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Original Research

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Effect of Early Initiation of Evolocumab on Lipid Profiles Changes in Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention

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AUTHOR'S SUMMARY

The C-STAR trial evaluated early triple lipid-lowering therapy with evolocumab, rosuvastatin 5 mg, and ezetimibe 10 mg in statin-naïve patients with acute coronary syndrome undergoing percutaneous coronary intervention. In this single-center randomized study of 108 patients, the evolocumab group achieved lower low-density lipoprotein cholesterol levels at 2 weeks compared with controls (31 vs. 63 mg/dL), corresponding to greater reductions (–77.5% vs. –53.3%) and higher target goal achievement (84.6% vs. 26.9%). Cognitive function, measured with the Everyday Cognition questionnaire, was comparable between groups. These results suggest early evolocumab addition provides potent lipid lowering and short-term safety, warranting longer-term outcome studies in high-risk patients.

ABSTRACT

Background and Objectives: Rapid reduction of low-density lipoprotein cholesterol (LDL-C) in acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI) is critical but challenging. This study evaluated the efficacy and safety of early triple lipid-lowering therapy with evolocumab, a moderate-intensity statin, and ezetimibe in statin-naïve ACS patients.
Methods: The C-STAR trial (Effect of Early Initiation of Evolocumab on Lipid Profile Changes in Patients with ACS Undergoing PCI) was a single-center, randomized, open-label trial conducted from December 2022 to January 2025. A total of 108 statin-naïve ACS patients undergoing PCI were randomized to evolocumab (140 mg) plus rosuvastatin 5 mg and ezetimibe 10 mg (n=54) or rosuvastatin 5 mg and ezetimibe 10 mg alone (n=54). The primary endpoint was LDL-C level at 2 weeks; cognitive safety was assessed using the Everyday Cognition (ECog) tool.
Results: Baseline LDL-C levels were similar between the 2 groups. At 2 weeks, LDL-C levels were lower in the evolocumab group compared to the non-evolocumab group

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Conflict of Interest
Dr. Yongcheol Kim reports research grants and speaker fees from Abbott Vascular, Medtronic, Boston Scientific, Merit Medical, HK inno.N, ChongKunDang, and Amgen. All other authors declare no competing interests.

Data Sharing Statement
The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Author Contributions
Conceptualization: Cho DK, Kim Y; Data curation: Roh JW, Lee OH, Heo SJ, Im E, Kim Y; Formal analysis: Heo SJ; Funding acquisition: Cho DK, Kim Y; Investigation: Roh JW, Lee OH, Kim Y; Methodology: Kim Y; Project administration: Kim Y; Resources: Cho DK, Kim Y; Supervision: Cho DK, Kim Y; Validation: Kim Y; Visualization: Kim Y; Writing - original draft: Roh JW, Lee OH; Writing - review & editing: Lee OH, Heo SJ, Im E, Cho DK, Kim Y.

(31±16 mg/dL vs. 63±17 mg/dL; p<0.001), with a greater percentage reduction (–77.5% vs. –53.3%, p<0.001). Target achievement rates were also higher in the evolocumab group (84.6% vs. 26.9%, p<0.001). Comparable cognitive functions were observed using ECog questionnaire (23.9±3.4 vs. 24.5±5.5; p=0.493).
Conclusions: Early initiation of evolocumab in combination therapy achieved greater LDL-C reduction and target achievement in ACS patients undergoing PCI.

Trial Registration: ClinicalTrials.gov Identifier: NCT05661552

Keywords: Acute coronary syndrome; Percutaneous coronary intervention; Evolocumab; Cognition

INTRODUCTION

Cardiovascular disease remains the leading cause of death globally, with acute coronary syndrome (ACS) representing one of the most critical manifestations of coronary artery disease.[1] The post-ACS period is associated with heightened vulnerability to recurrent ischemic events, particularly in the early weeks following the index event.[2] A cornerstone of secondary prevention strategies for ACS is the prompt lowering of low-density lipoprotein cholesterol (LDL-C) to target levels, as there is consistent evidence linking early lower LDL-C levels with improved clinical outcomes, including reduced rates of myocardial infarction, stroke and cardiovascular mortality.[3][4]

Current European and American guidelines both recommend achieving LDL-C levels below 55 mg/dL and at least a 50% reduction from baseline in very high-risk patients, such as those with ACS.[5][6] Despite the availability of high-intensity statins, achieving these stringent targets in a timely manner remains a challenge with statin intolerance, particularly in statin-naive patients or those with extremely elevated baseline LDL-C levels.[7] Recently, the strategy of adding ezetimibe while reducing the statin dose to overcome high-intensity statins intolerance has been in the spotlight.[8] Previous clinical studies have also demonstrated that the combination of moderate-dose statin with ezetimibe can achieve LDL-C lowering efficacy comparable to high-intensity statin monotherapy, with improved tolerability and adherence.[9] This challenge is also compounded by the dynamic changes in inflammation and lipid metabolism during the acute phase of ACS, where elevated circulating proprotein convertase subtilisin/kexin type 9 (PCSK9) levels reduce the number of LDL receptors.[10] PCSK9 inhibitors, such as evolocumab or alirocumab, have emerged as potent lipid-lowering agents capable of significantly reducing LDL-C by enhancing LDL receptor availability.[11] These agents have demonstrated their long-term efficacy and safety in large-scale clinical trials, showing reductions in cardiovascular events and coronary plaque burden.[3][4][12] However, their role in the early initiation during ACS, particularly when combined with other lipid-lowering therapies such as statin and ezetimibe, is less well-established. Therefore, this study aimed to evaluate the efficacy and safety of early triple lipid-lowering therapy by assessing LDL-C reduction, target LDL-C achievement rate, and cognitive function in statin-naïve patients with ACS, using rosuvastatin 5 mg and ezetimibe 10 mg as the baseline therapy to minimize statin-related intolerance.

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METHODS

Ethical statement

The study protocol was approved by the Institutional Review Board of Yongin Severance Hospital (approval number: 9-2022-0119), and the study received informed consent from all patients. All experiments were performed in accordance with the Declaration of Helsinki (2013).

Study design and population

This C-STAR (Effect of Early Initiation of Evolocumab on Lipid Profiles Changes in Patients with ACS Undergoing PCI) is an exploratory investigator-initiated, single-center, prospective, randomized, open-label trial designed to generate preliminary data on the efficacy and safety of early initiation of evolocumab or not in combination with moderate-intensity statin (rosuvastatin 5 mg) and ezetimibe 10 mg therapy in statin-naïve patients presenting with ACS undergoing percutaneous coronary intervention (PCI). Regarding the combination therapy with rosuvastatin 5 mg and ezetimibe 10 mg, prior clinical trials have provided evidence that combining a moderate-dose statin with ezetimibe can achieve LDL-C lowering efficacy comparable to high-intensity statin.[8)9)] Based on these findings, we selected rosuvastatin 5 mg plus ezetimibe 10 mg as the backbone regimen in this trial, aiming to approximate the LDL-C–lowering potency of high-intensity statin therapy while minimizing the risk of statin-related intolerance in the acute phase. This strategy also allowed us to evaluate the efficacy and safety of adding early evolocumab to a regimen of comparable potency to rosuvastatin 20 mg.

The trial is registered on ClinicalTrials.gov (Identifier: NCT05661552). Eligible participants are adults aged 19 years or older who present with ACS, including ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction, or unstable angina undergone PCI. Key exclusion criteria include prior statin or PCSK9 inhibitor users, contraindications to study medications, significant liver or renal dysfunction, active infection or inflammatory disease, and a life expectancy of less than one year.

Randomization and interventions

After providing informed consent, participants will be randomized 1:1 to 1 of 2 treatment groups following PCI. Evolocumab group received a single subcutaneous injection of evolocumab 140 mg within 24 hours after PCI, in addition to daily oral rosuvastatin 5 mg and ezetimibe 10 mg. The control group received daily oral rosuvastatin 5 mg and ezetimibe 10 mg without evolocumab. All participants received standard medical therapy for ACS according to current guidelines, including antiplatelet agents, beta-blockers and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, unless contraindicated.[6)]

Outcome measures

The primary efficacy endpoint is the change in LDL-C levels from baseline to 2 weeks post-PCI. Secondary endpoints include the proportion of participants achieving both >50% LDL reduction and LDL-C levels below 55 mg/dL at 2 weeks, changes in other lipid parameters (total cholesterol, high-density lipoprotein cholesterol [HDL-C], triglycerides). With respect to the exploratory safety endpoint, cognitive function at 2 weeks was assessed by self-assessment using a 23-item questionnaire that represented the executive and memory domain subscale of a modified shortened version of the Everyday Cognition (ECog) questionnaire (**Supplementary Table 1**). For each item, patients compared their current level of daily functioning to their retrospective assessment of their level at the start of the study

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(scores ranged from 1 to 5, with lower scores indicating better functioning). Total ECog mean scores and mean scores for each ECog domain were compared between 2 groups. In addition, the incidence of major adverse cardiovascular events (MACE) during the one-month and the occurrence of adverse events, including muscle-related symptoms, liver enzyme elevations, new-onset diabetes and neurocognitive effects, as also assessed by clinical and laboratory tests.

Data collection and follow-up

Baseline data, including demographics, medical history, and laboratory values, are collected prior to randomization. Follow-up visits are scheduled at 2 weeks (14 days±7 days), and 1 month (28 days±7 days) post-PCI to assess clinical status, medication adherence, and to perform laboratory assessments. Adverse events are monitored continuously throughout the study.

Statistical analysis

Sample size calculations were based on detecting a clinically significant difference in LDL-C reduction between the 2 groups at 2 weeks. Because LDL-C was repeatedly measured over time, we adopted a repeated-measures analysis of variance framework, which appropriately accounts for within-subject correlations and provides greater statistical efficiency than simple change-score analyses. The sample size was calculated using the wp.rmanova function in the WebPower package for R.[13] In the absence of prior studies to guide the expected effect size, we followed Cohen's statistical convention for a medium effect (f≈0.25) and set f=0.3 as a reasonable benchmark for the calculation. Accounting for a potential dropout rate of 5%, we determined that 54 participants per group would be required. Efficacy analyses are conducted on the intention-to-treat population, including all randomized participants. Continuous variables are expressed as means ± standard deviations or median (Q1, Q3) and compared using independent-samples t-tests or Mann-Whitney U tests, as appropriate. The normality assumption of the continuous variables was assessed using the Shapiro–Wilk test and graphical method, such as histogram and quantile-quantile plot. Categorical variables are presented as frequencies and percentages and analyzed using χ^2 tests or Fisher's exact tests. The primary and secondary endpoints are analyzed using the linear mixed model or linear quantile mixed model for differences in percentage changes between groups. Statistical significance was set at $p<0.05$. All statistical analyses were performed with R software (version 4.3.0; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

A total of 108 statin-naïve patients undergoing PCI for ACS were enrolled and randomized evenly into the evolocumab group (n=54) and the non-evolocumab group (n=54). Among them, 52 patients for each group whose primary efficacy and safety endpoints were investigated within the study period were finally enrolled in the study, excluding 2 patients from each group (**Figure 1**). All 4 patients were excluded because they did not come on the scheduled outpatient date and were unable to complete the blood test and questionnaire. The mean age was 61.0±11.3 years, and 86.1% of the 108 patients enrolled were male. Baseline demographic, clinical, and procedural characteristics were well-balanced between the 2 groups. The incidence of hypertension, diabetes mellitus, and dyslipidemia were similar between groups. The 49.1% of all the patients were STEMI. All patients received drug-eluting stents implanted, 76.9% underwent image-guided PCI and the duration of hospitalization did not differ significantly (**Table 1**).

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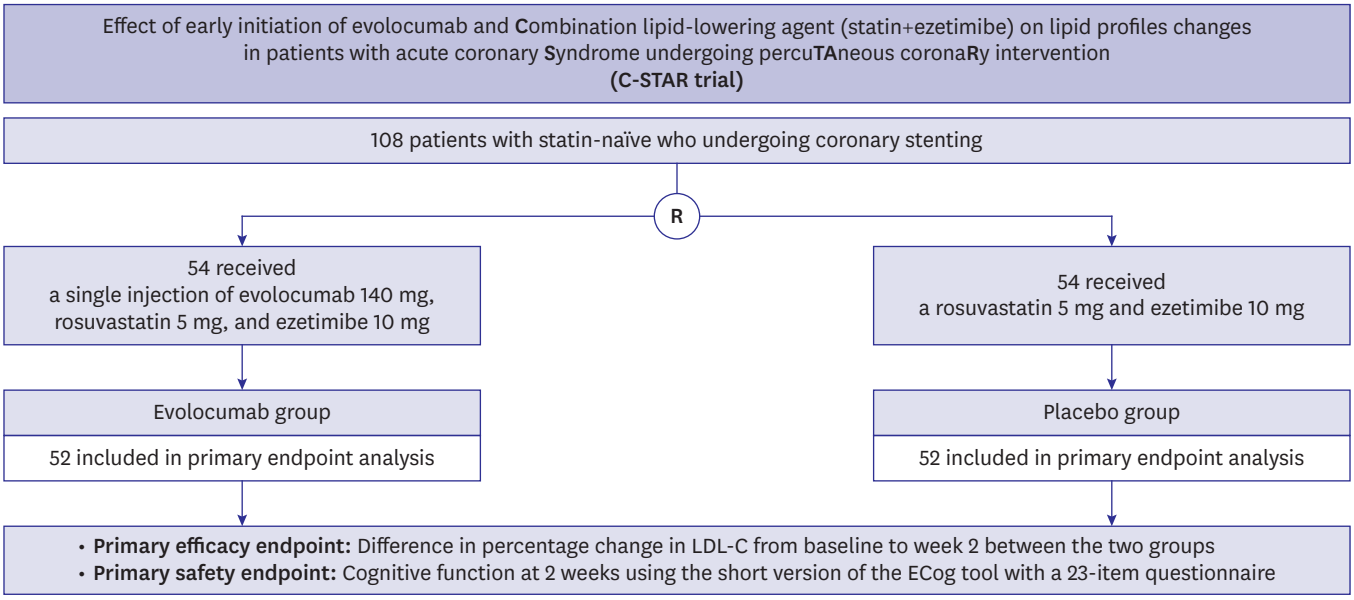

Figure 1. Study design of the C-STAR trial. Patients were randomized 1:1 to receive either a single injection of evolocumab 140 mg in combination with rosuvastatin 5 mg and ezetimibe 10 mg (evolocumab group), or rosuvastatin 5 mg and ezetimibe 10 mg alone (non-evolocumab group). The primary efficacy endpoint was the percentage change in LDL-C from baseline to 2 weeks. The primary safety endpoint was cognitive function at 2 weeks, assessed using the short version of the ECog questionnaire comprising 23 items.
ECog = Everyday Cognition; LDL-C = low-density lipoprotein cholesterol.

Lipid profile changes

Baseline LDL-C levels were not significantly different between groups (145±37 mg/dL vs. 139±31 mg/dL; p=0.607). At 2 weeks, LDL-C levels were lower in the evolocumab group compared to the non-evolocumab group (31±16 mg/dL vs. 63±17 mg/dL; p<0.001) (**Figure 2**). Compared with baseline LDL-C levels, all patients in both groups showed a trend toward decreased LDL-C levels after 2 weeks of treatment (**Supplementary Figure 1**). The mean percentage reduction in LDL-C from baseline was greater in the evolocumab group compared with the non-evolocumab group (−77.5%±12.5% vs. −53.3%±13.0%, p<0.001), with a mean difference of −24.1% between the groups (95% confidence interval [CI], −29.1 to −19.1, p<0.001) (**Figure 3A** and **Table 2**). The percentage of patients achieving both >50% LDL-C reduction and LDL-C <55 mg/dL at week 2 was higher in the evolocumab group (84.6% vs. 26.9%, p<0.001) (**Figure 3B**). At week 4, the mean percentage reduction in LDL-C still remained greater in the evolocumab group than in the non-evolocumab group (−62.1% vs. −55.6%, p=0.021), although the difference between the groups with both >50% LDL-C reduction and LDL-C <55 mg/dL at 4 weeks was not statistically significant (48.1% vs. 40.4%, p=0.435) (**Supplementary Figure 2**). In addition to statistical significance, the primary repeated-measures effect demonstrated a large effect size (Cohen's f=0.57). This magnitude of effect supports the robustness and practical relevance of the findings, and it is in line with the assumptions underlying the sample size calculation. Total cholesterol and non-HDL-C showed greater reductions at week 2 in the evolocumab group compared to the non-evolocumab group, but there were no significant differences between groups in HDL-C or triglyceride changes (**Table 2**). Regarding lipoprotein (Lp)(a) level at 2 weeks, there is a greater decrease in the evolocumab group (–4.2%, 95% CI, –36.4 to 22.6), while the non-evolocumab group exhibited an increase (53.3%, 95% CI, 9.8 to 90.0), resulting in a between-group difference of –56.4% (95% CI, –79.4 to –34.2; p<0.001).

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Table 1. Baseline characteristics

Characteristics	Total (n=108)	Evolocumab group (n=54)	Non-evolocumab group (n=54)	p value
Demographic characteristics				
Age (years)	61.0±11.3	60.9±11.0	61.1±11.7	0.906
Male sex	93 (86.1)	48 (88.9)	45 (83.3)	0.578
BMI (kg/m^2)	25.7±3.3	25.8±3.7	25.6±2.7	0.752
Systolic blood pressure (mmHg)	150±29	148±26	153±32	0.363
Diastolic blood pressure (mmHg)	84±14	84±13	84±16	0.915
Current smoking	47 (43.5)	23 (42.6)	24 (44.4)	>0.999
Medical history				
Hypertension	54 (50.0)	23 (42.6)	31 (57.4)	0.178
Diabetes mellitus	22 (20.4)	10 (18.5)	12 (22.2)	0.811
Dyslipidemia	78 (72.2)	36 (66.7)	42 (77.8)	0.283
Prior PCI	2 (1.9)	1 (1.9)	1 (1.9)	>0.999
Prior myocardial infarction	1 (0.9)	0 (0.0)	1 (1.9)	>0.999
Prior cerebrovascular accident	3 (2.8)	1 (1.9)	2 (3.7)	>0.999
Atrial fibrillation	5 (4.6)	3 (5.6)	2 (3.7)	>0.999
Clinical presentations				0.601
UAP	15 (13.9)	9 (16.7)	6 (11.1)	
STEMI	53 (49.1)	27 (50.0)	26 (48.1)	
NSTEMI	40 (37.0)	18 (33.3)	22 (40.7)	
LVEF (%)	49.14±9.09	49.65±10.45	48.62±7.52	0.561
PCI strategy				
Drug eluting stents	108 (100.0)	54 (100.0)	54 (100.0)	>0.999
Total number of stents	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 2.0)	0.256
Total stent length, mm	33.0 (24.0, 46.0)	33.0 (24.5, 45.8)	37.0 (24.5, 46.0)	0.471
Multivessel PCI	16 (14.8)	6 (11.1)	10 (18.5)	0.416
Image-guided PCI	83 (76.9)	40 (74.1)	43 (79.6)	0.648
Duration of hospitalization (day)	4 (3, 5)	4 (3, 5)	4 (2, 5)	0.669
Baseline medication				
Aspirin	104 (97.2)	51 (96.2)	53 (98.1)	0.987
$P2Y_{12}$ inhibitor	106 (99.1)	52 (98.1)	54 (100.0)	0.993
ACEi or ARB	46 (43.0)	24 (45.3)	22 (40.7)	0.780
Beta-blocker	42 (39.3)	22 (41.5)	20 (37.0)	0.783

Data are presented as mean ± standard deviation or median (Q1, Q3) for continuous variables and frequencies (%) for categorical variables.
p values were calculated by the independent 2 sample t-test or Wilcoxon rank-sum test for continuous variables and Pearson's χ^2 test for categorical variables.
ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; LVEF = left ventricular ejection fraction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; UAP = unstable angina pectoris.

Cognitive function assessment

Assessment of cognitive function at week 2 using the short version of the ECog questionnaire showed comparable differences between the 2 groups across total and scores (**Table 3**). The total ECog score was 23.9±3.4 in the evolocumab group and 24.5±5.5 in the non-evolocumab group (mean difference, −0.6; 95% CI, −2.4 to 1.2; p=0.493). Furthermore, comparable cognitive functions were observed in the individual domains of ECog between 2 groups.

Serial changes in biochemical measures during study period

A total of 104 participants were followed over a 4-week period, and serial changes in biochemical measures were compared between the evolocumab and non-evolocumab groups (**Supplementary Table 2**, **Supplementary Figure 3**). At baseline, the 2 groups had comparable lipid profiles, including levels of LDL-C, total cholesterol, HDL-C, non-HDL cholesterol, triglycerides and Lp(a). By week 2, LDL-C, total cholesterol and non-HDL cholesterol levels were lower in the evolocumab group than in the non-evolocumab group, suggesting an early treatment effect. However, this difference was not maintained by week 4. Regarding HDL-C or triglyceride levels, no intergroup differences were observed at any time point. Lp(a) levels at week 2 were different between both groups (21 [7–43] nmol/L in the evolocumab

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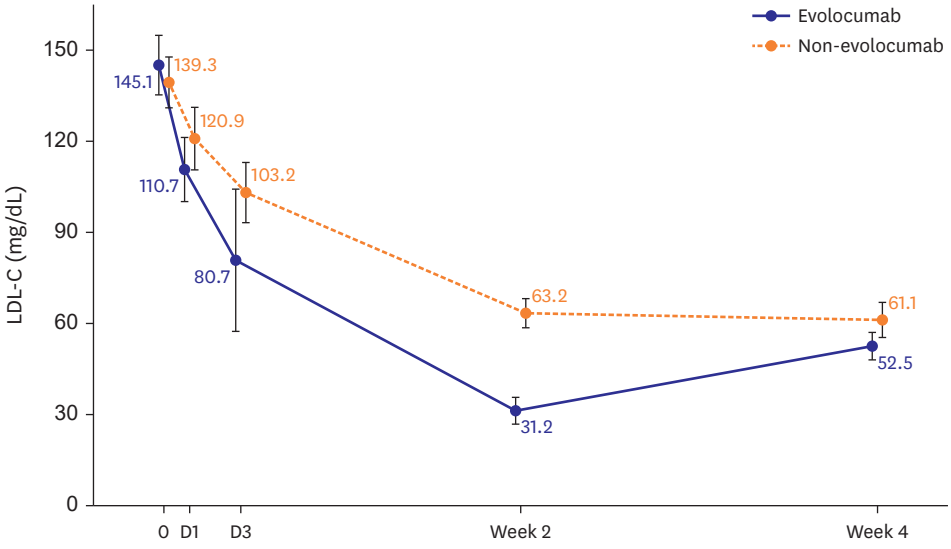

Figure 2. Temporal changes in LDL-C levels over 4 weeks in the evolocumab and non-evolocumab groups. Mean LDL-C levels (± standard error) are plotted at baseline (day 0), D1, D3, week 2, and week 4. The evolocumab group (oranged dashed line) showed a rapid and marked reduction in LDL-C levels, reaching a nadir at week 2 (31.2 mg/dL), followed by a slight increase at week 4 (52.5 mg/dL). In contrast, the non-evolocumab group (blue line) demonstrated a more gradual decline, with LDL-C levels of 63.2 mg/dL at week 2 and 61.1 mg/dL at week 4. Evolocumab group resulted in a greater reduction in LDL-C compared to the non-evolocumab group throughout the study period.
D1 = day 1; D3 = day 3; LDL-C = low-density lipoprotein cholesterol.

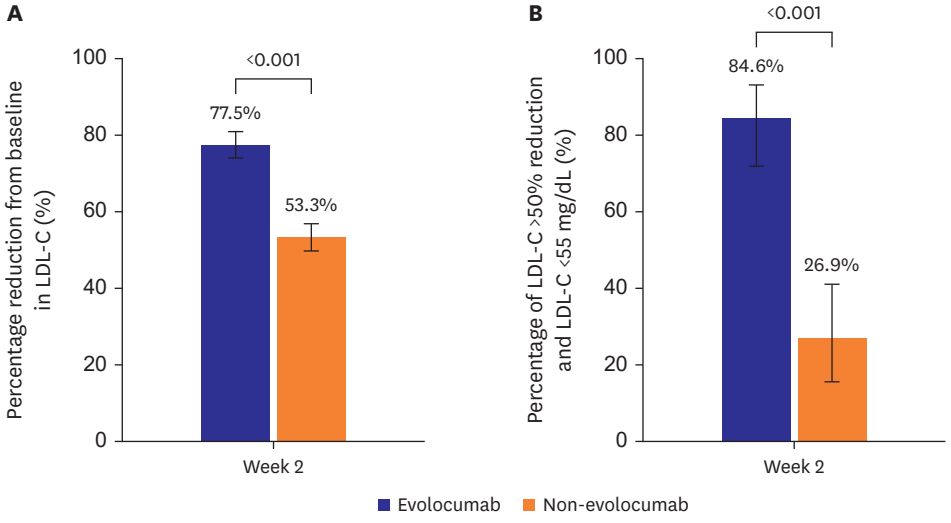

Figure 3. LDL-C lowering efficacy of evolocumab at 2 weeks. (A) Percentage reduction in LDL-C from baseline to week 2. The evolocumab group demonstrated a greater reduction in LDL-C (77.5%) compared to the non-evolocumab group (53.3%) (p<0.001). (B) Proportion of patients achieving both ≥50% reduction in LDL-C and an absolute LDL-C level <55 mg/dL at Week 2. A higher percentage of patients in the evolocumab group achieved this dual goal (84.6%) compared to the non-evolocumab group (26.9%) (p<0.001). Error bars represent standard error.
LDL-C = low-density lipoprotein cholesterol.

group vs. 34 [12–78] nmol/L in the non-evolocumab group, p=0.034). In term of other laboratory findings including creatinine, aspartate transaminase (AST), alanine transaminase (ALT), creatine kinase (CK), high-sensitivity C-reactive protein (CRP), there were not differences at week 2 and week 4, respectively, except for ALT at week 2 between 2 groups.

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Table 2. Change in biochemical measures from baseline to 2 weeks in the randomized population who received study drug*

Measurement	Evolocumab group			Non-evolocumab group			Difference in percentage change between groups (95% CI)	p value†
	Baseline (n=54)	Week 2 (n=52)	Percentage change	Baseline (n=54)	Week 2 (n=52)	Percentage change		
LDL-C (mg/dL)	145±37	31±16	−77.5±12.5	139±31	63±17	−53.3±13.0	−24.1 (−29.1, −19.1)	<0.001
Other lipid profiles (mg/dL)								
Total cholesterol	211±37	91±20	−56.2±10.0	206±36	123±23	−39.6±10.8	−16.6 (−20.7, −12.6)	<0.001
HDL-C	44±10	47±9	9.6±21.9	47±19	47±14	4.3±26.8	5.2 (−4.3, 14.8)	0.277
Non-HDL-C	167±35	44±20	−73.3±11.9	159±39	76±21	−49.6±21.3	−23.7 (−30.4, −17.0)	<0.001
Triglyceride	191±148	115±64	−22.0±47.6	220±150	116±54	−32.4±32.9	10.3 (−6.1, 26.7)	0.214
Lp(a) (nmol/L)	24 (11, 40)	21 (7, 43)	−4.2 (−36.4, 22.6)	18 (7, 42)	34 (12, 78)	53.3 (9.8, 90.0)	−56.4 (−79.4, −34.2)	<0.001

Data are presented as mean ± standard deviation or median (Q1, Q3).
The linear mixed model or linear quantile mixed model are used to calculate estimates of difference of percentage change between groups with 95% CI and p value.
CI = confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp = lipoprotein.
*Analyses were performed on the full analysis set (108 patients), but 4 patients were excluded due to missing serial biomarker data at 2 weeks.
†p value for the between-group comparison of difference in percentage change.

Table 3. Comparison of scores between groups in the Everyday Cognition questionnaire (modified short version) from the start of the study to week 2

Measurement	Evolocumab group* (n=52)	Non-evolocumab group† (n=52)	Mean difference (95% CI)	p value‡
Total score	23.9±3.4	24.5±5.5	−0.6 (−2.4, 1.2)	0.493
Memory	8.4±1.7	8.6±2.2	−0.3 (−1.0, 0.5)	0.494
Executive function (planning)	5.1±0.4	5.3±1.2	−0.2 (−0.5, 0.2)	0.272
Executive function (organization)	6.1±0.5	6.3±1.7	−0.2 (−0.7, 0.3)	0.436
Executive function (divided attention)	4.3±1.6	4.3±1.0	0.0 (−0.5, 0.6)	0.883

Data are presented as mean ± standard deviation.
p values and 95% CI were calculated by independent 2 sample t-test.
CI = confidence interval.
*Two patients in the evolocumab group with missing data at 2 weeks were excluded from the analysis.
†Two patients in the placebo group with missing data at 2 weeks were excluded from the analysis.
‡p value for between-group comparison.

Clinical safety outcomes at 1 month

At 1 month, there was one event in each group for MACE (**Supplementary Table 3**).
No patients discontinued treatment or required a dose adjustment due to intolerance. One patient in the evolocumab group experienced a reaction at the injection site, but this was not serious and the swelling and urticaria resolved within a day. There were no neurocognitive adverse events, and the incidence of other adverse events, such as myalgia, dizziness, gastrointestinal symptoms, and new-onset DM, was comparable between groups. Laboratory safety markers, including CK, AST, and ALT levels, also remained comparable without significant abnormalities in either group.

DISCUSSION

The C-STAR trial supports the potential benefits of early use of triple lipid-lowering approach with PCSK9 inhibitors, moderate-intensity statin and ezetimibe in statin-naïve ACS patients undergoing PCI. In this study, the evolocumab group showed a 77.5% reduction in LDL-C compared to 53.3% in the non-evolocumab group, with 84.6% achieving LDL-C >50% reduction and LDL-C levels below 55 mg/dL compared to only 26.9% in the non-evolocumab group at 2 weeks. This demonstrates that triple combination therapy provides superior LDL-C reduction and improves target goal achievement in statin-naïve ACS patients. Moreover, the rapid reduction in LDL-C in a 2-week period with a triple combination therapy, including a single dose of evolocumab, demonstrated a comparable safety profile regarding cognitive function.

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Until now, the European and American guidelines recommend a stepwise approach for treating ACS patients, starting with high or tolerable dose statin therapy, followed by the addition of ezetimibe if the target LDL-C level is not achieved, and considering PCSK9 inhibitors thereafter.[14][15] Therefore, in real-world practice, the use of PCSK9 inhibitors remains below 1% and is usually started several months after ACS, even if the LDL-C target is not achieved.[16] In addition, cost-effectiveness and the barrier of the injection prevent its further use, particularly in ACS patients with high-ischemic risk.[17] Recent studies suggest that PCSK9 levels rise early during myocardial ischemia especially on ACS and that inhibition of PCSK9 at this stage could reduce infarct size, post-infarct inflammation and plaque burden.[18] In addition, early administration of PCSK9 inhibitors has been shown to not only lower LDL-C level, but also to improve endothelial function, promote plaque stabilization, and improve long-term clinical outcomes when LDL-C is lowest in the early stages of ACS.[19]

Despite the hurdle of cost and accessibility due to injection, some pilot studies have shown that PCSK9 inhibitors can rapidly achieve target LDL-C levels with plaque stabilization when used alongside high-intensity statins. However, the use of ezetimibe in these studies was less than 5%.[20] In these days, the use of ezetimibe adding statins has been increased to further improve clinical outcomes.[21] In addition, the strategy of adding ezetimibe while reducing the dose of statins has been shown in large clinical trials to improve compliance while reducing the side effects of high dose statins, thereby maintaining consistently lower LDL levels.[8]

Therefore, the C-STAR trial investigated the need for PCSK9 inhibitors in patients with early ACS in terms of efficacy and safety. In our study, in statin-naïve patients with a basically high LDL-C level, we achieved a higher percentage of LDL-C target goals after 2 weeks (84.6%) using ezetimibe and early evolocumab without using high-dose statins, compared to the group that did not use evolocumab (26.9%). Importantly, as the statin was given at a moderate dose, no one stopped or changed their statin/ezetimibe dose during the trial.

Although early administration of evolocumab in combination with moderate-intensity statin and ezetimibe achieved rapid and substantial LDL-C reductions, the high cost and lack of reimbursement remain key barriers to generalization in real-world settings. Retrospective and meta-analytic data suggest potential benefits of early PCSK9 inhibitor use on cardiovascular outcomes, but definitive confirmation from large randomized controlled trial is warranted. [22][23] An evaluation of the cost-effectiveness of this strategy is essential to determine its feasibility on a large scale. The ongoing pragmatic, multicenter, international EVOLVE-MI (Evolocumab administered Very Early to Reduce the Risk of Cardiovascular Events in Patients Hospitalization With Acute Myocardial Infarction; NCT05284747) trial is designed to provide robust evidence regarding both clinical outcomes and cost-effectiveness of early evolocumab initiation after MI.

Interestingly, the early evolocumab group showed different changes in Lp(a) levels at 2 weeks compared to the non-evolocumab group. As elevated Lp(a) is an independent risk factor for recurrent cardiovascular events in ACS, this early reduction is clinically relevant.[24] Other studies have also shown that early PCSK9 inhibitor therapy can blunt the rise in Lp(a) after MI, supporting its role in the acute phase.[25][26] Therefore, PCSK9 inhibitors may serve as a dual-target therapy for LDL-C and Lp(a), especially beneficial for ACS patients with elevated baseline Lp(a).

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The largest randomized trials and their subgroup analyses have demonstrated the long-term safety of PCSK9 inhibitors in the chronic phase of low LDL-C,[27] while several investigations have explored their efficacy in reducing LDL-C during the acute phase but have not focused on the safety of the lowest LDL-C levels.[20][25][26] Therefore, concerns remain about their safety in the acute phase with evolocumab, particularly with regard to cognitive function. In this study, the safety of a rapid LDL-C reduction of over 100 mg/dL within approximately 2 weeks in statin-naïve patients with a baseline LDL-C of around 140 mg/dL was assessed using a cognitive function questionnaire, revealing results comparable to those of the control group. However, it should be noted that the trial was not powered to assess neurocognitive outcomes, and the absence of differences between groups should be interpreted with caution. Furthermore, the ECog questionnaire is a self-report tool with limited sensitivity for detecting subtle or short-term cognitive changes. Larger, dedicated trials with more comprehensive cognitive assessments and longer follow-up are warranted.

This study has several limitations that should be acknowledged. First, the primary endpoint of this study was the LDL-C level at 2 weeks, chosen to evaluate the early lipid-lowering efficacy of the regimen. While this provides mechanistic insight into the acute-phase response, it does not establish long-term cardiovascular outcomes or the durability of lipid control, thereby limiting the clinical interpretability of our findings with respect to MACE prevention. Furthermore, because only a single dose of PCSK9 inhibitor was administered rather than the standard biweekly regimen, a rebound in LDL-C levels was observed at 4 weeks. Although our study design employed a single administration of evolocumab to evaluate the acute lipid-lowering effect, the LDL-C rebound observed at 4 weeks indicates that this approach is not clinically viable as a long-term treatment strategy. Therefore, our findings should be interpreted as exploratory evidence of the short-term efficacy and safety of early PCSK9 inhibition rather than as support for a single-dose regimen. Second, while this study focused on statin-naïve patients, its applicability to those already on lipid-lowering therapy remains unclear. Additional research is needed to explore the role of early PCSK9 inhibitor initiation in different patient subgroups, including those with prior statin use. Finally, although our study employed rosuvastatin 5 mg in combination with ezetimibe 10 mg to approximate the lipid-lowering potency of high-intensity statin therapy, this regimen is not currently recommended as standard initial therapy in major international guidelines. Furthermore, the supporting evidence for this baseline strategy was largely derived from studies conducted in chronic, stable ASCVD populations rather than in acute-phase ACS.[8][9] While these findings informed our rationale, extrapolation to ACS patients should be interpreted with caution given the distinct pathophysiological dynamics and heightened vulnerability in the early post-ACS period. Given its single-center design, modest sample size, and short follow-up, our trial should be regarded as exploratory and hypothesis-generating, warranting confirmation in larger, dedicated studies in ACS populations.

In conclusion, in statin-naïve patients with ACS undergoing PCI, early initiation of a single dose of evolocumab in combination with moderate-intensity statin and ezetimibe led to greater LDL-C reductions and higher target achievement rates compared to statin and ezetimibe alone. This lipid-lowering strategy also demonstrated a favorable safety profile, with comparable cognitive function or adverse events. These findings support the potential utility of early triple combination therapy as an effective and well-tolerated approach to optimize lipid management during the early phase of ACS with high ischemic risk.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1
Everyday Cognition questionnaire (modified short version)

Supplementary Table 2
Serial changes in biochemical measures during study period

Supplementary Table 3
One-month clinical and biochemical safety outcomes

Supplementary Figure 1
LDL-C reduction at week 2 in each groups.

Supplementary Figure 2
LDL-C lowering efficacy at 4 weeks. (A) Percentage reduction in LDL-C from baseline to week 4 and (B) proportion of patients achieving both ≥50% LDL-C reduction and an absolute LDL-C level <55 mg/dL at week 4.

Supplementary Figure 3
Serial changes in lipid profiles at baseline, week 2, and week 4 in (A) evolocumab and (B) non-evolocumab group.

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