BMJ Open

High-Intensity Statin versus Upfront Equivalent-Dose Combination of Moderate-Intensity Statin with Ezetimibe Following Acute Myocardial Infarction (ROSUZET-AMI): protocol of a multicentre, open-label, randomised non-inferiority trial

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To cite: Choo EH, Kim CJ, Hwang B-H, *et al*. High-Intensity Statin versus Upfront Equivalent-Dose Combination of Moderate-Intensity Statin with Ezetimibe Following Acute Myocardial Infarction (ROSUZET-AMI): protocol of a multicentre, open-label, randomised non-inferiority trial. *BMJ Open* 2025;**15**:e104127. doi:10.1136/bmjopen-2025-104127

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2025-104127).

Received 23 April 2025
Accepted 07 August 2025

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ABSTRACT

Introduction High-intensity statin therapy is recommended as a first-line strategy for lowering low-density lipoprotein cholesterol (LDL-C) levels in patients with acute myocardial infarction (AMI). A combination of moderate-intensity statin and ezetimibe at an equivalent dose to high-intensity statin may achieve similar LDL-C reduction with fewer side effects. This study evaluates the long-term efficacy and safety of this approach, initiated following AMI, compared with high-intensity statin monotherapy.

Methods and analysis The ROSUZET-AMI trial is a multicentre, prospective, open-label, randomised, non-inferiority trial. Patients with AMI who underwent percutaneous coronary intervention were randomised 1:1 to receive either moderate-intensity statin with ezetimibe (rosuvastatin 5 mg with ezetimibe 10 mg) or high-intensity statin monotherapy (rosuvastatin 20 mg). The primary endpoint is the composite of cardiovascular death, major coronary events (non-fatal myocardial infarction, documented unstable angina requiring hospitalisation and all coronary revascularisation events occurring at least 30 days after randomisation), or non-fatal stroke.

Ethics and dissemination Ethics approval for this study was obtained from the Institutional Review Board of Seoul St. Mary's Hospital (No. 2020-0424-0003). Informed consent is obtained from every participant before randomisation. 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 registration number NCT04499859.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Investigates statin and ezetimibe combination therapy in myocardial infarction patients.
⇒ Compares therapies with similar lipid-lowering capacity: combination versus monotherapy.
⇒ Evaluates cardiovascular outcomes, safety, medication adherence and diabetes risk.
⇒ 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.

INTRODUCTION

Effective lipid-lowering therapy is a cornerstone of secondary prevention after acute myocardial infarction (AMI). High-intensity statin therapy, validated for reducing low-density lipoprotein-cholesterol (LDL-C) and preventing cardiovascular events, is recommended as a first-line treatment in patients with AMI.[1 2] However, high-intensity statin therapy is linked to both short-term side effects—including myalgia, hepatic and renal toxicity—as well as long-term risks, such as diabetes and potential cataracts. These side effects may compromise patients' quality of life and adherence to treatment, resulting in the underuse and discontinuation of statins among high-risk patients.[3 4]

Upfront combination therapy with a moderate-intensity statin plus ezetimibe is an

attractive alternative to high-intensity statin monotherapy, as it produces comparable LDL-C reductions while offering superior tolerability and persistence.[5–7] However, prior studies either doubled the dose of moderate-intensity statin (still within the moderate-intensity range) instead of adding ezetimibe[5 6] or evaluated combination regimens that were not lipid-lowering equivalent to high-intensity statin therapy, primarily in stable atherosclerotic cohorts.[7] Whether beginning combination therapy during the index AMI hospitalisation can match the early pleiotropic benefits of high-intensity statins—whose anti-inflammatory and anti-thrombotic actions may be clinically relevant in this setting[8]—remains unknown. Imaging studies further show that greater LDL-C lowering is associated with plaque regression and fewer future events, underscoring the need for more effective yet tolerable early strategies.[9 10] This clinical equipoise calls for a dedicated randomised trial in AMI patients.

We, therefore, designed the ROSUZET-AMI trial, a prospective, multicentre, open-label study that randomises patients within 7 days of AMI to rosuvastatin 5 mg plus ezetimibe 10 mg or to rosuvastatin 20 mg. The trial will test whether the combination regimen is non-inferior to high-intensity statin monotherapy with respect to hard cardiovascular outcomes, both early and long-term, while also comparing LDL-C goal attainment, safety and treatment adherence.

METHODS

Study design and population

ROSUZET-AMI trial is a prospective, multicentre, randomised, open-label, non-inferiority trial to compare the efficacy of upfront low-dose rosuvastatin plus ezetimibe combination therapy at an equivalent dose to high-dose rosuvastatin on clinical outcomes in patients with AMI undergoing percutaneous coronary intervention (PCI). We hypothesise that starting with ezetimibe/low-dose rosuvastatin combination therapy will be non-inferior to starting with high-dose rosuvastatin monotherapy after AMI in the first occurrence of an adverse cardiovascular event. The study flow chart is shown in figure 1.

The ROUSZET-AMI trial is being performed at 34 major centres in South Korea. The trial is enrolling men and women who have been hospitalised for ST-segment elevation MI or non-ST-segment elevation MI and were treated with PCI. The definition of AMI is based on the fourth universal definition of MI.[11]

Detailed inclusion and exclusion criteria are presented in box 1.

Randomisation and treatment protocol

If they met all inclusion and none of the exclusion criteria, volunteered to participate and signed the informed consent form, patients were randomised during their index hospitalisation within 7 days from the index AMI event. Eligible patients are randomly assigned either to (1) upfront ezetimibe 10 mg plus rosuvastatin 5 mg daily (treatment group) or to (2) rosuvastatin 20 mg daily (control group) for LDL-C lowering efficacy in a 1:1 ratio. Randomisation was performed in the interactive web-based response system. The randomisation sequence was created by an independent statistician using SAS V.9.3 (SAS Institute) and was stratified by type of AMI (ST-segment elevation MI or non-ST-segment elevation MI) and age (≥75 years or <75 years) with a 1:1 allocation using hidden random block size. Follow-up visits occur at the end of 1 and 3 months, 12 months and every 12 months thereafter. Investigators will follow the patients by office visits (preferred) or telephone contact, as necessary.

A lipid panel, including total cholesterol, triglyceride, high-density lipoprotein cholesterol, LDL-C and serum C reactive protein level, was mandatory to measure at

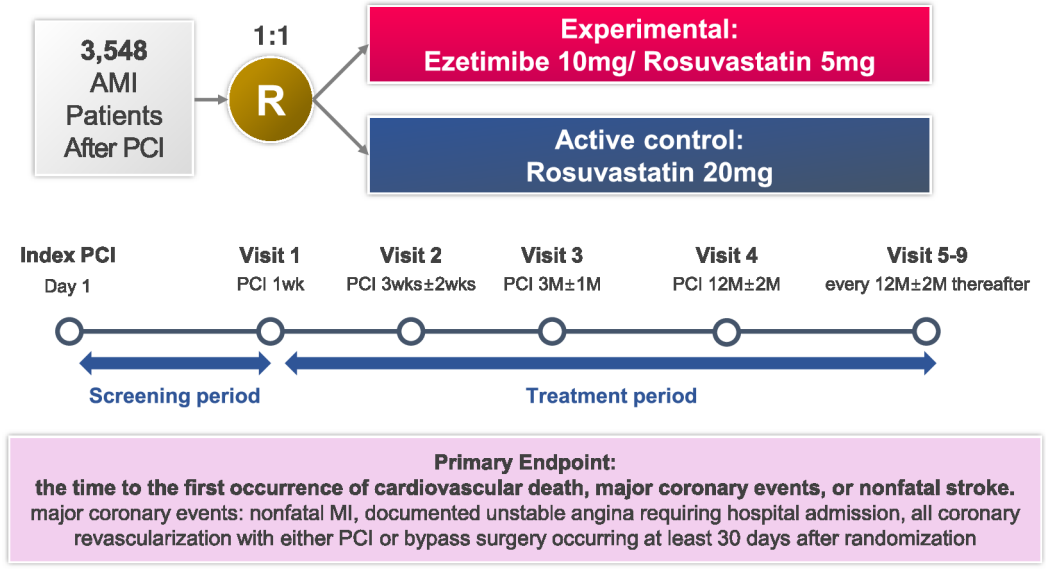

Figure 1 Study flow diagram of the ROSUZET-AMI Trial. AMI, acute myocardial infarction; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Box 1 Study inclusion and exclusion criteria

Inclusion criteria

1. Adults aged 19 and up.
2. Patients diagnosed with myocardial infarction (both ST-segment elevation and non-ST segment elevation) who were treated with percutaneous coronary intervention (myocardial infarction is defined as in the 4th Universal Definition of Myocardial Infarction).
3. For female patients who are of childbearing age, subjects who agreed to take a mandatory pregnancy test.
4. Patients who agreed and signed the informed consent form.

Exclusion criteria

1. Patients with a life expectancy of a year or less due to malignancy.
2. Patients with chronic liver disease.
3. Patients with sensitivity to the active ingredient of the drugs for the trial (ezetimibe and/or rosuvastatin) or patients who are prohibited from taking ezetimibe and/or rosuvastatin.
4. Pregnant and/or breastfeeding.
5. Female patients who are unable to use any means of contraception.
6. Patients receiving haemodialysis, peritoneal dialysis patients and/or kidney transplant patients due to end-stage renal disease.
7. Patients who participated in other clinical trial(s) within 3 months from the screening (except non-interventional observational study).
8. Patients were considered unfit for the study for any other reason(s) by the inspector(s).

index hospitalisation for AMI, 3 months, 12 months and every 12 months. An additional lipid panel, including apolipoprotein A1, apolipoprotein B, apolipoprotein C3 and lipoprotein(a), was also recommended to measure at each visit. Subjects with LDL-C higher than 100 mg/dL after treatment with the allocated drug may be given an additional 10 mg of ezetimibe (if randomised to rosuvastatin 20 mg) or the rosuvastatin dose increased to 20 mg (if randomised to ezetimibe 10 mg plus rosuvastatin 5 mg). Any lipid-lowering agent other than the study drug is prohibited during the trial. Muscle side effects are monitored 3 months after index AMI (visit 3) using a dedicated questionnaire assessing the Statin Associated Muscle Symptom Clinical Index (table 1).[12] If the subject presents with muscle pain or weakness, creatine kinase level is assessed immediately and managed according to recent European guidelines (box 2). Regular checks of HbA1c (Hemoglobin A1c) or glucose are recommended to monitor new-onset diabetes mellitus.

Study endpoints and clinical follow-up

The primary efficacy endpoint is the time from randomisation until the first occurrence of one of the following: cardiovascular death, major coronary events (non-fatal MI, documented unstable angina requiring hospital admission, all coronary revascularisation with either PCI or bypass surgery occurring at least 30 days after randomisation) or non-fatal stroke.

Secondary efficacy endpoints measure the time from randomisation until the first occurrence of (1) death from any cause, a major coronary event or a non-fatal stroke; (2) cardiovascular death, non-fatal MI or non-fatal stroke; (3) each component of primary endpoints and (4) achievement rate of LDL-C cholesterol level ≤70 mg/dL or 55 mg/dL at visit 3. Detailed definitions of the clinical events are in online supplemental appendix A.

Safety secondary endpoints include occurrence rate of (1) statin-associated muscle symptoms assessed by questionnaire at 3 months, (2) drug discontinuation or dose reduction, (3) drug non-adherence by pill count during follow-up, (4) new-onset diabetes and (5) cataract.

Clinical endpoints are prospectively collected during follow-up, supplemented by hospital records, patient interviews, death certificates and related reports (autopsy, biopsy, diagnostic output). Investigators complete case report forms for all events and provide source documents for central review. An independent committee will adjudicate all clinical endpoints.

Clinical follow-up is performed at 1, 3 and 12 months and then annually. All subjects are followed until the last enrolled subject completes the 2-year follow-up, which is scheduled to end in August 2026. Patients are asked about interim clinical events, clinical symptoms and adherence to the study drug at each visit. Concomitant medications are systematically collected during follow-up. Baseline waist circumference, height and weight were collected.

Statistical considerations

The present study aims to demonstrate non-inferiority in the treatment group with the upfront combination of ezetimibe and rosuvastatin 5 mg versus the control group with rosuvastatin 20 mg monotherapy for the first occurrence of the primary endpoint (incidence of cardiovascular death, major coronary events or non-fatal stroke) during follow-up in the intention-to-treat population. Population size was determined using a non-inferiority test for the log-rank test of non-inferiority, assuming the proportional hazards assumption holds. Significance level alpha was set at one-sided 0.025, and type II error (β) at 0.20. The power of the test was maintained at 80% with 4.5 years of accrual time and 2 years of follow-up. We defined the non-inferiority boundary as an upper limit of the one-sided 97.5% CI of the relative risk at 2 years of less than 1.17. Based on the event rates of previous pivotal trials,[5 13] we assumed a 2-year rate of primary endpoint would be 20% in both groups. The estimated sample size was 3548 (1774 patients per group), calculated by a non-inferiority log-rank test analysis, considering 3% of lost to follow-up. Sample size calculation was performed using PASS program (V.2020, NCSS).

All principal analyses will be performed in the intention-to-treat population, defined as all subjects randomised, regardless of the treatment received. Secondary analyses will be performed in the per-protocol population, defined as randomised patients who received their assigned treatment, and in the as-treated population, defined as patients who received treatment. Baseline demographic and clinical variables will be summarised for each randomised group.

Table 1 Statin-Associated Muscle Symptom Clinical Index (SAMS)

SAMS			
| Instructions | ► Use with patients who have had muscle symptoms that were new or increased after starting a statin regimen. ► A statin regimen includes any statin at any dose or frequency, including a statin the patient has used previously at the same or a different dose. ► Muscle symptoms may include aches, cramps, heaviness, discomfort, weakness or stiffness. ► Interpret overall score in light of other possible causes of the muscle symptoms, such as recent physical exertion, hypothyroidism, changes in exercise patterns, drug interaction with statin, concurrent illness, underlying muscle disease.			
A. Location and pattern of muscle symptoms (If more than one category applies, record the highest number.)			Enter score:
Symmetric, hip flexors or thighs		3	
Symmetric, calves		2	
Symmetric, proximal upper extremity		2	
Asymmetric, intermittent or not specific to any area		1	
B. Timing of muscle symptom onset in relation to starting statin regimen			Enter score:
<4 weeks		3	
4–12 weeks		2	
>12 weeks		1	
C. Timing of muscle symptom improvement after withdrawal of statin (If the patient is still taking a statin, stop the regimen and monitor symptoms.)			Enter score:
<2 weeks		2	
2–4 weeks		1	
No improvement after 4 weeks		0	
Rechallenge the patient with a statin regimen (even if the same statin compound or regimen as above), then complete the final question:			
D. Timing of recurrence of similar muscle symptoms in relation to starting the second regimen			Enter score:
<4 weeks		3	
4–12 weeks		1	
>12 weeks or similar symptoms did not reoccur		0	
All four scores above must be entered before totaling			Total
Interpretation			
Total score	2–6	7–8	9–11
Likelihood that the patient's muscle symptoms are due to statin use:	Unlikely	Possible	Probable

Continuous variables will be compared by t-tests or Wilcoxon rank sum tests, and categorical variables by χ^2 or Fisher's exact tests, as appropriate. HRs and 95% CIs comparing the upfront ezetimibe/rosuvastatin combination and rosuvastatin monotherapy will be provided using this model. Because revascularisations occurring up to 30 days after randomisation will not be included in the prespecified endpoints, the effect of these events will be assessed by sensitivity analyses on the primary endpoint. HRs and 95% CIs for categories determined by age, sex, type of AMI, diabetes, left ventricular ejection fraction and renal function will be provided for the primary endpoint using the Cox proportional hazard model. Kaplan-Meier estimates for time to the primary endpoints will be plotted. The hypothesis for each secondary endpoint is that the upfront ezetimibe/rosuvastatin combination compared with rosuvastatin monotherapy will equally reduce the incidence of the composite secondary endpoint with clinical outcomes (efficacy secondary endpoint numbers 1–3). HRs and 95% CIs between the two treatments will be calculated using the same Cox model to analyse the primary endpoint. Kaplan-Meier estimates for time to each secondary endpoint will be analysed. LDL-C lowering efficacy (efficacy secondary endpoint number 4) will be analysed using the χ^2 or Fisher's exact test. Safety secondary endpoints will be analysed using the χ^2, Fisher's exact test or Kaplan-Meier analysis with log-rank test. Primary and major secondary endpoints will be analysed in prespecified subgroups to evaluate the consistency of results. The outcome will be evaluated in subgroups: polyvascular disease with peripheral artery disease or stroke, baseline LDL-C or already on statin treatment, C reactive

Box 2 Management of the subjects with muscle pain and the elevation of CK

If ≥4×ULN

⇒ If CK >10×ULN: stop treatment, check renal function, and monitor CK every 2 weeks.
⇒ If CK <10×ULN: if no symptoms, continue lipid-lowering therapy while monitoring CK between 2 and 6 weeks.
⇒ If CK < 10×ULN: if symptoms present, stop statin and monitor normalisation of CK, before rechallenge with a lower statin dose.
⇒ Consider the possibility of transient CK elevation for other reasons such as exertion.
⇒ Consider myopathy if CK remains elevated.
⇒ Consider combination therapy or an alternative drug.

If <4×ULN

⇒ If no muscle symptoms, continue statin (patient should be alerted to report symptoms; check CK).
⇒ If muscle symptoms, monitor symptoms and CK regularly.
⇒ If symptoms persist, stop the statin and re-evaluate symptoms after 6 weeks; re-evaluate the indication for statin treatment.
⇒ Consider rechallenge with the same or another statin.
⇒ Consider a low-dose statin, alternate day or once/twice weekly dosing regimen, or combination therapy.

CK, creatine kinase; ULN, upper limit of normal.

protein level after treatment, baseline apoB (triglyceride remnant lipoprotein) and lipoprotein (a) level, and prediabetic and obese patients. All statistical analyses will be performed using SAS software, V.9.3 or higher (SAS Institute). Further details are provided in online supplemental appendix B.

Study organisation

The ROSUZET-AMI trial is an investigator-initiated trial funded by the Seoul St. Mary's Hospital, The Catholic University of Korea, with grant support from Hanmi Pharmaceutical (Seoul, Korea). The sponsor has no role in protocol development, study implementation, data management, analysis or report writing. The authors alone are responsible for the design and performance of the trial, statistical analyses and data interpretation, and all aspects of manuscript preparation. An executive committee oversees all aspects of trial execution, data analysis and publications. The committee approved the final trial design and protocol issued to the Data and Safety Monitoring Board (DSMB) and the clinical sites. A steering committee will provide operational expertise and advise the executive committee. The DSMB will review safety data and make recommendations based on analyses of endpoint events and protocol deviations. The DSMB may call a meeting if safety is a concern. The Clinical Events Adjudicaton Committee (CEAC) will develop specific criteria to categorise protocol-based clinical events. The CEAC will establish explicit rules outlining the minimum data required and the algorithm to classify a clinical event. The CEAC will regularly review and adjudicate all clinical events for which the required minimum data are available. All members of the CEAC will be blinded to the patients' allocation and the primary results of the trial.

Ethics and dissemination

The study adheres to ethical principles consistent with the Declaration of Helsinki 2013, ICH Good Clinical Practice guidelines, and applicable regulatory requirements. The study protocol and informed consent were reviewed and approved by the corresponding health authorities and ethics boards/institutional research boards for all participating study sites. The objective, potential benefits and risks will be fully explained to trial participants and their guardians. All patients must provide informed written consent prior to randomisation to confirm voluntary participation (online supplemental appendix C). 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.

STUDY STATUS

Between October 2020 and August 2024, a total of 3548 patients from 32 sites in South Korea were enrolled and randomised. Follow-up of the last enrolled patient will be completed in August 2026, and the primary results of the ROSUZET-AMI trial are expected in early 2027.

DISCUSSION

The ROSUZET-AMI trial is designed to determine whether the upfront combination of ezetimibe and rosuvastatin 5 mg at an equivalent dose to high-intensity statin as the first-line strategy after PCI for AMI is non-inferiority to rosuvastatin 20 mg monotherapy in reducing the risk of a composite of cardiovascular death, non-fatal MI, documented unstable angina requiring hospital admission, all coronary revascularisation with either PCI or bypass surgery occurring at least 30 days after randomisation, or non-fatal stroke.

Current guidelines underscore the importance of achieving an LDL-C goal of less than 55 mg/dL and a reduction of more than 50% from baseline for patients with AMI.[1] However, achieving these stringent targets remains challenging with high-intensity statin therapy alone, the recommended first-line treatment. Studies have demonstrated that many high-risk patients do not reach the target LDL-C levels.[14–16] Doubling the statin dose yields only an additional 6%–7% reduction in LDL-C.[17] Ezetimibe, a cholesterol absorption inhibitor, can reduce LDL-C by 15%–22% when added to statin.[1 18] Combining ezetimibe with moderate-intensity statins has been shown to achieve greater LDL reduction than doubling the dose of moderate-intensity statins to high-intensity statins.[19] Ezetimibe can provide additive benefits in lowering LDL-C and reducing the risk of cardiovascular events when combined with statins.[5 6] This combination of statin and ezetimibe is currently recommended for patients

who do not achieve the desired LDL-C goals with statins alone.[1 2]

Given the potential side effects of high-intensity statins, an upfront combination of ezetimibe and moderate-intensity statins may offer a safer yet equally effective alternative in post-AMI patients. Adding ezetimibe to low or moderate-intensity statins showed similar or superior LDL-C lowering capacity compared with high-intensity statins.[20 21] The RACING trial, a large randomised controlled trial, demonstrated that moderate-intensity statin plus ezetimibe combination therapy was non-inferior to high-intensity statin monotherapy in reducing 3-year major cardiovascular events among high-risk patients. However, it compared rosuvastatin 20 mg with rosuvastatin 10 mg plus ezetimibe 10 mg and reported lower LDL-C levels in the combination group (58 mg/dL vs 66 mg/dL), suggesting greater lipid-lowering efficacy rather than equivalency. In contrast, prior comparative data have shown that rosuvastatin 5 mg plus ezetimibe 10 mg and rosuvastatin 20 mg achieve similar LDL-C reductions (56% vs 54%) and comparable on-treatment LDL-C levels (63 vs 69 mg/dL), while rosuvastatin 10 mg plus ezetimibe 10 mg resulted in a 59% reduction and LDL-C of 59 mg/dL.[21] These findings justify the regimen selection in our trial and enable a true non-inferiority comparison of clinical outcomes.

High-intensity statins are linked to myalgia (5%–10%), elevations in hepatic enzymes (1%–3%), rises in creatine-kinase suggestive of muscle injury (0.3%–1.0%), renal dysfunction (<0.5%), and a 9%–12% relative increase in new-onset diabetes.[3 4 12] The occurrence of adverse effects substantially impairs adherence, with up to 25% of patients discontinuing statin therapy. Moreover, some patients never initiate treatment because of toxicity fears despite the absence of symptoms. Both patterns of non-adherence are independently associated with higher rates of recurrent cardiovascular events.[4 12 22] The combination of ezetimibe and lower-intensity statin reduced drug-related adverse events (mainly muscle symptoms)[23] and lowered discontinuation or dose reduction caused by intolerance[7] compared with high-intensity statin monotherapy. Unlike statin uptitration, adding ezetimibe did not affect glucose metabolism[15 24] and showed no adverse safety signals at very low achieved LDL-C levels.[25] Although lifelong exposure to lower LDL-C levels mediated by genetic variants of NPC1L1, the target of ezetimibe, was linked to an increased risk of diabetes,[26] robust long-term clinical evidence on the metabolic sequelae of ezetimibe remains limited.[27] Therefore, ROSUZET-AMI builds an extensive safety programme—capturing statin-associated muscle symptoms with a validated questionnaire and prospectively tracking discontinuation, dose modification and incident diabetes—while directly comparing rosuvastatin 5 mg+ezetimibe 10 mg with rosuvastatin 20 mg. By coupling lipid-lowering equivalence with comprehensive tolerability surveillance, the trial aims to define a more patient-centred approach to secondary prevention after AMI.

The ROSUZET-AMI trial is based on the hypothesis that initiating lipid-lowering therapy with rosuvastatin 5 mg plus ezetimibe 10 mg—rather than the guideline-recommended rosuvastatin 20 mg—may provide similar efficacy with improved tolerability and adherence in post-AMI patients. While current guidelines recommend adding ezetimibe if LDL-C targets are not achieved with high-intensity statins, our approach simply reverses the sequence: starting with a well-tolerated combination and escalating statin dose (eg, to rosuvastatin 10 or 20 mg) and, if necessary, adding a PCSK9 inhibitor in high-risk patients. Importantly, rosuvastatin 5 mg plus ezetimibe 10 mg has demonstrated LDL-C-lowering efficacy comparable to rosuvastatin 20 mg, suggesting that the initial target achievement rate would be similar between these two regimens. The clinical significance of this approach lies in its potential to improve safety, adherence and persistence without compromising lipid-lowering potency. This trial, therefore, aims to redefine the initial strategy of secondary prevention after AMI, positioning the combination regimen as a practical and patient-centred first-line alternative.

Some limitations of the ROSUZET-AMI trial deserve discussion. First, this is an open-label trial. Physicians and patients may be aware of group assignments, which could potentially have led to bias in reporting patient symptoms. The nocebo effect of the statin therapy should be considered. However, an independent clinical endpoint committee would be masked to the therapy assignment and adjudicate all clinical events. Second, follow-up may also not be sufficiently long to see the event curves separate between the two groups, especially in terms of new-onset diabetes. Third, since ezetimibe combination therapy is currently more expensive than high-intensity statins, if it is non-inferior in preventing major adverse cardiovascular events and shows no difference in the incidence of new-onset diabetes, there may be debate about maintaining ezetimibe combination therapy in patients without statin-associated muscle symptoms. Fourth, this study exclusively enrolled Korean patients; therefore, the results should be applied with caution to other populations.

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Contributors KC, EHC, B-HH, KYL and GCO contributed to the conceptualisation of the study. KC secured funding for the project. EHC, CJK, KYL, GCO, IJC, D-BK, OSK, SLe, YC, C-SP, S-HH, H-YK, HCL, TSK, JKS, S-IW, HSP, KHY, ROSUZET-AMI investigators participated in the investigation. KC, EHC, B-HH, KYL and GCO developed the methodology. KC and EHC managed the overall administration of the project. KC supervised the research process. EHC drafted the original version of the manuscript. KC reviewed and edited the manuscript for critical content. KC is responsible for the overall content as guarantor.

Funding This research was supported by a grant from Hanmi Pharmaceutical (Seoul, Korea).

Competing interests KC reports that financial support was provided by Hanmi Pharmaceuticals. The other authors have nothing to disclose.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

1 Mach F, Baigent C, Catapano AL, *et al*. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;41:111–88.
2 Grundy SM, Stone NJ, Bailey AL, *et al*. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019;139:e1046–81.
3 Mach F, Ray KK, Wiklund O, *et al*. Adverse effects of statin therapy: perception vs. the evidence - focus on glucose homeostasis, cognitive, renal and hepatic function, haemorrhagic stroke and cataract. *Eur Heart J* 2018;39:2526–39.
4 Thompson PD, Panza G, Zaleski A, *et al*. Statin-Associated Side Effects. *J Am Coll Cardiol* 2016;67:2395–410.
5 Cannon CP, Blazing MA, Giugliano RP, *et al*. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N Engl J Med* 2015;372:2387–97.
6 Hagiwara N, Kawada-Watanabe E, Koyanagi R, *et al*. Low-density lipoprotein cholesterol targeting with pitavastatin + ezetimibe for patients with acute coronary syndrome and dyslipidaemia: the HIJ-PROPER study, a prospective, open-label, randomized trial. *Eur Heart J* 2017;38:2264–76.
7 Kim B-K, Hong S-J, Lee Y-J, *et al*. Long-term efficacy and safety of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in patients with atherosclerotic cardiovascular disease (RACING): a randomised, open-label, non-inferiority trial. *Lancet* 2022;400:380–90.
8 Piorkowski M, Fischer S, Stellbaum C, *et al*. Treatment with ezetimibe plus low-dose atorvastatin compared with higher-dose atorvastatin alone: is sufficient cholesterol-lowering enough to inhibit platelets? *J Am Coll Cardiol* 2007;49:1035–42.
9 Nicholls SJ, Hsu A, Wolski K, *et al*. Intravascular ultrasound-derived measures of coronary atherosclerotic plaque burden and clinical outcome. *J Am Coll Cardiol* 2010;55:2399–407.
10 Tsujita K, Sugiyama S, Sumida H, *et al*. Impact of Dual Lipid-Lowering Strategy With Ezetimibe and Atorvastatin on Coronary Plaque Regression in Patients With Percutaneous Coronary Intervention: The Multicenter Randomized Controlled PRECISE-IVUS Trial. *J Am Coll Cardiol* 2015;66:495–507.
11 Thygesen K, Alpert JS, Jaffe AS, *et al*. Fourth Universal Definition of Myocardial Infarction (2018). *Circulation* 2018;138:e618–51.
12 Rosenson RS, Baker S, Banach M, *et al*. Optimizing Cholesterol Treatment in Patients With Muscle Complaints. *J Am Coll Cardiol* 2017;70:1290–301.
13 Cannon CP, Braunwald E, McCabe CH, *et al*. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350:1495–504.
14 Bangalore S, Fayyad R, Kastelein JJ, *et al*. 2013 Cholesterol Guidelines Revisited: Percent LDL Cholesterol Reduction or Attained LDL Cholesterol Level or Both for Prognosis? *Am J Med* 2016;129:384–91.
15 Gitt AK, Lautsch D, Ferrières J, *et al*. Cholesterol target value attainment and lipid-lowering therapy in patients with stable or acute coronary heart disease: Results from the Dyslipidemia International Study II. *Atherosclerosis* 2017;266:158–66.
16 Ridker PM, Mora S, Rose L, *et al*. Percent reduction in LDL cholesterol following high-intensity statin therapy: potential implications for guidelines and for the prescription of emerging lipid-lowering agents. *Eur Heart J* 2016;37:1373–9.
17 Bays HE, Ose L, Fraser N, *et al*. A multicenter, randomized, double-blind, placebo-controlled, factorial design study to evaluate the lipid-altering efficacy and safety profile of the ezetimibe/simvastatin tablet compared with ezetimibe and simvastatin monotherapy in patients with primary hypercholesterolemia. *Clin Ther* 2004;26:1758–73.
18 Sudhop T, Lütjohann D, Kodal A, *et al*. Inhibition of intestinal cholesterol absorption by ezetimibe in humans. *Circulation* 2002;106:1943–8.
19 Bays HE, Averna M, Majul C, *et al*. Efficacy and safety of ezetimibe added to atorvastatin versus atorvastatin uptitration or switching to rosuvastatin in patients with primary hypercholesterolemia. *Am J Cardiol* 2013;112:1885–95.
20 Oh PC, Jang AY, Ha K, *et al*. Effect of Atorvastatin (10 mg) and Ezetimibe (10 mg) Combination Compared to Atorvastatin (40 mg) Alone on Coronary Atherosclerosis. *Am J Cardiol* 2021;154:22–8.
21 Kim K-J, Kim S-H, Yoon YW, *et al*. Effect of fixed-dose combinations of ezetimibe plus rosuvastatin in patients with primary hypercholesterolemia: MRS-ROZE (Multicenter Randomized Study of ROsuvastatin and eZEtimibe). *Cardiovasc Ther* 2016;34:371–82.
22 Giral P, Neumann A, Weill A, *et al*. Cardiovascular effect of discontinuing statins for primary prevention at the age of 75 years: a nationwide population-based cohort study in France. *Eur Heart J* 2019;40:3516–25.
23 Ran D, Nie H-J, Gao Y-L, *et al*. A randomized, controlled comparison of different intensive lipid-lowering therapies in Chinese patients with non-ST-elevation acute coronary syndrome (NSTE-ACS): Ezetimibe and rosuvastatin versus high-dose rosuvastatin. *Int J Cardiol* 2017;235:49–55.
24 Koh KK, Oh PC, Sakuma I, *et al*. Vascular and metabolic effects of ezetimibe combined with simvastatin in patients with hypercholesterolemia. *Int J Cardiol* 2015;199:126–31.
25 Giugliano RP, Wiviott SD, Blazing MA, *et al*. Long-term Safety and Efficacy of Achieving Very Low Levels of Low-Density Lipoprotein Cholesterol: A Prespecified Analysis of the IMPROVE-IT Trial. *JAMA Cardiol* 2017;2:547–55.
26 Lotta LA, Sharp SJ, Burgess S, *et al*. Association Between Low-Density Lipoprotein Cholesterol-Lowering Genetic Variants and Risk of Type 2 Diabetes: A Meta-analysis. *JAMA* 2016;316:1383–91.
27 Choo EH, Moon D, Choi IJ, *et al*. Efficacy and diabetes risk of moderate-intensity statin plus ezetimibe versus high-intensity statin after percutaneous coronary intervention. *Cardiovasc Diabetol* 2024;23:396.