

BMJ Open Discontinuation of β -blocker therapy in stabilised patients after acute myocardial infarction (SMART-DECISION): rationale and design of the randomised controlled trial

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ABSTRACT

Introduction There is a lack of evidence to support the effectiveness of prolonged β -blocker therapy after stabilisation of patients with acute myocardial infarction (AMI) without heart failure (HF) or left ventricular systolic dysfunction.

Methods and analysis The SMart Angioplasty Research Team: DEcision on Medical Therapy in Patients with Coronary Artery Disease or Structural Heart Disease Undergoing Intervention (SMART-DECISION) trial is a multicentre, prospective, open-label, randomised, non-inferiority trial designed to determine whether discontinuing β -blocker therapy after ≥ 1 year of maintenance in stabilised patients after AMI is non-inferior to continuing it. Patients eligible for participation are those without HF or left ventricular systolic dysfunction (ejection fraction $>40\%$) who have been continuing β -blocker therapy for ≥ 1 year after AMI. A total of 2540 patients will be randomised 1:1 to continuation of β -blocker therapy or not. Randomisation will be stratified according to the type of AMI (ie, ST-segment-elevation MI or non-ST-segment-elevation MI), type of β -blocker (carvedilol, bisoprolol, nebivolol or other) and participating centre. The primary study endpoint is a composite of all-cause death, MI and hospitalisation for HF over a median follow-up period of 3.5 years (minimum, 2.5 years; maximum, 4.5 years). Adverse effects related to β -blocker therapy, the occurrence of atrial fibrillation, medical costs and Patient-reported Outcomes Measurement Information system-29 questionnaire responses will also be collected as secondary endpoints.

Ethics and dissemination Ethics approval for this study was granted by the Institutional Review Board of Samsung Medical Center (no. 2020-10-176). Informed consent is obtained from every participant before randomisation. The

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This is a new concept of study to demonstrate the efficacy and safety of β -blocker discontinuation for patients without heart failure or left ventricular systolic dysfunction after acute myocardial infarction.
- ⇒ Detailed secondary endpoints including cost-effectiveness analysis and patient-reported outcome will provide the impact of β -blocker discontinuation for healthcare costs and the patient's change of symptoms.
- ⇒ The potential for bias in event detection cannot be dismissed due to the open-label trial design.
- ⇒ One of the limitations is the enrolment of patients from a single ethnic background.

results of this study will be submitted for publication in international peer-reviewed journals and the key findings will be presented at international scientific conferences.

Trial registration number ClinicalTrials.gov, NCT04769362.

INTRODUCTION

β -blockers are a crucial part of secondary prevention after acute myocardial infarction (AMI) to attenuate sympathetic activation, thereby reducing myocardial oxygen consumption, preventing fatal cardiac arrhythmias and limiting adverse cardiac remodelling.¹ The clinical benefits of using β -blockers in patients with reduced left ventricular ejection fraction (LVEF) after the development of AMI are well-established.^{2–4}

However, evidence of the therapeutic effects of β -blockers in patients with AMI without heart failure (HF) or LV systolic dysfunction is relatively sparse.⁵ More importantly, most existing evidence for the benefits of β -blockers in patients with AMI was generated when primary percutaneous coronary intervention was not the standard of care for AMI. Given that appropriate revascularisation improves prognosis by increasing myocardial salvage, reducing infarct size and decreasing the risk of arrhythmia,^{6,7} the role of β -blockers in AMI needs to be redefined in contemporary practice.

Although the current guidelines recommend the long-term use of β -blockers in all patients with AMI without contraindications to β -blocker therapy,^{8,9} the optimal duration of β -blocker treatment after stabilised AMI without reduced LVEF or HF remains uncertain. Theoretically, discontinuing β -blockers in survivors of AMI without a reduced LVEF or HF may prevent unnecessary overtreatment, save medical costs, limit potential side effects and improve quality of life or adherence to other medications. In this regard, some observational studies have been conducted to evaluate the long-term maintenance effects of β -blockers beyond 1 year after AMI, but the non-randomised nature of such studies limits their conclusions due to the presence of selection bias.^{10–13} Therefore, the SMart Angioplasty Research Team: DEcision on Medical Therapy in Patients with Coronary Artery DIsease or Structural Heart Disease Undergoing InterventiON (SMART-DECISION) trial will investigate whether the discontinuation of β -blocker therapy after ≥ 1 year of β -blocker therapy is non-inferior to the continuation of β -blocker therapy in patients without HF or LV systolic dysfunction after AMI.

METHODS AND ANALYSIS

Trial design, objectives and hypothesis

The SMART-DECISION trial is a prospective, randomised, open, multicentre, non-inferiority study that will be conducted by 25 centres in the Republic of Korea. A study overview is presented in figure 1. The primary

objective of this trial will be to determine whether the discontinuation of β -blocker therapy after ≥ 1 year of β -blocker treatment is non-inferior to the continuation of these medications in patients without HF or LV systolic dysfunction after AMI. We hypothesised that discontinuing β -blocker therapy after AMI stabilisation would be non-inferior to continuing β -blocker therapy in terms of a composite of all-cause death, MI or hospitalisation for HF in patients with AMI without HF or LV systolic dysfunction. We will also assess whether the discontinuation of β -blocker therapy after ≥ 1 year of β -blocker therapy influences quality of life, the occurrence of new atrial fibrillation and medical costs, respectively.

Study population

Patients with stabilised AMI who have been continuing β -blocker therapy for ≥ 1 year will be screened and invited to participate in this trial. The definition of AMI used in this trial has been adapted from the Fourth Universal Definition of MI.¹⁴ A full list of inclusion and exclusion criteria is provided in box 1. In brief, consenting adult patients (≥ 19 years old) without HF or LV systolic dysfunction who have continued with β -blocker therapy for ≥ 1 year after the development of AMI are eligible for participation in the study. Patients will be excluded if they have a reduced LVEF ($<40\%$), sustained treatment for HF, contraindication to β -blocker therapy or history of atrial fibrillation.

Randomisation and interventions in allocated arms

Eligible patients who agreed to participate in this study by signing the informed consent form will be randomised to either the β -blocker discontinuation group or the β -blocker maintenance group at the time of enrolment in a 1:1 ratio using a web-based case report form in the Clinical Data Management System from the Korea National Institute of Health. Randomisation will be stratified according to the type of MI (ST-segment-elevation MI or non-ST-segment-elevation MI), the type of β -blocker (carvedilol, bisoprolol, nebivolol or other) and the participating centre. According to randomisation, the β -blocker

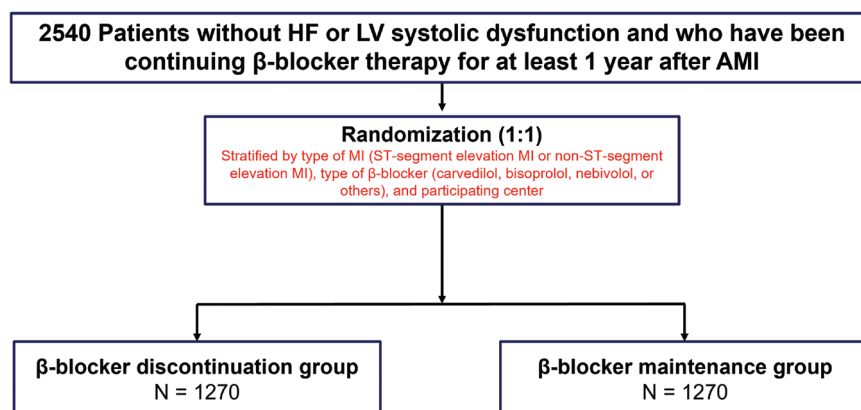


Figure 1 Study flowchart. AMI, acute myocardial infarction; HF, heart failure; LV, left ventricular.

Box 1 Study inclusion and exclusion criteria

Inclusion criteria

- ⇒ Subject is ≥19 years of age.
- ⇒ Subject has continued β-blocker therapy for ≥1 year after acute myocardial infarction regardless of the time of diagnosis.
- ⇒ Subject can verbally confirm their understanding of the risks and benefits of this trial, and they or their legally authorised representative has provided written informed consent prior to any study-related procedure.

Exclusion criteria

- ⇒ Subject has a left ventricle ejection fraction of <40% according to echocardiography performed after acute myocardial infarction or they never received echocardiography.
- ⇒ Subject is continuing treatment for heart failure.
- ⇒ Subject has a contraindication to β-blocker therapy (eg, history of uncontrolled bronchial asthma or chronic obstructive pulmonary disease, second-degree or third-degree atrioventricular block, cardiac pacemaker implantation or another case where β-blocker therapy cannot be used per the judgement of the clinician).
- ⇒ Subject has a non-cardiac comorbid condition with a life expectancy of <1 year or that may result in protocol non-compliance (per site investigator's medical judgement).
- ⇒ Subject has a history of atrial fibrillation.
- ⇒ Subject is pregnant or breastfeeding.

discontinuation group will stop β-blocker treatment, while the β-blocker maintenance group will continue with β-blocker treatment.

Study endpoints

The primary endpoint of this study is a composite of all-cause death, MI or hospitalisation for HF, over the total individual follow-up period. Secondary endpoints will include individual components of the primary endpoint; cardiac death; any hospitalisation; hospitalisation specifically for acute coronary syndrome; all-cause death or MI; cardiac death or MI; MI or hospitalisation for HF; any revascularisation; MI or any revascularisation; a composite of cardiac death, MI or hospitalisation for HF; a composite of cardiac death, MI or any revascularisation; changes in LVEF; changes in N-terminal pro-brain natriuretic peptide level; the occurrence of new atrial fibrillation; medical cost; Patient-reported Outcome Measurement Information System-29 Profile (PROMIS-29) questionnaire results; and adverse effects related to β-blocker therapy.

All deaths will be considered cardiac in nature unless an undisputed non-cardiac cause can be identified. For this study, MI will be defined by elevated cardiac enzymes (troponin or myocardial band fraction of creatine kinase) above the upper reference limit with ischaemic symptoms or electrocardiography findings indicative of ischaemia. HF hospitalisation will be defined by admission for ≥24 hours with a primary diagnosis of HF with at least one symptom of HF; at least two physical examinations, laboratory or invasive findings of HF; and the current status of receiving an HF-specific treatment.¹⁵

Revascularisation will be considered clinically driven if the diameter stenosis of the revascularised coronary segment is ≥50% by quantitative coronary angiography and any of the following criteria for ischaemia are met: (1) a positive functional study; (2) ischaemic electrocardiography changes at rest; (3) typical ischaemic symptoms; (4) positive invasive physiological test (fractional flow reserve ≤0.80 or instantaneous wave-free ratio ≤0.89); or (5) presence of stenosis with ≥70% diameter stenosis, even in the absence of other criteria. Patient-reported outcomes will be collected at baseline prior to randomisation; after 6, 12 and 24 months; and at the end of follow-up through the PROMIS-29 questionnaire.¹⁶

Data collection and follow-up

An overview of the data-collection process during screening, enrolment and treatment follow-up to the study end is presented in [table 1](#). All patients will be surveyed at 6, 12, 24 and 30 months, then yearly thereafter. The follow-up duration of the study will be ≥2.5 years after the last patient enrolment (the expected median follow-up will be 3.5 years, assuming a constant inclusion rate).

Sample size calculations

Originally, we assumed that the recruitment of study patients would occur at a constant rate over 3 years and that study patients would be followed-up with for an additional 2 years after the recruitment of the last patient (median follow-up of 3.5 years; range, 2–5 years). However, the enrolment rate has already exceeded our initial expectations (actual accrual period of 2 years), prompting us to perform a revised sample size calculation. To maintain a median follow-up duration of 3.5 years (range, 2.5–4.5 years), we have decided to extend the follow-up period to 2.5 years after the recruitment of the last patient. According to data from previous Korean nationwide observational studies, the annual incidence of the primary endpoint is estimated to be 3% in the β-blocker maintenance group.¹² The non-inferiority margin of the HR selected was 1.4. With a sampling ratio of 1:1, we estimated that 2540 patients (1270 per group) would result in ≥80% power at a one-sided type I error of 2.5% and a 2% attrition rate.

Statistical analyses

All primary and secondary endpoints will be analysed on an intention-to-treat basis. No imputation methods will be used to infer missing values of baseline variables. Continuous variables will be presented using mean±SD values and compared using the independent t-test or the Wilcoxon rank-sum test, as appropriate. Categorical variables will be presented as counts and percentages and compared with the χ^2 or Fisher's exact test as appropriate. Cumulative event rates will be estimated with the Kaplan-Meier method and compared using log-rank tests. HRs with 95% CIs will be estimated with the Cox proportional hazards method. If the upper limit of the one-sided 97.5% CI of the HR of the discontinuation group is less

Table 1 Schedule of measurements

Visit	Screening and baseline	Follow-up					End of treatment ± 90 days
		6 months ± 90 days	12 months ± 90 days	24 months ± 90 days	30 months ± 90 days and annually thereafter		
Medical history	o						
Inclusion and exclusion criteria	o						
Informed consent	o						
Weight, height	o						
Echocardiography	o		o	o			
Randomisation	o						
Angiographic and procedural data	o						
Vital status	o	o	o	o	o		o
Laboratory measurement	o		o	o			
ECG	o	o	o	o	o		o
Prescription and adherence to β -blocker therapy	o	o	o	o	o		o
Other medications	o	o	o	o	o		o
Complications and adverse events	o	o	o	o	o		o
Endpoint events		o	o	o	o		o
Medical cost		o	o	o	o		o
PROMIS-29	o	o	o	o			
PROMIS-29, Patient-reported Outcome Measurement Information System 29 Profile.							

than the prespecified non-inferiority margin, discontinuation of β -blocker therapy will be considered non-inferior to β -blocker therapy continuation. All models will be adjusted for the stratification factors (type of MI, type of β -blocker and participating centre). Per-protocol analysis among patients who adhere to the study protocol will be performed as a sensitivity analysis. For per-protocol analyses, participants will be censored if they deviate from their original treatment plan (whether or not to use β -blockers) without any clinical reason, as defined by Hernan and Robins.¹⁷ For the secondary outcomes, such as LVEF, N-terminal pro-brain natriuretic peptide level and quality of life per PROMIS-29, we will use linear mixed-effect models including main effects for visits (indicator terms for each visit) and visit—group interaction terms to assess differences in outcome alterations between the intervention and control groups. Random intercepts will be included to allow for variations in outcomes across study participants at baseline. Any cost-effective analysis performed will follow the Consolidated Health Economic Evaluation Reporting Standards guidelines.¹⁸ The outcome of the cost-effectiveness analysis will be expressed as the difference in quality-adjusted life years (QALYs) between the two strategies. QALYs represent a patient's survival time weighted by the quality of life, represented by a utility weight. The cost-effectiveness of discontinuation of β -blocker therapy will be expressed as the incremental cost-effectiveness ratio, defined as the

difference in the cumulative costs divided by the difference in cumulative QALYs.

Prespecified subgroup analysis

A set of 13 prespecified subgroup analyses will be performed using interaction models based on the primary endpoint. Detailed prespecified subgroups are listed in table 2. Estimates will be presented as HRs for each subgroup alongside p values for interaction.

Patient and public involvement

There was no patient or public involvement in this trial.

Study organisation

Steering committee and Data Safety Monitoring Board

The steering committee, composed of this study's chairperson and the principal investigators of the main investigating centres, has approved the study design, protocol and amendments issued to the Data Safety Monitoring Board (DSMB) and the participating centres. An independent DSMB will review the safety data from the study and construct recommendations for adverse events/serious adverse events, protocol deviation and follow-up case reports. No interim analysis is planned, but scheduled DSMB meetings will include discussions of safety or compliance issues and generate advice on modifying or stopping the study as needed. However, the final decisions regarding changes in the study protocol will remain

Table 2 Prespecified subgroups

Prespecified subgroup	
Age	≥65 vs <65 years
Sex	Male vs female
Body mass index	≥25 vs <25 kg/m ²
Diabetes mellitus	Presence vs absence
Hypertension	Presence vs absence
Chronic kidney disease*	Presence vs absence
LVEF	41–49% vs ≥50%
Systolic blood pressure	≥140 vs <140 mm Hg
Heart rate	≥60 vs <60 beats/min
Type of MI	STEMI vs NSTEMI
Type of β-blocker	Carvedilol vs bisoprolol vs nebivolol vs other
Revascularisation strategy	PCI vs CABG
Time from index MI to randomisation	1–2 vs 2–3 vs ≥3 years

*Chronic kidney disease was defined by estimated glomerular filtration rate <60 mL/min/1.73 m². CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST-segment-elevation MI; PCI, percutaneous coronary intervention; STEMI, ST-segment-elevation MI.

in the hands of the steering committee. In addition, the DSMB will help to conduct the trial appropriately by reviewing and reporting the cumulative investigational data for accuracy and completeness, ensuring protocol compliance. The DSMB will develop a consensus understanding of all trial endpoints and definitions used in the event-adjudication process.

Clinical event adjudication committee

The study clinical event adjudication committee (CEAC) is composed of interventional cardiologists who are not participants in the study. This committee is charged with the development of specific criteria based on protocol that will be used for the categorisation of clinical events and clinical endpoints in the study. At the onset of the trial, the CEAC established explicit rules outlining the minimum amount of data required as well as the algorithm to be followed to classify a clinical event. All members of the CEAC will be blinded to the primary results of the trial.

ETHICAL AND DISSEMINATION

The trial protocol has been approved by the relevant ethics committees (institutional review board no. 2020-10-176) and registered with ClinicalTrials.gov and the Clinical Research Information Service in Korea (KCT0005903). The current protocol V.4.3, dated 19 February 2024. Written informed consent for participation in the study will be obtained from all participating patients. The results of this study will be submitted for publication in international peer-reviewed journals and the key findings will be presented at international scientific conferences.

Trial status and timeline

The first patient was randomised on 27 April 2021, and the last patient (no. 2540) was randomised on 7 April 2023 (figure 2). The follow-up period is planned to last for ≥2.5 years after the last patient enrolment; therefore, it will end in October 2025.

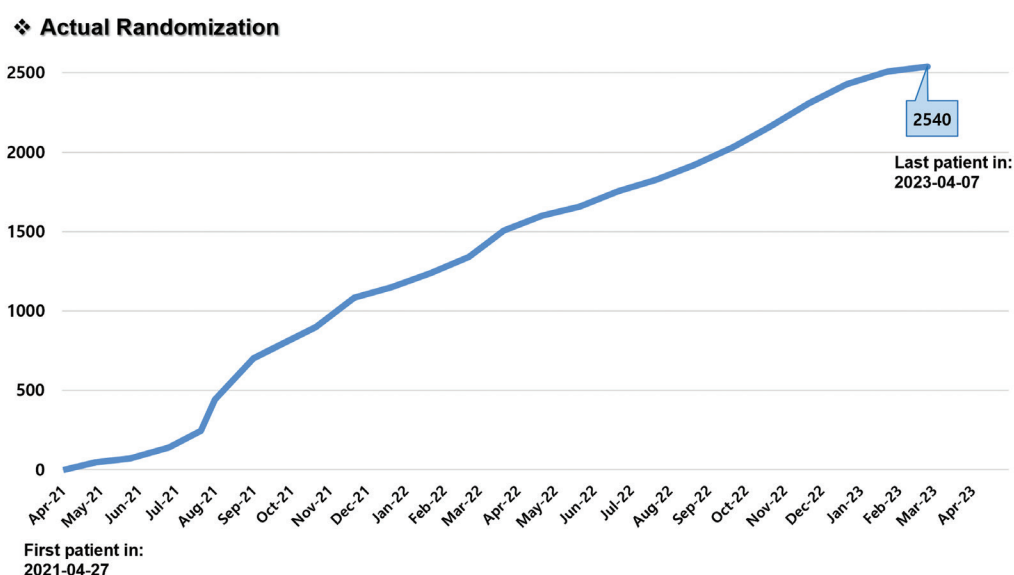


Figure 2 Enrolment curve over the 24 months of the study accrual period.

DISCUSSION

The SMART-DECISION trial aims to evaluate the efficacy and safety of β -blocker discontinuation after ≥ 1 year of β -blocker therapy in stabilised patients with AMI without HF or LV systolic dysfunction. If it is proven that discontinuation of β -blockers is non-inferior to maintenance of β -blockers in this population, socioeconomic benefits could be achieved by reducing unnecessary drug use and patient quality of life could be improved by achieving freedom from β -blocker side effects. If the study does not demonstrate non-inferiority for the primary endpoint in the β -blocker discontinuation group, this will strengthen the recommendation for long-term maintenance of β -blockers, even in stabilised patients with AMI without HF or LV systolic dysfunction.

β -blockers have been widely used and recommended after AMI on the basis of pivotal trials conducted in the pre-reperfusion era.^{19–21} However, clinical practice patterns have changed significantly in the current era given the introduction of high-sensitivity troponin for faster diagnosis of AMI; timely revascularisation strategies of occluded coronary arteries; and improved medical therapies for secondary prevention, such as high-intensity statins.^{22–24} In addition, unlike the abundant evidence for the benefits of β -blockers in patients with AMI with reduced LVEF, there has been a lack of data for the treatment effect of β -blockers in those without LV systolic dysfunction. The Carvedilol Post-intervention Long-term Administration in Large-scale Randomised Controlled Trial (CAPITAL-RCT) investigated the long-term efficacy of β -blockers in 801 patients with AMI with LVEF $\geq 40\%$ and found no beneficial effects of β -blockers during a median follow-up of 3.9 years.⁵ However, this trial was prematurely terminated and underpowered to identify a difference in the treatment effect concerning adverse cardiac events. In this regard, several large-sized randomised trials are currently ongoing to test the effects of long-term treatment with β -blockers in patients with AMI without reduced LVEF, including BETAblocker Treatment After acute Myocardial Infarction in revascularised patients without reduced LVEF (BETAMI) (NCT03646357), the Danish trial of β -blocker treatment after myocardial infarction without reduced ejection fraction (DANBLOCK) (NCT03778554), TREatment With Beta-blockers After myOcardial Infarction with Out Reduced Ejection fraction (REBOOT) (NCT03596385) and a randomised evaluation of decreased usage of β -blockers after acute myocardial infarction (REDUCE-AMI) (NCT03278509).^{25–29} The results of these trials will provide robust evidence to guide early-phase prescription of β -blockers to patients discharged after AMI without reduced LVEF.

However, a clinically important but difficult decision about β -blocker therapy after AMI not covered by the above four trials concerns the duration of β -blocker therapy in patients without HF or LV systolic dysfunction. Using data from a nationwide prospective French registry, Puymirat *et al* previously reported that early use of β -blockers was associated with reduced 30-day

mortality, but discontinuation of β -blockers at 1-year was not associated with higher 5-year mortality in patients with AMI without HF or LV systolic dysfunction.¹¹ This result might suggest a progressively decreasing benefit of β -blocker treatment over time. On the other hand, retrospective nationwide cohort studies from France and Korea have identified that discontinuation of β -blockers beyond 1-year after AMI was associated with an increased risk of death or recurrent MI in stabilised patients without HF.^{12–13} Therefore, we are conducting the SMART-DECISION trial to confirm the safety of β -blocker discontinuation after ≥ 1 year of β -blocker therapy in stabilised patients with AMI without HF or LV systolic dysfunction. The Assessment of β -blocker interruption 1Year after an uncomplicated myocardial infarction on Safety and Symptomatic cardiac events requiring hospitalisation (A β YSS) (NCT03498066) trial is also currently ongoing with a concept similar to that of our study.³⁰ These two trials will be helpful in determining the optimal duration of β -blocker therapy after post-MI patients without HF or LV systolic dysfunction are stabilised.

This trial has an open-label design with no placebo treatment; however, this is expected to have a limited impact on the hard outcomes of the primary composite endpoint, and a blinded adjudication of the endpoints by an independent CEAC may overcome the potential for overestimation of the treatment effects. Patients with ST-segment-elevation or non-ST-segment-elevation MI are included in this trial despite the expectation of some differences in the pathophysiology and prognosis between them. However, stratified randomisation is planned to minimise the potential selection bias. Furthermore, the time from index MI to randomisation is not the same for all patients. However, to evaluate the efficacy and safety of β -blocker discontinuation according to the differential period from the index MI, a prespecified subgroup analysis will be performed among patients randomised at 1–2 years from index MI versus 2–3 years versus ≥ 3 years.

SMART-DECISION is a non-inferiority trial to test the efficacy and safety of β -blocker therapy discontinuation in stabilised patients with AMI without HF or LV systolic dysfunction. Differences in the risk for a composite of all-cause death, MI or hospitalisation for HF will be assessed over a median follow-up period of 3.5 years. The results of the SMART-DECISION trial will add important scientific evidence about the optimal duration of β -blocker therapy after stabilisation of AMI without HF or LV systolic dysfunction.

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Contributors KHC and J-YH (guarantor) had full access to all data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript. Conceived and designed the research: KHC, Juwon Kim, J-YH. Acquisition, analysis, or interpretation of data: KHC, DK, J-HD, Juhan Kim, YHP, SGA, WK, JPP, SMK, B-RC, C-WN, JHC, S-JJ, JS, J-OJ, WJ, C-HY, J-YH, S-HL, E-SS, BJK, CWY, S-HH, HKK, KTP, Jihoon Kim, TKP, J-ML, JC, JHY, YBS, SHC, H-CG and J-YH. Drafting of the manuscript: KHC and Juwon Kim. Made critical revision of the manuscript for key intellectual content: YBS, TKP, J-ML, JC, JHY, SHC, H-CG, EG and J-YH. Statistical analysis: DK, JC and EG. Obtaining funding: J-YH.

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