0.65; 95% CI, 0.45–0.96; $P = 0.029$ (unadjusted HR was similar: HR, 0.65; 95% CI 0.44–0.95; $P = 0.027$). Secondary outcomes did not differ between the two groups: all-cause death occurred in 17 (6.3%) in the discontinuation group vs. 82 (6.0%) in the continuation group (aHR, 0.97; 95% CI, 0.57–1.64; $P = 0.91$); the composite of cardiovascular death or myocardial infarction occurred in 15 (5.6%) in the discontinuation group vs. 110 (8.1%) in the continuation group (aHR, 0.65; 95% CI, 0.38–1.11; $P = 0.12$). The negative control outcome of non-cardiac death was similar in both groups, occurring in 9 (3.4%) patients in the discontinuation group vs. 47 (3.5%) in the continuation group (aHR, 0.79; 95% CI, 0.37–1.67; $P = 0.53$).

Subgroup analysis

Figure 3 shows the Forest plot for the primary outcome subgroup analysis. Interaction terms and main effects are reported in Supplementary material online, *Table S5*. The type of ACS at index hospitalization showed an interaction with beta-blocker discontinuation on the risk of primary outcome ($P_{interaction} = 0.005$): beta-blocker discontinuation was associated with a lower risk of primary outcome in NSTE-ACS [18 of 162 (11.1%) vs. 133 of 786 (16.9%) in beta-blocker discontinuation vs. continuation, respectively, aHR, 0.56; 95% CI, 0.3–0.97; $P = 0.040$], but not in STEMI, where beta-blocker discontinuation was associated with a numerically higher rate of primary outcome [27 of 157 (17.2%) vs. 118 of 971 (12.2%) in beta-blocker discontinuation vs. continuation, respectively, aHR, 1.46; 95% CI, 0.99–2.16; $P = 0.056$]. Of note, subgroup analysis with three ACS categories (STEMI, NSTEMI, and unstable angina) showed similar interaction ($P_{interaction} = 0.033$) but without significant effect of beta-blocker discontinuation within the NSTEMI [18 of 153 (11.8%) vs. 114 of 729 (15.6%) in beta-blocker discontinuation vs. continuation, respectively, aHR, 0.70; 95% CI, 0.40–1.22; $P = 0.21$] or unstable angina subgroup [0 of 9 (0%) vs. 19 of 57 (33.3%) in beta-blocker discontinuation vs. continuation, respectively, aHR, 0.00; 95% CI, 0.00-undefined; $P = 1.0$]. In contrast, there was no effect modification by LVEF: the aHR of primary outcome for beta-blocker discontinuation was 1.02 (95% CI, 0.71–1.47; $P = 0.91$) in the LVEF ≥50% subgroup compared with 0.88 (95% CI, 0.47–1.63; $P = 0.68$) in the LVEF 40–49% subgroup ($P_{interaction} = 0.68$).

Table 1 Baseline characteristics of patients 1 year after index acute coronary syndrome

		Before weighting			After weighting	
	Overall ($n = 2077$)	Beta-blocker disc. ($n = 319$)	Beta-blocker continuation ($n = 1758$)	*P* value	Beta-blocker disc. ($n = 319$)	Beta-blocker continuation ($n = 1758$)
Age (years)	62.6 ± 12.1	62.8 ± 11.9	62.6 ± 12.1	0.70	64.0 ± 11.6	62.7 ± 12.1
Female sex (*n*, %)	429 (20.7%)	66 (20.7%)	363 (20.6%)	0.99	87 (26.0%)	363 (20.7%)
BMI (kg/m^2)	27.3 ± 4.3	26.8 ± 3.6	27.4 ± 4.4	0.06	27.4 ± 4.0	27.2 ± 4.3
Index ACS diagnosis: STEMI (vs. NSTE-ACS) (*n*, %)	1128 (54.3%)	157 (49.2%)	971 (55.2%)	0.047	192 (57.5%)	954 (54.4%)
Angina pectoris (*n*, %)	169 (8.1%)	25 (7.8%)	144 (8.2%)	0.38	27 (8.2%)	143 (8.2%)
Associated conditions						
Arterial hypertension (*n*, %)	1069 (51.5%)	125 (39.2%)	944 (53.7%)	<0.001	183 (54.9%)	907 (51.7%)
Diabetes mellitus (*n*, %)	330 (15.9%)	32 (10.0%)	298 (17.0%)	0.002	46 (13.8%)	279 (15.9%)
Current smoker (*n*, %)	839 (40.4%)	140 (43.9%)	699 (39.8%)	0.17	136 (40.8%)	695 (39.6%)
Family history of CAD (*n*, %)[a]	578 (27.8%)	91 (28.5%)	487 (27.7%)	0.76	92 (27.6%)	482 (27.5%)
Hypercholesterolaemia (*n*, %)	1252 (60.3%)	199 (62.4%)	1053 (59.9%)	0.36	226 (67.7%)	1042 (59.4%)
Prior myocardial infarction (*n*, %)	241 (11.6%)	32 (10.0%)	209 (11.9%)	0.35	33 (9.8%)	204 (11.6%)
Prior stroke or TIA (*n*, %)	57 (2.7%)	7 (2.2%)	50 (2.8%)	0.52	7 (2.0%)	51 (2.9%)
COPD (*n*, %)	61 (2.9%)	11 (3.4%)	50 (2.8%)	0.55	11 (3.2%)	49 (2.8%)
History of cancer (*n*, %)	135 (6.5%)	20 (6.3%)	115 (6.5%)	0.87	22 (6.6%)	117 (6.7%)
Medication						
Antithrombotic therapy (*n*, %)[b]	2057 (99.0%)	311 (97.5%)	1746 (99.3%)	0.002	332 (99.4%)	1740 (99.2%)
Lipid-lowering therapy (*n*, %)[c]	1937 (93.3%)	269 (84.3%)	1668 (94.9%)	<0.001	313 (93.7%)	1640 (93.5%)
ACEI or ARB (*n*, %)	1189 (57.2%)	134 (42.0%)	1055 (60%)	<0.001	209 (62.6%)	1008 (57.5%)
Beta-blocker prior to ACS (*n*, %)[d]	412 (19.8%)	29 (9.1%)	383 (21.8%)	<0.001	74 (22.2%)	349 (19.9%)
Echocardiographic parameters						
Median LVEF (%, IQR)	55.0 (50, 60)	55.0 (50, 60)	55.0 (50, 60)	0.32	54.5 ± 8.4	54.6 ± 8.3

Variables used for inverse probability weighting were: age, sex, index ACS diagnosis, LVEF, angina pectoris (none vs. CCS I vs. CCS II-IV), arterial hypertension, diabetes mellitus, prior myocardial infarction, antithrombotic therapy (any combination of single/dual antiplatelet therapy and/or oral anticoagulation), lipid-lowering therapy (any combination of statin and/or other lipid-lowering drugs), ACE inhibitor or ARB therapy, and beta-blocker therapy at index ACS.

ACEI, denotes angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin II receptor blocker; BMI, body mass index; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; COPD, chronic obstructive pulmonary disease; disc., discontinuation; IQR, interquartile range; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TIA, transient ischaemic attack.

[a]First degree relative, male relatives <55 years, female relatives <65 years.

[b]Defined as any combination of single/dual antiplatelet therapy and/or oral anticoagulation.

[c]Defined as any combination of statin and/or other lipid-lowering drugs.

[d]Refers to patients who were on beta-blocker therapy at the time of index ACS, 1 year prior to inclusion in the study.

Discussion

Beta-blocker discontinuation within 12 months following ACS in patients with an LVEF ≥40% at discharge was not associated with an increased risk of MACE (cardiovascular death, myocardial infarction, stroke or transient ischaemic attack, unplanned coronary revascularization, or hospitalization for unstable angina) compared with long-term beta-blocker continuation over a follow-up of 4 years, i.e. 5 years post-ACS (aHR, 0.98; 95% CI, 0.72–1.34). Secondary outcomes showed similar findings. Subgroup analysis found a potential interaction with the ACS category, with a higher risk of primary outcome with beta-blocker discontinuation in the STEMI subgroup compared with NSTEMI or unstable angina. To place the current findings in perspective of the recent REDUCE-AMI trial that included patients with LVEF ≥50%, we found no interaction with the LVEF category (40–49 vs. ≥50%).

Prior contemporary evidence

To our knowledge, only three contemporary randomized controlled trials studied the effect of long-term beta-blocker use after ACS without reduced ejection fraction, and showed conflicting results. The recent REDUCE-AMI randomized controlled trial[14] showed that, in patients with ACS and a preserved LVEF (≥ 50%), early beta-blocker therapy was not associated with a lower risk of all-cause death or myocardial infarction compared with no beta-blocker therapy after a median follow-up of 3.5 years. Notably, patients with an LVEF 40–49% were not included. In addition, the present study tested a strategy of early beta-blocker therapy followed by discontinuation within 12 months with long-term follow-up (median 5 years after ACS), while the REDUCE-AMI trial tested early beta-blocker therapy upon discharge from index hospitalization with a median follow-up of 3.5 years after ACS. The recent ABYSS randomized controlled trial[15] was

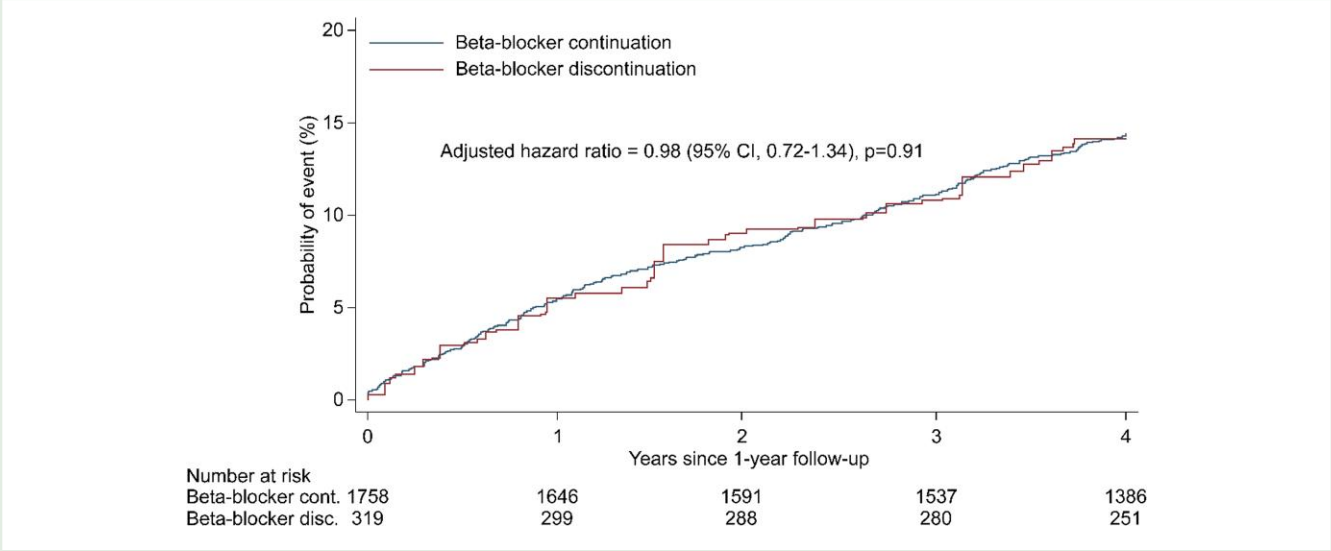


Figure 2 Kaplan–Meier plot showing the cumulative probability of major adverse cardiovascular events beyond 1 year after acute coronary syndromes in patients who continued vs. discontinued beta-blocker therapy. The data displayed are from the inverse probability weighting-adjusted population. Cont. denotes continuation; disc., discontinuation; CI, confidence interval.

Table 2 Four-year outcomes (5 years after index acute coronary syndrome)

	Beta-blocker disc. (*n* = 319)	Beta-blocker continuation (*n* = 1758)	Hazard ratio (95% CI)	*P* value	IPW Hazard ratio (95% CI)	*P* value
Primary outcome (*n*, %)	45 (14.1%)	251 (14.3%)	0.99 (0.72–1.36)	0.94	0.98 (0.72–1.34)	0.91
Secondary outcomes						
All-cause death (*n*, %)	17 (5.3%)	82 (4.7%)	1.14 (0.68–1.92)	0.63	1.08 (0.64–1.80)	0.78
Cardiovascular death or myocardial infarction	23 (7.2%)	121 (6.9%)	1.05 (0.67–1.64)	0.83	0.97 (0.62–1.52)	0.89
Non-cardiovascular death (*n*, %)	9 (2.8%)	47 (2.7%)	1.05 (0.52–2.15)	0.89	0.82 (0.39–1.76)	0.62

CI, denotes confidence interval; disc., discontinuation; IPW, inverse probability weighting.

designed to assess the non-inferiority of beta-blocker discontinuation compared with continuation among patients with an LVEF ≥40% who were stable >6 months after myocardial infarction. ABYSS did not show the non-inferiority of beta-blocker discontinuation compared with continuation with respect to all-cause death, myocardial infarction, stroke, or cardiovascular hospitalization, after a median 3.0-year follow-up. While superiority comparisons were not pre-specified, the risk of primary outcome was in fact higher in the discontinuation group (HR, 1.16, 95% CI, 1.01–1.33). Of note, ABYSS randomized patients a median 2.9 years after index myocardial infarction, potentially selecting patients who tolerated beta-blockers well, and excluding patients for whom beta-blockers had already been discontinued at the time of screening. In contrast, the present study assessed beta-blocker discontinuation within 12 months after ACS. In addition, in our real-world cohort, beta-blocker discontinuation was likely driven by clinically motivated decision-making. Moreover, primary outcome results in ABYSS were mostly driven by cardiovascular hospitalizations, which is a softer endpoint than in the present study as well as REDUCE-AMI. Finally, the CAPITAL-RCT trial[4] (*n* = 801) reported no reduction in the composite of all-cause death, myocardial infarction, heart failure hospitalization, or ACS hospitalization with carvedilol use compared with no beta-blocker during a median 3.9-year follow-up after STEMI with an LVEF ≥40% (HR, 0.75; 95% CI, 0.47–1.16; *P* = 0.2). That trial, however, was underpowered with respect to its primary endpoint and was terminated prematurely after enrolment of 801 patients out of an original target of 7600 (subsequently amended to 1300 patients).

Data from contemporary observational studies have also been conflicting. One meta-analysis[20] of observational studies found some evidence of prognostic benefit of beta-blocker use following STEMI with preserved ejection fraction (median follow-up not reported). However, the authors assessed the effect of beta-blocker use immediately after STEMI rather than a strategy of early treatment with subsequent discontinuation. In another meta-analysis[10] of 10 observational studies (*n* = 40 873), beta-blocker therapy after acute myocardial infarction was associated with a reduction in mortality; however, the effect disappeared when analysis was restricted to studies with a follow-up longer than 1 year.

More recently, several large registry studies with follow-up durations ranging 3–5 years have also suggested a time-dependent effect of beta-blocker use after ACS, with any potential prognostic benefit of beta-

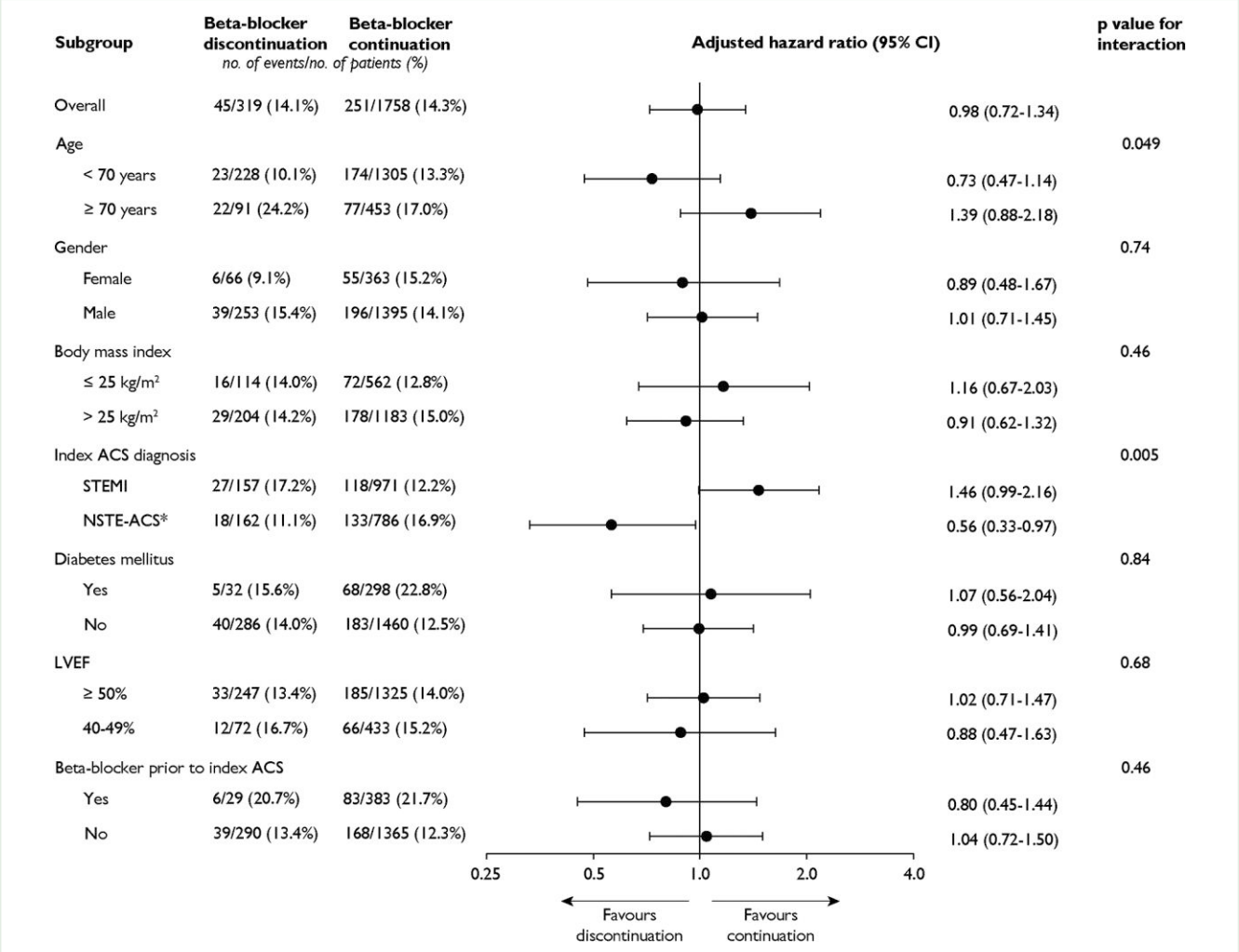


Figure 3 Subgroup analysis of the primary outcome. *See text for NSTEMI and unstable angina subgroups. ACS denotes acute coronary syndrome; CI, confidence interval; LVEF, left ventricular ejection fraction; NSTE-ACS, non-ST-elevation acute coronary syndrome; STEMI, ST-elevation myocardial infarction.

blocker continuation disappearing beyond 1–12 months after ACS,[6,8,9] even when there was a benefit of early treatment.[6] In contrast, other registry studies reported prognostic benefit of beta-blocker continuation beyond 1–2 years and over median follow-up durations of 3.5–3.8 years.[21,22]

To our knowledge, the present study is the first to assess the long-term effect of beta-blocker discontinuation within 12 months after ACS with preserved or mildly reduced ejection fraction using target trial emulation based on data from a real-world prospective cohort. Our design sought to emulate a randomized controlled trial in which patients who were prescribed beta-blocker therapy at discharge after the index ACS would be randomized at 1 year to discontinue or continue beta-blocker therapy for an additional 4 years. Our results suggest that beta-blocker discontinuation within 12 months after ACS is safe, and is not associated with harm >1.34 for the aHR of MACE (the upper bound of the 95% CI), compared with long-term beta-blocker continuation.

Subgroup and sensitivity analysis

Our finding that the subgroup of patients presenting with STEMI at index hospitalization tended to exhibit a higher rate of MACE following beta-blocker discontinuation warrants a cautious approach, granted the limitations of subgroup analysis. Of note, while there was significant interaction of ACS subgroup and beta-blocker discontinuation on the risk of primary outcome, beta-blocker discontinuation was not associated with significant harm in either ACS subgroup when analysed separately. In addition, post-hoc subgroup analysis of the secondary hard outcome of cardiovascular death or myocardial infarction showed no interaction of ACS type (see Supplementary material online, *Table S6*). Regarding potential explanations for a different effect in STEMI vs. NSTE-ACS, there was no effect modification by LVEF within the STEMI subgroup (see Supplementary material online, *Data*). Likewise, overall prognosis hardly explains the interaction: there were numerically fewer primary outcome events in the STEMI subgroup compared with NSTE-ACS. This finding is consistent with prior studies.[23,24] Moreover, while STEMI is associated with a higher rate of MRI-detectable myocardial scar compared with NSTEMI,[25] the long-term risk of sudden death does not differ by ACS type in the reperfusion era.[26] From the available data, the interaction between ACS subtype and long-term beta-blocker therapy therefore remains unclear and deserves further investigation in dedicated trials. Nevertheless, the

present results warrant caution regarding beta-blocker discontinuation following STEMI.

The interaction between age category (≥70 years vs. <70 years) and beta-blocker discontinuation on the risk of primary outcome ($P = 0.049$) should be interpreted with caution. Notably, when analysed separately, the effect of beta-blocker discontinuation on the risk of primary outcome remained non-significant in both age subgroups. In addition, interaction *P* value was close to the significance threshold without correction for multiple hypothesis testing, which was forgone given the exploratory nature of the analysis. In the REDUCE-AMI[14] and ABYSS[15] trials, age category (≥75 years vs. < 75 years) did not alter the effect of treatment allocation on outcomes. The elderly population, however, remains heterogeneous and insufficiently studied; dedicated trials are needed to characterize this population.

In the present study, there was no effect modification by LVEF category (preserved vs. mildly reduced ejection fraction). Of note, the overwhelming majority of the present cohort did not exhibit clinical heart failure, which was present in 20 of 2077 (1.0%) patients. The present results may therefore not apply to heart failure patients. In a recent observational study[27] on 2109 patients hospitalized with heart failure with mildly reduced ejection fraction (HFmrEF), of which 20.5% presented with acute myocardial infarction and 57.9% had ischaemic cardiomyopathy, beta-blocker therapy was associated with lower all-cause mortality compared with no beta-blockers over a median 30-month follow-up (27 vs. 35%, respectively; HR, 0.74; 95% CI, 0.62–0.88; $P = 0.001$).

Pre-specified per-protocol analysis found that beta-blocker discontinuation was associated with a lower risk of MACE compared with long-term beta-blocker use. This result should be interpreted with caution, as the per-protocol analysis was made by excluding a proportion of study participants, potentially resulting in bias. For example, one may hypothesize that patients in the discontinuation group who eventually resumed beta-blocker therapy did so because of angina symptoms or other cardiovascular events; their exclusion from the discontinuation group could have disproportionately removed high-risk patients.

Potential harm of beta-blocker use in patients with preserved ejection fraction

Beta-blocker therapy has established side effects that may adversely impact quality of life in a subset of patients, often resulting in discontinuation or poor compliance.[28] In addition, there is a growing body of evidence indicating potential harm of beta-blocker use in some populations with an LVEF ≥40%. In the above-mentioned meta-analysis by Bangalore et al.,[2] landmark analysis showed that beta-blockers in the reperfusion era led to an increase in heart failure and cardiogenic shock at 30 days, and to an increase in heart failure between 30 days and 1 year after ACS (without a net effect on all-cause or cardiovascular mortality). Indirect evidence of harm has also been reported in other populations that likely overlap with the post-ACS population.[29–32] Beta-blockers have been associated with a higher risk of new-onset diabetes mellitus.[33] Moreover, in heart failure with preserved ejection fraction (HFpEF), beta-blocker-induced heart rate lowering has been linked to higher filling pressures,[34] lower functional capacity,[35] and a higher risk of heart failure hospitalization.[31,32] Conversely, beta-blocker discontinuation was shown to improve functional capacity in HFpEF patients with chronotropic incompetence[35] and may improve response to exercise training.[36] Beta-blocker de-prescription might therefore lead to improved quality of life in selected patients, as well as lower health costs. Of note, the ABYSS trial[15] found no improvement in quality of life among patients who were randomized to beta-blocker discontinuation. In the present study, beta-blocker discontinuation was associated with apparent benefit in the NSTE-ACS subgroup, which might suggest harm of long-term beta-blocker therapy. This result should however be interpreted with caution given the limitations of subgroup analysis.

Further randomized trial data are needed and several ongoing trials are set to clarify the effect of long-term beta-blocker use after ACS and preserved left ventricular ejection fraction. Those include REBOOT-CNIC (NCT03596385), BETAMI (NCT03646357), and DANBLOCK (NCT03778554).

Limitations

A main limitation of the present study is its observational design, which limits causal inference. Likewise, residual bias cannot be formally excluded despite the use of state-of-the-art tools to minimize bias, including target trial emulation, IPW, Cox regression, sensitivity analysis, and negative control outcome.

Despite a relatively large patient cohort, sample size remains a limitation given the smaller proportion (15%) of patients in the beta-blocker discontinuation group, resulting in non-negligible uncertainty in aHR estimation and reduced robustness of IPW to adjust for confounding factors. Nevertheless, standardized mean differences within the weighted population (see Supplementary material online, *Table S1*) were small (<0.25 for all baseline characteristics,[37]), indicating that balance was achieved on these known confounders. Given these limitations, however, exploratory subgroup analysis should be interpreted with caution as the study was not sufficiently powered to allow conclusive inference regarding subgroups. For the same reason, secondary outcomes should be interpreted as exploratory due to a small number of expected events. Given the nature of the analysis on a pre-existing cohort, sample size was constrained and not based on sample size calculation. Of note, the small proportion of beta-blocker discontinuation in this real-world cohort is reflective of clinical practice and of the reluctance of physicians to discontinue these agents in this patient population despite a lack of contemporary evidence of long-term benefit.

The study included a small proportion (3.2%) of patients who initially presented with unstable angina. While this is representative of the population hospitalized for ACS in the era of high-sensitivity troponin assays,[38] it may introduce heterogeneity. Conversely, the power of the subgroup analysis focusing on myocardial infarction patients (STEMI/NSTEMI) might be reduced compared with the overall cohort.

The high proportion of missing data on the timing of cross-overs between years one and five limits the reliability of our per-protocol analysis, which, therefore, consisted in cross-over exclusion rather than censoring. Likewise, an inverse causal relation between outcomes and cross-overs cannot be excluded and might introduce bias in the per-protocol analysis. The overall high rate of cross-over during the 4-year follow-up period could also lead to the underestimation of any potential difference between the two groups in the primary ITT analysis. Of note, a comparable rate of cross-overs was reported in the REDUCE-AMI trial.[14]

It should be noted that 12.5% of the patients were either lost to follow-up (4.8%) or withdrew (7.7%), i.e. declined to undergo the 5-year visit (*Figure 1*). In the absence of any follow-up data, these patients were excluded from the analysis, which may be a source of potential bias. Of note, vital status was established by contacting trusted

family members, primary care physicians, or by consulting registry offices; it is therefore very unlikely that death would be misclassified as loss to follow-up. The proportion of loss to follow-up/withdrawal was similar in both groups: 46/365 (12.6%) in the discontinuation group and 251/2009 (12.5%) in the continuation group. Moreover, post-hoc sensitivity analysis with multiple imputation of the primary endpoint for the 297 (12.5%) patients who were lost to follow-up found primary endpoint results to be robust.

We acknowledge that the reason for beta-blocker introduction, discontinuation, or resumption, was rarely reported and cannot be analysed meaningfully. Because this study is based on real-world data, adherence was not monitored beyond routine clinical practice. Information on beta-blocker molecule and dose was also not available. Possible indications for beta-blocker therapy other than ACS that might not have been accounted for represent a potential source of residual bias.

Ventricular arrhythmia events were not collected as an individual outcome in the SPUM-ACS cohort and cannot be analysed specifically. Nevertheless, fatal ventricular arrhythmias including sudden cardiac death were accounted for in the composite primary and secondary outcomes as cardiovascular death and all-cause death events.

Conclusions

Compared with long-term beta-blocker use, beta-blocker discontinuation within 12 months following ACS in patients with an LVEF ≥40% at discharge was not associated with an increased risk of MACE over a 4-year follow-up period. In subgroup analysis, beta-blocker discontinuation tended to be associated with a higher risk of MACE in the STEMI subgroup, but not in NSTEMI or unstable angina patients. There was no interaction with the LVEF category (40–49 vs. ≥50%). Given the lack of evidence for sustained long-term benefit of beta-blocker use beyond 1 year after ACS with preserved or mildly reduced ejection fraction in the reperfusion era, and pending further randomized trial data, beta-blocker discontinuation within 12 months may be deemed safe, particularly after NSTE-ACS.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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Authors contributions

Conceptualization: B.G., N.J., M.B., S.B. Data curation: M.B., N.J. Formal analysis: M.B., N.J., B.G., S.B. Funding acquisition: B.G., F.M., N.R., S.W., C.M.M., T.F.L., L.R., D.N. Investigation: N.J., M.B., D.C., S.B., D.N., E.T., L.R., T.F.L., C.M.M., S.W., N.R., F.M., B.G. Methodology: N.J., M.B., D.C., S.B., D.N., E.T., L.R., T.F.L., C.M.M., S.W., N.R., F.M., B.G. Project administration: B.G., N.J., F.M., N.R., S.W., C.M.M., T.F.L., L.R., D.N., D.C. Resources: B.G., F.M., N.R., S.W., C.M.M., T.F.L., L.R., D.N. Supervision: B.G., F.M., N.R., S.W., C.M.M., T.F.L., L.R., D.N., D.C., E.T., S.B. Validation: B.G., N.J., M.B., D.C., S.B., D.N., E.T., L.R., T.F.L., C.M.M., S.W., N.R., F.M. Visualization: N.J., M.B., B.G., S.B. Writing—original draft: N.J., B.G., M.B. Writing—review and editing: B.G., N.J., M.B., D.C., S.B., D.N., E.T., L.R., T.F.L., C.M.M., S.W., N.R., F.M. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Data availability

Data will be made available upon reasonable request to the corresponding author.

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