ORIGINAL ARTICLE

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Short-term effects of PCSK-9 inhibitors on percutaneous coronary intervention in patients with acute coronary syndrome

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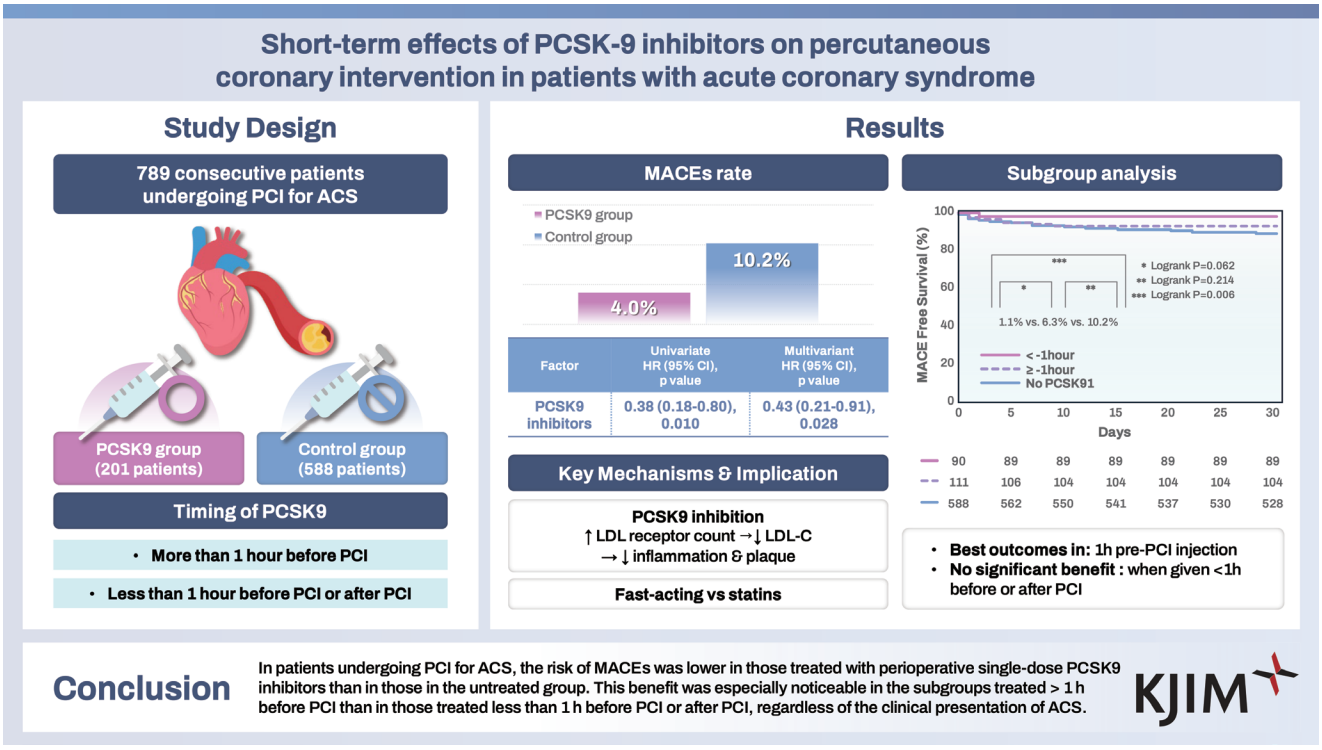

Background/Aims: Proprotein-converting enzyme subtilisin-kexin type 9 (PCSK9) inhibitors act more promptly and efficiently than statins and reduce the risk of cardiovascular events in patients with acute coronary syndrome (ACS). This study aimed to assess the short-term effects of perioperative administration of a single-dose PCSK9 inhibitor in patients with ACS.

Methods: This study included 789 consecutive patients undergoing percutaneous coronary intervention (PCI) for ACS. The primary clinical endpoint was the occurrence of major adverse cardiovascular events (MACEs) within one month, including cardiac death, non-fatal myocardial infarction, unanticipated revascularization, stroke, stent thrombosis, and rehospitalization for ischemic causes or heart failure.

Results: PCSK9 inhibitors were administered to 201 of 789 patients. MACEs occurred in eight patients (4.0%) in the treated

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group and 60 patients (10.2%) in the non-treated group for one month (hazard ratio 0.38, 95% confidence interval 0.18 to 0.80, $p = 0.010$). The benefit of PCSK9 inhibitors in terms of MACEs was greater in the subgroup of patients treated more than 1 hour before PCI than in the subgroup treated less than 1 hour before PCI or treated after PCI and in the non-treated group.

Conclusions: In patients undergoing PCI for ACS, the risk of MACEs was lower in those treated with perioperative single-dose PCSK9 inhibitors than in those in the untreated group. This benefit was especially noticeable in the subgroups treated > 1 hour before PCI than in those treated less than 1 hour before PCI or after PCI, regardless of the clinical presentation of ACS.

Keywords: PCSK9 inhibitors; Perioperative care; Acute coronary syndrome; Percutaneous coronary intervention; Cardiovascular diseases

INTRODUCTION

Hyperlipidemia, particularly low-density lipoprotein cholesterol (LDL-C), is a major risk factor for atherosclerotic cardiovascular disease [1]. Clinical event incidence positively correlated with total LDL-C exposure; for every 1 mmol/L drop in LDL-C level, the risk of cardiovascular events decreased by approximately 22% [2,3].

In addition to the traditional lipid-lowering medications statins and ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are now considered essential lipid-lowering medications because they can decrease the degradation of LDL receptors (LDLRs) and enhance the clearance of LDL-C [4-6]. PCSK9 monoclonal antibodies such as evolocumab and alirocumab are the most commonly used PCSK9 inhibitors in clinical practice. PCSK9 inhibitors lower LDL-C and the levels of other lipids, such as apolipoprotein B, lipoprotein (a), and non-high-density lipoprotein cholesterol, stabilize plaques, stop inflammation, and lower the risk of cardiovascular events [7-9].

High-dose statin pretreatment is recommended for patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI) [10,11]. PCSK9 inhibitors act more promptly and efficiently than statins and reduce the risk of cardiovascular events in patients with ACS [12,13]. Additionally, recent research suggests that early PCSK9 inhibitor use has considerable advantages in lowering lipid levels and reversing plaques in patients with ACS [13-15]. A PCSK9 inhibitor should be added soon after the event (if possible, during hospitalization for the ACS event) in patients who present with ACS and whose LDL-C levels are not at the goal despite taking a maximally tolerated statin dose and ezetimibe before the event [11,16]. However, it is still unknown whether single-dose perioperative use of PCSK9 inhibitors, regardless of LDL-C levels or prior statin use can benefit patients and whether PCSK9 inhibitors should be administered before or after the procedure.

This study aimed to assess the short-term effects of perioperative administration of a single-dose PCSK9 inhibitor in patients with ACS.

METHODS

Study population

In this retrospective observational cohort study, we obtained actual case data from the Cardiovascular Center of Chosun University Hospital. The study protocol was approved by the Research Ethics Committee of Chosun University Hospital (approval number: CHOSUN 2022-06-013), with a waiver of informed consent granted due to the retrospective nature of the study. The study population included 789 consecutive patients with ACS who underwent PCI between December 2019 and November 2021.

Procedures and periprocedural medications

Coronary interventions and medical therapy were performed per relevant standard recommendations [17]. Prior to PCI, all patients had been administered loading doses of aspirin (300 mg), P2Y12 inhibitors (clopidogrel 300–600 mg, prasugrel 60 mg, or ticagrelor 180 mg), and high-dose statins (atorvastatin 80 mg or rosuvastatin 40 mg) unless they had already taken these drugs. Anticoagulation had been performed using low-molecular-weight or unfraction-

ated heparin to obtain an active clotting time of 250 to 300 seconds during PCI. The treatment plans for the stenting method, access site, type of drug-eluting stent or drug-eluting balloon, use of glycoprotein IIb/IIIa inhibitors, use of PCSK9 inhibitors, and use of intravascular imaging or invasive physiological evaluation had been left to the discretion of the operators.

Outcome measures and follow-up

The primary clinical endpoint of interest in this analysis was the occurrence of major adverse cardiovascular events (MACEs) within one month, including cardiac death, non-fatal myocardial infarction, unanticipated revascularization, stroke, stent thrombosis, and rehospitalization for ischemic causes or heart failure.

The PCI to PCSK9 inhibitors injection time calculation

The PCI to PCSK9 inhibitors injection time was defined as the PCSK9 inhibitor injection time minus the PCI (wiring or ballooning) time. For example, if a PCSK9 inhibitor is administered 1 hour before PCI, the PCI to PCSK9 inhibitors time

Table 1. Baseline characteristics

Characteristic	Total (n = 789)	Usual care[c] with PCSK9I injection (n = 201)	Usual care[c] only (n = 588)	*p* value
Age (yr)	66.3 ± 12.9	65.6 ± 12.2	66.5 ± 13.1	0.379
Sex, male	588 (74.5)	149 (74.1)	439 (74.7)	0.882
Hypertension	384 (48.7)	102 (50.7)	282 (48.0)	0.495
Diabetes mellitus	245 (31.1)	57 (28.4)	188 (32.0)	0.339
Chronic kidney disease	37 (4.7)	10 (5.0)	27 (4.6)	0.824
Atrial fibrillation	21 (2.7)	7 (3.5)	14 (2.4)	0.402
Cerebrovascular disease history	53 (6.7)	16 (8.0)	37 (6.3)	0.415
Dyslipidemia	75 (9.5)	19 (9.5)	56 (9.5)	0.976
Prior PCI history	146 (18.5)	33 (16.4)	113 (19.2)	0.378
Statin naïve	579 (73.4)	150 (74.6)	429 (73.0)	0.644
Smoking[a]	245 (31.1)	61 (30.3)	184 (31.3)	0.803
Heart failure history	24 (3.0)	5 (2.5)	19 (3.2)	0.596
Presented as STEMI	346 (43.9)	91 (45.3)	255 (43.4)	0.638
Presented as NSTEMI	255 (32.3)	58 (28.9)	197 (33.5)	0.224
Presented as unstable angina	188 (23.8)	52 (25.9)	136 (23.1)	0.431
LDL-C (mg/dL)	101 ± 42	101 ± 42	100 ± 42	0.739
Creatinine (mg/dL)	1.16 ± 1.10	1.17 ± 1.24	1.16 ± 1.04	0.876
eGFR (mL/min/1.73 m^2)[b]	77.1 ± 29.2	77.2 ± 26.4	77.1 ± 30.1	0.985
NT-proBNP (pg/mL)	2,962 ± 7,800	2,323 ± 6,246	3,181 ± 8,257	0.124
hs-CRP (mg/dL)	1.05 ± 2.37	0.90 ± 2.12	1.10 ± 2.45	0.299
LVEF (%)	53.5 ± 11.0	52.2 ± 11.8	54.0 ± 10.6	0.046

Values are presented as mean ± standard deviation or number (%).
PCSK9I, proprotein convertase subtilisin/kexin type 9 inhibitor; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-STEMI; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; hs-CRP, high-sensitivity C-reactive protein; LVEF, left ventricular ejection fraction.
[a]"Smoking" represents active smokers as well as ex-smokers who stopped smoking less than 1 year before PCI.
[b]eGFR was calculated using the Modification of Diet in Renal Disease formula; GFR = 186.3 × (serum creatinine) $^{-1.54}$ × (age) $^{-0.203}$ × (0.742 if female).
[c]Usual care was provided to all patients per the ACC/AHA 2014 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction.

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is -1 hour; if a PCSK9 inhibitor is administered 1 hour after PCI, the PCI to PCSK9 inhibitors time is +1 hour.

Data collection procedures

Data for both baseline characteristics and outcomes of interest, including the primary endpoint and patient-, disease-, and procedure-related factors, were collected from the Chosun University Hospital electronic medical record system, primarily by reviewing the physicians' notes documented during admission, outpatient cardiology clinic visits, emergency visits, and the results of all laboratory and diagnostic investigations conducted during the study.

Statistical analysis

All values are expressed as means ± standard deviation or number (percentage). Continuous variables were compared using Student's t-test or the Mann–Whitney U test, as appropriate. Chi-square (statistical) analysis was used to compare baseline characteristics between the groups for non-continuous variables.

Table 2. Angiographic and procedural data

Characteristic	Total (n = 789)	Usual care[a] with PCSK9I injection (n = 201)	Usual care[a] only (n = 588)	*p* value
Vessel treated				
LM	52 (6.6)	12 (6.0)	40 (6.8)	0.681
LAD	476 (60.3)	122 (60.7)	353 (60.0)	0.902
LCx	203 (25.7)	43 (21.4)	160 (27.2)	0.103
RCA	310 (39.3)	92 (45.8)	218 (37.1)	0.029
Multivessel disease	424 (53.7)	105 (52.2)	319 (54.3)	0.621
Stent type				
DES	736 (93.3)	188 (93.5)	548 (93.2)	0.870
Total stent number	1.41 ± 0.68	1.38 ± 0.68	1.42 ± 0.69	0.448
Total stent length (mm)	39.9 ± 23.1	39.2 ± 24.0	40.1 ± 22.8	0.658
Imaging guided PCI	23 (2.9)	5 (2.5)	18 (3.1)	0.676

Values are presented as number (%) or mean ± standard deviation.
PCSK9I, proprotein convertase subtilisin/kexin type 9 inhibitor; LM, left main coronary artery; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; RCA, right coronary artery; DES, drug-eluting stent.
[a]Usual care was provided to all patients per the ACC/AHA 2014 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction.

Table 3. Event rates

Characteristic	Total (n = 789)	Usual care[a] with PCSK9I injection (n = 201)	Usual care[a] only (n = 588)	*p* value
Primary endpoint	68 (8.6)	8 (4.0)	60 (10.2)	0.007
Cardiac death	48 (6.1)	7 (3.5)	41 (7.0)	0.074
Rehospitalization	16 (2.0)	1 (0.5)	15 (2.6)	0.075
Non-fatal reinfarction	2 (0.3)	0 (0.0)	2 (0.3)	0.408
Unanticipated revascularization	4 (0.5)	0 (0.0)	4 (0.7)	0.241
Stroke	2 (0.3)	0 (0.0)	2 (0.3)	0.408
Stent thrombosis	4 (0.5)	0 (0.0)	4 (0.7)	0.241

Values are presented as number (%).
PCSK9I, proprotein convertase subtilisin/kexin type 9 inhibitor.
[a]Usual care was provided to all patients per the ACC/AHA 2014 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction.

The Kaplan–Meier method was used to calculate event-free survival and the log-rank test was used to compare the results. Multivariate Cox regression models were used to examine the potential independent relationship between PCSK9 inhibitors and MACE-free survival. Baseline clinical and procedural parameters ($p < 0.05$) were entered into a multivariate Cox proportional hazards model. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal time interval between PCI and PCSK9 inhibitor injections to maximize the reduction in MACEs. The area under the curve was determined using 95% confidence intervals (CIs). All tests were two-tailed, with a significance threshold of 0.05. Statistical analyses were performed using SPSS 29.0.0.0 (IBM Corp., Armonk, NY, USA) and MedCalc (version 22.007; MedCalc Software Ltd., Ostend, Belgium).

RESULTS

Baseline characteristics of the cohort

Of the 789 patients, 201 (25.5%) received PCSK9 inhibitors. Evolocumab (140 mg) was the most commonly used PCSK9 inhibitor (190 patients), whereas alirocumab (150 mg) was administered to only 11 patients. The mean age was 66.3 ± 12.9 years; most patients were male (74.5%). Tables 1 and 2 summarize the patients' baseline clinical and procedural characteristics. The proportions of patients with hypertension (48.7%), diabetes mellitus (31.1%), chronic kidney disease (4.7%), atrial fibrillation (2.7%), cerebrovascular disease history (6.7%), dyslipidemia (9.5%), prior PCI history (18.5%), smoking (31.1%), and heart failure history (3.0%) were similar between the two groups (with and without PCSK9 injection). The prevalence (%) of clinical presentations of ACS, such as ST-segment elevation myocardial infarction (STEMI), non-STEMI (NSTEMI), and unstable angina were comparable. In addition, there were no significant differences in the blood levels of LDL-C, renal function, N-terminal pro-B-type natriuretic peptide (NT-proBNP), or high-sensitivity C-reactive protein. Patients who received PCSK9 inhibitors had a lower ejection fraction and more right coronary artery interventions than patients who had not been given PCSK9 inhibitors.

Clinical outcomes

MACEs occurred in 68 patients (8.6%) during the 1-month follow-up period, with 60 (10.2%) in the usual care group and only eight (4.0%) in the PCSK9 inhibitor injection group. In terms of the cases of MACEs, the usual care group was more likely to experience cardiac death (7.0%) and rehospitalization for ischemic reasons or heart failure (2.6%) than were patients who had been given PCSK9 inhibitor. PCSK9 inhibitor significantly reduce the likelihood of these two types of events (3.5% cardiac death, $p = 0.074$; 0.5% rehospitalization, $p = 0.075$) (Table 3).

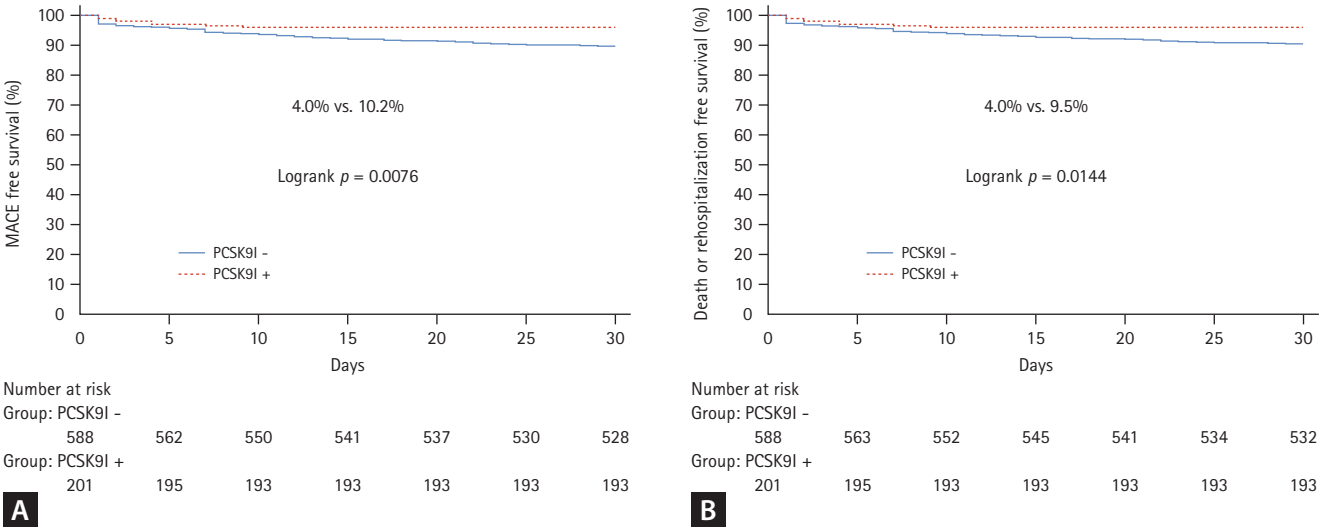

Figure 1. MACEs free survival and death or rehospitalization-free survival according to PCSK9Is. MACEs free survival (A), death or rehospitalization-free survival (B). MACEs, major adverse cardiovascular events; PCSK9Is, proprotein convertase subtilisin/kexin type 9 inhibitors.

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Survival analyses

Upon performing the Kaplan–Meier analysis of the data, we found that the incidence of MACEs in the month following a procedure was lower in patients in the PCSK9 inhibitor injection group compared to the corresponding results in the usual care group ($p = 0.0076$) (Fig. 1A). Additionally, during treatment, patients in the PCSK9 inhibitor injection group had a lower incidence of cardiac mortality or rehospitaliza-

Table 4. Cox proportional hazard analyses for determining the significant and independent predictors of MACE

Factor	Univariate		Multivariate	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
PCSK9 inhibitors	0.38 (0.18–0.80)	0.010	0.43 (0.21–0.91)	0.028
Age ≥ 66 yr	3.03 (1.75–5.24)	< 0.001	1.96 (1.06–3.66)	0.033
Sex, female	2.25 (1.39–3.64)	< 0.001	1.09 (0.63–1.87)	0.768
Hypertension	2.10 (1.27–3.47)	0.004	1.47 (0.86–2.53)	0.162
Chronic kidney disease	2.92 (1.39–6.10)	0.004	0.96 (0.43–2.12)	0.913
Presented as myocardial infarction	2.82 (1.29–6.18)	0.009	2.12 (0.95–4.76)	0.067
eGFR ≤ 77.8 mL/min/1.73 m^2	2.68 (1.58–4.55)	< 0.001	1.44 (0.81–2.58)	0.220
NT-proBNP ≥ 234 pg/mL	4.05 (2.25–7.29)	< 0.001	1.55 (0.78–3.08)	0.213
hsCRP ≥ 0.18 mg/dL	2.65 (1.56–4.51)	< 0.001	1.50 (0.84–2.66)	0.172
LVEF ≤ 54%	2.86 (1.67–4.90)	< 0.001	1.88 (1.07–3.32)	0.029
LM PCI	2.92 (1.53–5.56)	0.001	1.26 (0.59–2.68)	0.553
LAD PCI	3.98 (2.04–7.79)	< 0.001	3.38 (1.70–6.75)	< 0.001
Multivessel disease	2.12 (1.26–3.58)	0.005	1.50 (0.87–2.57)	0.141
Imaging-guided PCI	2.70 (1.09–6.71)	0.033	1.90 (0.67–5.37)	0.229

MACE, major adverse cardiovascular event; HR, hazard ratio; CI, confidence interval; PCSK9, proprotein convertase subtilisin/kexin type 9; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; hsCRP, high-sensitivity C-reactive protein; LVEF, left ventricular ejection fraction; LM, left main coronary artery; PCI, percutaneous coronary intervention; LAD, left anterior descending coronary artery.

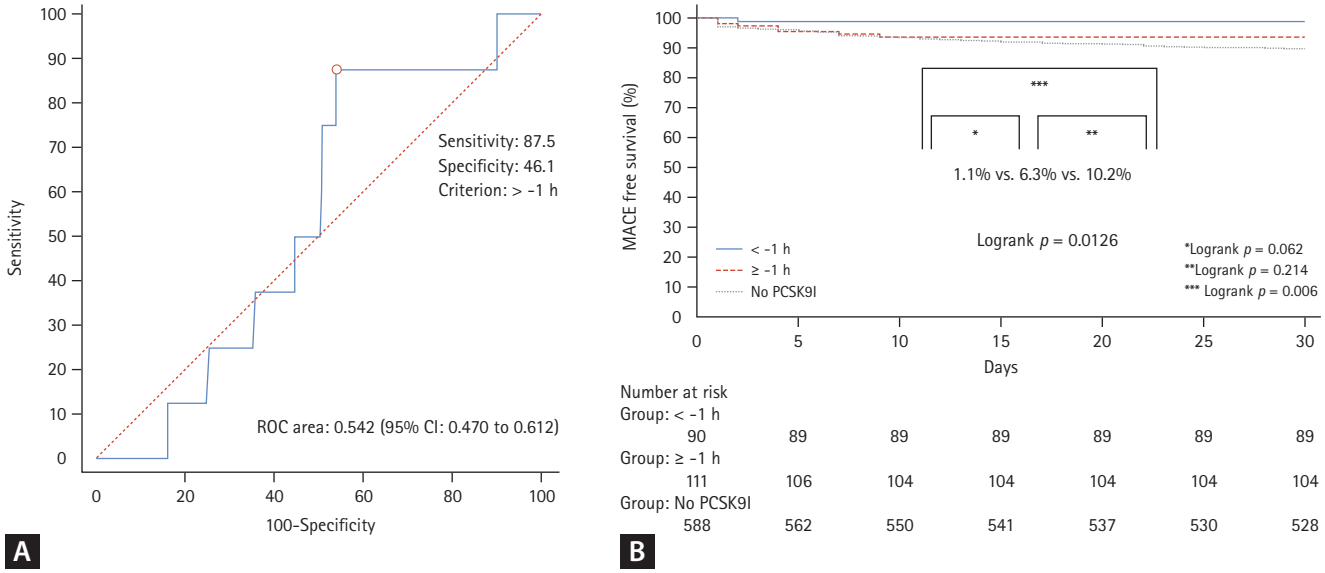

Figure 2. Impact of PCSK9Is injection timing. The ROC curve of the PCI to PCSK9Is time predicts the likelihood of MACEs (A), MACEs free survival based on PCI to PCSK9Is time (B). ROC, receiver operating characteristic; CI, confidence interval; PCSK9Is, proprotein convertase subtilisin/kexin type 9 inhibitors; PCI, percutaneous coronary intervention; MACEs, major adverse cardiovascular events.

tion owing to ischemic causes or heart failure ($p = 0.0144$) (Fig. 1B). There were no significant differences between the two groups of patients in terms of nonfatal myocardial infarction, unexpected revascularization, stroke, or stent thrombosis during the therapy period.

Cox hazard analysis of MACEs

Cox hazard analysis was performed to determine whether there were any interactions between the administration of PCSK9 inhibitor injections and other clinical variables in the case of MACEs. PCSK9 inhibitors were found to have reduced the risk of MACEs (hazard ratio 0.38, 95% CI 0.18–0.80, $p = 0.010$). From the univariate analysis, the following factors were significantly associated ($p < 0.05$) with occurrence of MACEs: age ≥ 66 years, female, hypertension, chronic kidney disease, the presence of myocardial infarction, low estimated glomerular filtration rate, high NT-proBNP, high sensitivity C-reactive protein, low left ventricular ejection fraction (LVEF), left main PCI, left anterior descending (LAD) PCI, multivessel disease, and imaging-guided PCI. These factors were included in the Cox proportional hazard model, which showed that PCSK9 inhibitors were beneficial in lowering the risk of MACEs regardless of age, clinical presentation of myocardial infarction, low LVEF, or LAD PCI (Table 4).

Timing of injection of PCSK9 inhibitors

The median PCI to PCSK9 inhibitors injection time was -0.87 hours (-52 minutes [25th–75th percentiles -12.7 to +1.7 hours]). ROC curve analysis was performed to determine the most appropriate time to inject PCSK9 inhibitors to reduce MACEs. The optimal PCI to PCSK9 inhibitor injection time cutoff value (distinguishing patients with and without MACEs) was > 1 hour (Fig. 2A). Supplementary Table 1 demonstrates baseline and procedural characteristics between patients who received PCSK9 inhibitors > 1 hour before PCI and those who received them within 1 hour. Kaplan–Meier analysis showed a trend toward fewer MACEs in patients receiving PCSK9 inhibitors 1 hour or more before PCI than in patients receiving PCSK9 inhibitors 1 hour or less before PCI or after PCI (log-rank $p = 0.062$, Fig. 2B). MACEs were significantly lower in individuals who received PCSK9 inhibitors > 1 hour before PCI than in those who did not receive PCSK9 inhibitors (log-rank $p = 0.006$, Fig 2B). There was no significant difference in the incidence of MACEs between patients who received PCSK9 inhibitors within 1 hour before or after PCI and those who did not receive PCSK9 inhibitors (log-rank $p = 0.214$, Fig. 2B).

Effectiveness of PCSK9 inhibitors on MACEs based on clinical presentations of ACS

We performed a subgroup analysis of patients with STEMI, NSTEMI, and unstable angina to determine whether the efficacy of PCSK9 inhibitors differed according to the clinical presentation of ACS. Among STEMI patients, those who received PCSK9 inhibitors for more than 1 hour before PCI

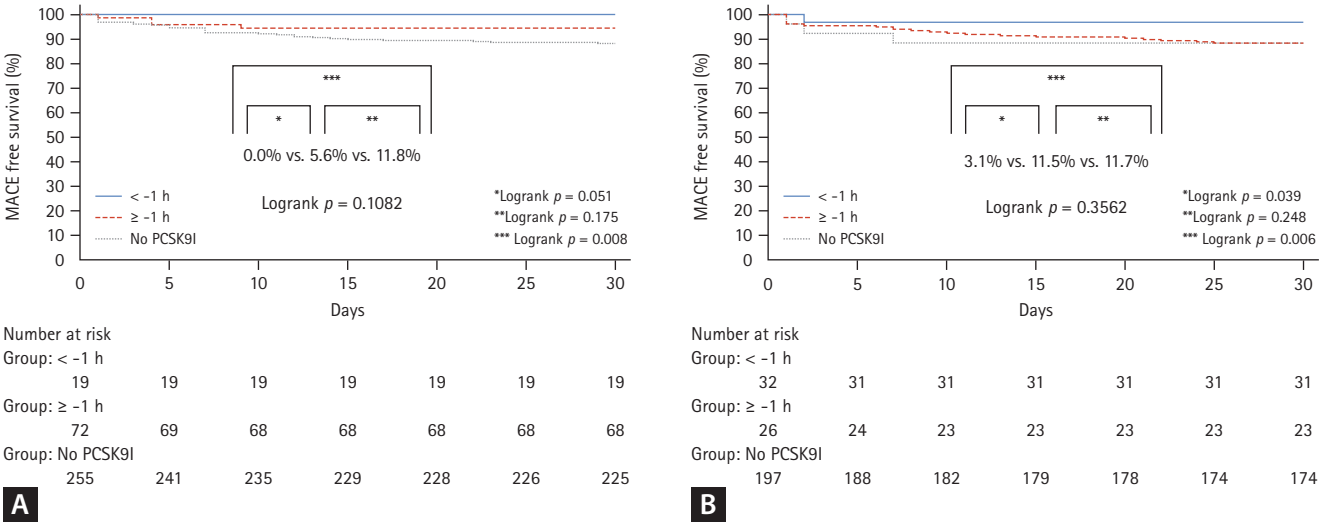

Figure 3. MACEs free survival based on PCSK9Is injection timing and ACS presentation. ST-segment elevation myocardial infarction (A), non-ST-segment elevation myocardial infarction (B). MACEs, major adverse cardiovascular events; PCSK9Is, proprotein convertase subtilisin/kexin type 9 inhibitors; ACS, acute coronary syndrome.

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tended to have lower MACEs than those who received them within 1 hour before or after PCI (log-rank $p = 0.051$, Fig. 3A), and had significantly lower MACEs than those who did not receive PCSK9 inhibitors (log-rank $p = 0.008$, Fig. 3A). Among patients with NSTEMI, those who received PCSK9 inhibitors for more than 1 hour before PCI had significantly fewer MACEs than those who received PCSK9 inhibitors within 1 hour before or after PCI (log-rank $p = 0.039$, Fig. 3B) and considerably fewer MACEs than those who did not receive PCSK9 inhibitors (log-rank $p = 0.006$, Fig 3B). There were no MACEs in unstable angina patients who were using PCSK9 inhibitors.

DISCUSSION

In this study, we aimed to determine the short-term effects of single-dose PCSK9 inhibitors administered before or after PCI in patients with ACS. According to our findings, the perioperative use of single-dose PCSK9 inhibitors considerably reduced the 30-day incidence rate of MACEs. This effect was unrelated to other clinical variables such as age, LVEF, clinical presentation of myocardial infarction, and PCI location of the coronary artery. Additionally, we found that the timing of the PCSK9 inhibitor injection was important. PCSK9 inhibitors administered > 1 hour before PCI (wiring or ballooning) reduced MACEs more effectively than PCSK9 inhibitors administered within 1 hour or after PCI. Surprisingly, there was no statistically significant difference in the MACEs rate between the group with PCSK9 inhibitors administered within 1 hour before or after PCI and the group receiving no PCSK9 inhibitors. However, fewer MACEs were observed in the PCSK9 inhibitor group. These results were similar in both the STEMI and NSTEMI subgroups. The data demonstrates that administration of PCSK9 inhibitors at least 1 hour before PCI in patients with ACS is highly effective in improving short-term clinical outcomes.

The enzyme PCSK9, which is mostly generated in the liver, attaches to the LDLR on the surface of hepatocytes, causing LDLR degradation, and increasing plasma LDL-C levels [18,19]. PCSK9 inhibitors (evolocumab and alirocumab) are innovative lipid-lowering medications that inhibit PCSK9, leading to an increase in the number of LDLRs, a rapid and substantial reduction in LDL-C levels by 50–60%, and a decreased risk of cardiovascular events [12,20,21]. In the EVOPACS study, evolocumab lowered LDL-C levels by 40.7% in ACS patients with high LDL-C levels [13]. Patients with non-ST-segment elevation ACS in the EVACS study received a single dose of evolocumab, and at one month, the LDL-C levels were lower in this group [22]. When given as soon as possible after ACS, both evolocumab and alirocumab showed signs of plaque stabilization and regression in intracoronary imaging studies of patients with ACS [15,23]. In the PACMAN-AMI study, alirocumab resulted in higher coronary plaque regression and stability at 52 weeks than the placebo on a background of rosuvastatin 20 mg daily in non-infarct-related arteries [15].

PCSK9 inhibitors are currently recommended for patients whose LDL-C target is not achieved after 4–6 weeks of maximally tolerated statin dose in combination with ezetimibe [11]. When a patient has ACS and their LDL-C levels are above the target despite taking ezetimibe and a maximum tolerated statin dose before the incident, a PCSK9 inhibitor should be introduced as soon as possible (ideally during hospitalization for an ACS event) [11,16].

As patients with ACS have a significant incidence of recurrent episodes in the early post-onset period, lowering LDL-C levels during this period would prevent early recurrence [24-26]. Therefore, pre-treatment with high-dose statins is recommended for patients with ACS who are undergoing PCI [10,11]. PCSK9 inhibitors work faster and more effectively than statins in minimizing the risk of cardiovascular events in patients with ACS [12]. Recently, studies have focused on lipid profiles and clinical outcomes of PCSK9 inhibitors administered during the peri-PCI period. A retrospective single-center study of patients with acute myocardial infarction (AMI) indicated that a single dose of 140 mg of evolocumab administered during the peri-PCI period resulted in a significantly greater reduction in LDL-C levels and a higher proportion of patients reaching the target LDL-C level in the early phase of AMI than those who did not receive evolocumab [27]. The EPIC-STEMI study used a regimen to administer PCSK9 inhibitors before PCI [28]. Alirocumab lowered LDL-C levels by 22% compared with a sham control in this randomized study of routine early initiation of PCSK9 inhibitors in patients with primary PCI for STEMI on a background of high-intensity statin treatment [28]. A multicenter, prospective, randomized, controlled superiority study is being conducted in 530 statin-naïve patients with myocardial infarction to evaluate differences in 12-month MACEs between those who received evolocumab before PCI and those who did not [29].

Interestingly, in this study, the baseline LDL-C levels were near optimal and there was no statistically significant difference between the PCSK9 and non-PSK9 inhibitor groups. These findings suggested that the short-term clinical effects of PCSK9 inhibitors are not limited to patients with high LDL-C levels.

From this perspective, our findings offer the first evidence that the administration of PCSK9 inhibitors before PCI in patients with ACS may enhance short-term clinical outcomes. In addition, this is the first study to demonstrate the time effect of PCSK9 inhibitors administration before PCI by modeling the PCI-to-injection time as a continuous variable using a real-world database. PCSK9 inhibitors have rapid pharmacodynamic effects on PCSK9, with maximal inhibition occurring within 4 hours [30]. Although PCSK9 inhibitors take effect much more rapidly than statins, the effect is not instantaneous. Adequate time is needed; more precisely, PCSK9 injections should be administered at least 1 hour before PCI to achieve a short-term effect.

Limitations

This study had several limitations. First, our study had a modest sample size and was performed at a single center. Second, this was a retrospective observational study. Consequently, the findings and conclusions should be viewed in the context of these constraints. Third, some information was not assessed and could not be retrospectively examined, such as the follow-up LDL-C level, postprocedural myocardial ischemia such as cardiac biomarkers (Creatine Kinase-MB, high-sensitivity troponin), and inflammatory markers at one month, which would have been interesting.

Conclusions

This study revealed that patients who received perioperative single-dose PCSK9 inhibitors treatment while undergoing PCI for ACS, regardless of LDL-C levels or prior statin use, had a decreased risk of MACEs within one month compared to those who did not receive treatment. This effect was more significant in patients who were given the injection more than 1 hour before PCI compared to those who were given the injection less than 1 hour before PCI or after PCI, independent of the clinical manifestations of ACS. Prospective studies involving larger patient populations are required to support these conclusions.

KEY MESSAGE

1. The short-term effects of perioperative administration of a single-dose PCSK9 inhibitor were evaluated in patients with ACS.
2. Patients who received perioperative single-dose PCSK9 inhibitor treatment while undergoing PCI for ACS, regardless of LCL-C levels or prior statin use, had a decreased risk of MACEs within one month compared to those who did not receive treatment.
3. This effect was more significant in patients treated more than 1 hour before PCI than in those treated less than 1 hour before PCI or after PCI, independent of the clinical manifestations of ACS.

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Supplementary Table 1. Baseline and procedural characteristics according to PCSK9I injection time

Characteristic	Total (n = 201)	PCSK9I injection > 1-hour pre-PCI (n = 90)	PCSK9I injection ≤ 1-hour pre-PCI or after PCI (n = 111)	*p* value
Age (yr)	65.6 ± 12.2	68.2 ± 12.1	63.5 ± 11.9	0.005
Sex, male	149 (74.1)	58 (64.4)	91 (82.0)	0.005
Hypertension	102 (50.7)	53 (58.9)	49 (44.1)	0.038
Diabetes mellitus	57 (28.4)	31 (34.4)	26 (23.4)	0.085
Chronic kidney disease	10 (5.0)	5 (5.6)	5 (4.5)	0.733
Atrial fibrillation	7 (3.5)	5 (6.6)	2 (1.8)	0.149
Cerebrovascular disease history	16 (8.0)	10 (11.1)	6 (5.4)	0.137
Dyslipidemia	19 (9.5)	11 (12.2)	8 (7.2)	0.227
Prior PCI history	33 (16.4)	20 (22.2)	13 (11.7)	0.045
Statin naïve	150 (74.6)	60 (66.7)	90 (81.1)	0.021
Smoking[a)]	61 (30.3)	20 (22.2)	41 (36.9)	0.024
Heart failure history	5 (2.5)	3 (3.3)	2 (1.8)	0.488
Presented as STEMI	91 (45.3)	19 (21.1)	72 (64.9)	< 0.001
Presented as NSTEMI	58 (28.9)	32 (35.6)	26 (23.4)	0.059
Presented as unstable angina	52 (25.9)	39 (43.3)	13 (11.7)	< 0.001
LDL-C (mg/dL)	101 ± 42	93 ± 42	106 ± 41	0.028
Creatinine (mg/dL)	1.17 ± 1.24	1.08 ± 0.89	1.25 ± 1.47	0.354
eGFR (mL/min/1.73 m^2)[b)]	77.2 ± 26.4	77.4 ± 25.5	77.0 ± 27.1	0.911
NT-proBNP (pg/mL)	2,323 ± 6,246	2,175 ± 4,962	2,443 ± 7,139	0.763
hs-CRP (mg/dL)	0.90 ± 2.12	0.96 ± 2.16	0.85 ± 2.11	0.711
LVEF (%)	52.2 ± 11.8	53.0 ± 12.4	51.5 ± 11.2	0.366
Vessel treated				
LM	12 (6.0)	8 (8.9)	4 (3.6)	0.116
LAD	122 (60.7)	57 (63.3)	65 (58.6)	0.491
LCx	43 (21.4)	24 (26.7)	19 (17.1)	0.101
RCA	92 (45.8)	33 (36.7)	59 (53.2)	0.020
Multivessel disease	105 (52.2)	50 (55.6)	55 (49.5)	0.397
Stent type				
DES	188 (93.5)	84 (93.3)	104 (93.7)	0.918
Total stent number	1.38 ± 0.68	1.46 ± 0.69	1.32 ± 0.67	0.161
Total stent length (mm)	39.2 ± 24.0	41.2 ± 24.3	37.6 ± 23.8	0.304
Imaging guided PCI	5 (2.5)	2 (2.2)	3 (2.7)	0.828
Admission to PCI time (h)	14.8 ± 20.6	23.8 ± 22.5	7.43 ± 15.6	< 0.001

Values are presented as mean ± standard deviation or number (%).

PCSK9I, proprotein convertase subtilisin/kexin type 9 inhibitor; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-STEMI; LDL-C, Low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; hs-CRP, high-sensitivity C-reactive protein; LVEF, left ventricular ejection fraction; LM, left main coronary artery; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; RCA, right coronary artery; DES, drug-eluting stent.

[a)]"Smoking" represents active smokers as well as ex-smokers who stopped smoking less than 1 year before PCI.

[b)]eGFR was calculated using the Modification of Diet in Renal Disease formula; GFR = 186.3 × (serum creatinine)$^{-1.54}$ × (age)$^{-0.203}$ × (0.742 if female).