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Potent $P2Y_{12}$ inhibitors in patients with acute myocardial infarction and cardiogenic shock

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Abstract

Background Although potent $P2Y_{12}$ inhibitors, such as ticagrelor and prasugrel, are standard treatment in patients with acute myocardial infarction (AMI), evidence for their efficacy and safety compared with clopidogrel is limited in patients with AMI complicated by cardiogenic shock.

Methods Among 28,949 patients from the nationwide pooled registry of KAMIR-NIH and KAMIR-V, a total of 1482 patients (5.1%) with AMI and cardiogenic shock who underwent percutaneous coronary intervention of the culprit vessel were selected. Primary outcome was major adverse cardiovascular event (MACE, a composite of cardiac death, MI, repeat revascularization and definite stent thrombosis) and major secondary outcome was Bleeding Academic Research Consortium (BARC) type 2 or greater bleeding at 2 years.

Results Among the study population, 537 patients (36.2%) received potent $P2Y_{12}$ inhibitors and 945 patients (63.8%) received clopidogrel after index procedure. The risk of MACE was significantly lower in the potent $P2Y_{12}$ inhibitors group than in the clopidogrel group (16.6% versus 24.7%; adjusted hazard ratio [HR], 0.76 [95% CI 0.59–0.99]; $P=0.046$). Regarding BARC type 2 or greater bleeding, there was no significant difference between the potent $P2Y_{12}$ inhibitors group and the clopidogrel group (12.5% versus 10.7%; adjusted HR, 1.36 [95% CI 0.98–1.88]; $P=0.064$). Significant interaction was observed in patients aged ≥ 75 years (interaction $P=0.021$) or venoarterial extracorporeal membrane oxygenator (VA-ECMO) use (interaction $P=0.015$) for significantly increased risk of BARC type 2 or greater bleeding following the use of potent $P2Y_{12}$ inhibitors.

Conclusions In patients with AMI complicated by cardiogenic shock, the use of potent $P2Y_{12}$ inhibitors was associated with a lower risk of MACE compared with clopidogrel, without an increased risk of BARC type 2 or greater bleeding. The current data supports the use of potent $P2Y_{12}$ inhibitors in patients with AMI and cardiogenic shock, except in patients aged ≥ 75 years or receiving VA-ECMO support.

Keywords Acute myocardial infarction, Cardiogenic shock, $P2Y_{12}$ inhibitors, Major cardiovascular event, Bleeding

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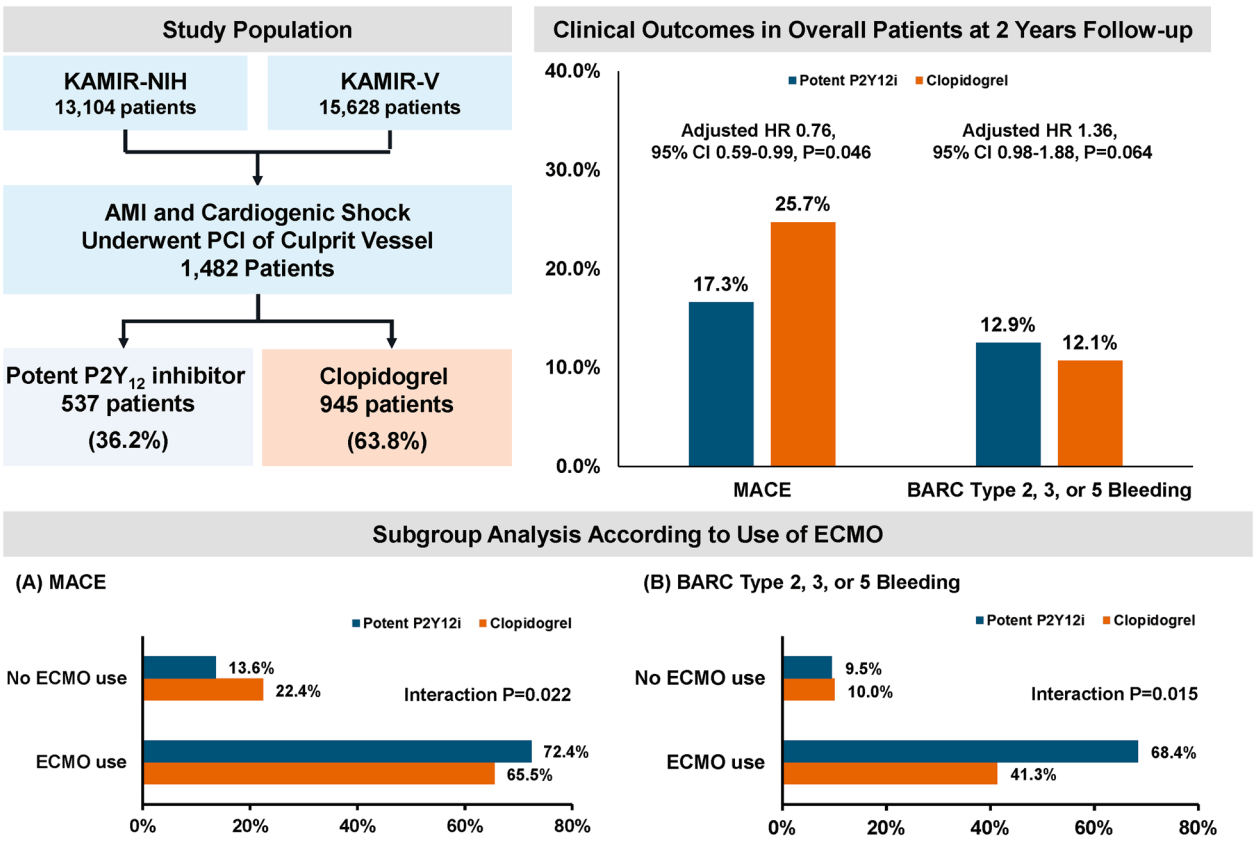
Graphical abstract



Background

Acute myocardial infarction (AMI) places a significant burden on healthcare systems worldwide and requires timely and effective coronary revascularization and therapeutic interventions to improve mortality [1]. After successful percutaneous coronary intervention (PCI), dual antiplatelet therapy (DAPT) plays a key role in preventing thrombotic complications and reducing the risk of recurrent cardiovascular events [1]. Based on several randomized clinical trials, potent $P2Y_{12}$ inhibitors, such as ticagrelor and prasugrel, have become the standard of care for the treatment of AMI, offering more potent and consistent platelet inhibition compared to clopidogrel [1–3].

Among AMI patients, 5–10% of patients present with cardiogenic shock, and is associated with nearly 30% to 50% of in-hospital mortality despite advanced management [4]. In patients with AMI and cardiogenic shock where both thrombotic and bleeding risks are elevated, the selection of $P2Y_{12}$ inhibitors presents a significant challenge to clinicians [5]. A number of factors inherent to the pathophysiology of cardiogenic shock may influence the antiplatelet efficacy of $P2Y_{12}$ inhibitors, including alterations in drug absorption, metabolism, and platelet reactivity [5–7]. Furthermore, other therapeutic interventions, such as mechanical circulatory support, renal replacement therapy, or targeted temperature management, influence both thrombotic and bleeding risks, and interact with antithrombotic drug absorption and metabolism [5, 6].

However, despite the established clinical efficacy of potent $P2Y_{12}$ inhibitors in AMI, evidence for their efficacy and safety compared with clopidogrel is limited in patients with AMI and cardiogenic shock. The landmark trials comparing potent $P2Y_{12}$ inhibitors to clopidogrel excluded patients with cardiogenic shock, and previous non-randomized studies with limited sample size presented conflicting results on the comparative efficacy of potent $P2Y_{12}$ inhibitors in patients with AMI and cardiogenic shock [2, 3, 8–10].

Therefore, we sought to evaluate the prognostic impact of potent $P2Y_{12}$ inhibitors in patients with AMI and cardiogenic shock, using the nationwide, multicenter, prospective KAMIR (Korea Acute Myocardial Infarction Registry) registries.

Methods

Study protocols and patient selection

The current study is an individual patient level pooled data analysis of two independent AMI-dedicated registries: the KAMIR-NIH (Korea Acute Myocardial Infarction Registry-National Institutes of Health) and the KAMIR-V (Korea Acute Myocardial Infarction Registry-V). KAMIR-NIH is a registry that consecutively enrolled patients with AMI at 20 tertiary university hospitals in Korea capable of primary percutaneous coronary intervention (PCI) from November 2011 to December 2015. KAMIR-V is a registry of consecutive patients with AMI at 43 cardiovascular centers in Korea from January 2016 to June 2020. The detailed study protocols of registries were previously described [11, 12]. The protocol of the KAMIR-NIH and KAMIR-V registries were approved by the ethics committee at each participating center, and all patients provided written informed consent. The registry protocols were conducted according to the principles of the Declaration of Helsinki.

Among a total of 28,949 patients enrolled in the KAMIR-NIH and KAMIR-V registries, we selected patients with AMI complicated by cardiogenic shock. Both ST-segment elevation MI (STEMI) and non-ST-segment elevation MI (NSTEMI) were included. STEMI was defined as new ST-segment elevation in ≥ 2 contiguous leads measuring ≥ 0.1 mV, or a new left bundle branch block on 12-lead ECG, with a concomitant increase of at least one cardiac biochemical marker of necrosis [13]. NSTEMI was defined as AMI without the abovementioned criteria of new ST-segment elevation [13].

Cardiogenic shock was defined as 1 of the following: Killip class 4, Society for Cardiovascular Angiography and Interventions stages C to E, or systolic blood pressure < 90 mmHg for more than 30 min with clinical evidence of end-organ hypoperfusion (at least one cool extremity, decreased urine output, increased lactic acidosis, or altered mental status) [14]. For the current analysis, patients were additionally excluded if they died within 24 h after index procedure, with unavailable follow-up data, or changed $P2Y_{12}$ inhibitors during hospitalization. As a result, 1482 patients were selected for the current analysis and classified according to use of potent $P2Y_{12}$ inhibitors such as ticagrelor or prasugrel (Fig. 1).

Patient management

Patients were managed in accordance with contemporary guidelines. The adoption of treatment strategies, including the intervention techniques, type of stents, and the use of medications, intravascular imaging, or hemodynamic support devices, were left to the operator's discretion. Regarding DAPT, a loading dose of aspirin 300 mg was given before PCI, unless patients were already on aspirin therapy for at least 7 days. A loading dose of clopidogrel 600 mg, prasugrel 60 mg, or ticagrelor 180 mg was given before PCI, unless patients were already on $P2Y_{12}$ inhibitor therapy for at least 7 days. All patients were recommended to take aspirin and a $P2Y_{12}$ inhibitor at least for 12 months after index procedure unless there was an undisputed reason for discontinuing antiplatelet agents. Medications including beta-blockers, renin–angiotensin–aldosterone system inhibitors, statins, and oral anticoagulants were prescribed according to practice guidelines.

Data collection and follow-up

Demographics, cardiovascular risk factors and symptoms were recorded by detailed interview with patient or guardian, or review of electronic medical records. Admission data including clinical presentation, initial vital signs, electrocardiographic and laboratory findings were collected at the emergency department. Findings of coronary angiography and procedural characteristics of PCI, as well as information about complications, and discharge medications were collected during hospitalization. Procedural success was defined as the final residual stenosis was $< 30\%$ with Thrombolysis In Myocardial Infarction (TIMI) grade 3 flow. After discharge, patients were followed at 6, 12, and 24 months by outpatient visit or telephone contact. All data were collected by independent clinical research coordinators, using a web-based case report form in the internet-based Clinical Research and Trial management system (iCReaT). Clinical events were independently adjudicated by an independent event adjudication committee.

Study outcomes

The primary outcome was major adverse cardiovascular events (MACE), a composite of cardiac death, MI, repeat revascularization, and definite stent thrombosis at 2 years of follow-up. The major secondary outcome was Bleeding Academic Research Consortium (BARC) type 2 or greater bleeding at 2 years. Other secondary outcomes were the individual components of MACE, all-cause death, and cerebrovascular event at 2 years. Clinical outcomes within 30 days were also analyzed as secondary outcomes. Death of unknown cause was considered

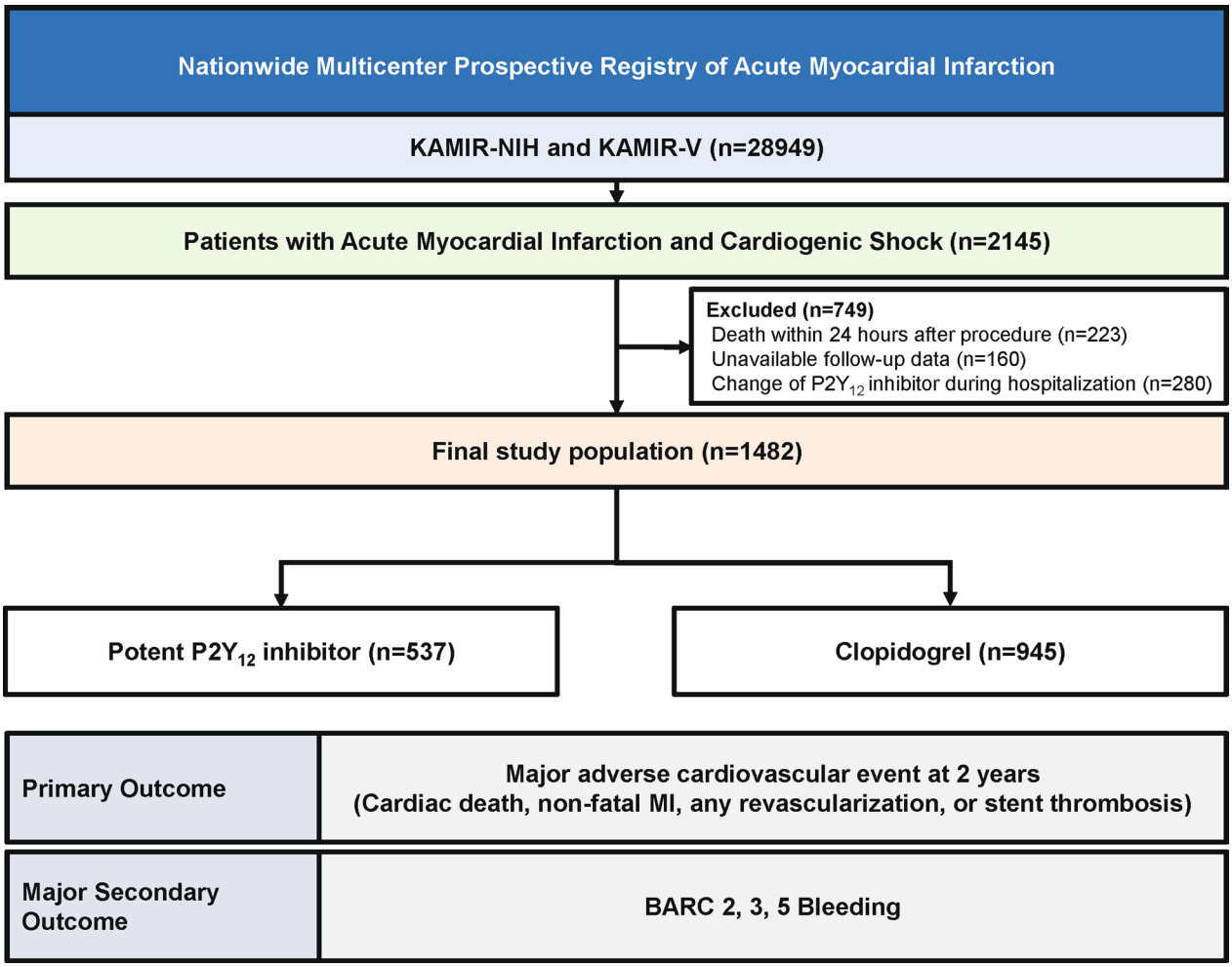


Fig. 1 Study Flow. The study population was derived from the nationwide, multicenter, prospective KAMIR-NIH (Korea Acute Myocardial Infarction Registry-National Institute of Health) and KAMIR-V (Korea Acute Myocardial Infarction Registry-V) registries. Abbreviations: BARC, Bleeding Academic Research Consortium; MI, myocardial infarction

cardiac death according to the definitions of the Academic Research Consortiums (ARC) [15]. Recurrent MI was defined as the recurrence of symptoms or the presence of electrocardiographic changes with a rise in cardiac biomarker levels above the upper limit of normal. Periprocedural MI was not included as a clinical event in this study. A repeat revascularization event was defined as clinically-driven unplanned revascularization. Planned staged PCI was coded separately and was not included as a clinical event. Definite stent thrombosis was defined according to the ARC definitions [15].

Statistical analysis

Categorical variables are presented as frequencies with percentages, and continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range) according to their distribution, checked by Kolmogorov–Smirnov test. To examine the significance of differences in baseline characteristics among groups, we used the Chi-square test for categorical variables and Student's t test or Mann–Whitney U test for continuous variables according to their distribution. Cumulative event rates were calculated based on Kaplan–Meier estimates and comparison of clinical outcomes between groups was performed with the log-rank test. For the calculation of the cumulative primary outcome, only the first event from the composite endpoint (e.g., cardiac death, MI, repeat revascularization, or definite stent thrombosis) was counted for each patient.

Multiple sensitivity analyses were performed to adjust the confounders. First, a multivariable Cox regression model was used. Covariables in the multivariable model were selected if significantly different between the two groups or clinically relevant. Adjusted variables were age, sex, presented with STEMI, previous MI, previous cerebrovascular accident, heart failure, atrial fibrillation,

diabetes mellitus, hypertension, current smoking, three-vessel disease, acute renal failure during hospitalization, oral anticoagulant use and use of venoarterial extracorporeal membrane oxygenation (VA-ECMO) and intra-aortic balloon pump. The assumption of proportionality was assessed using the log-minus-log plot and Cox proportional hazard models for all clinical outcomes satisfied the proportional hazards assumption. Second, propensity-score matched cohort and inverse-probability weighted Cox proportional hazard regressions were performed. For propensity score-matching and inverse probability treatment of weighting (IPTW) analysis, the logistic regression model for use of $P2Y_{12}$ inhibitor was used to calculate propensity scores. Patients with clopidogrel were matched 1:1 with patients with potent $P2Y_{12}$ inhibitor by "nearest-neighbor matching" (a greedy match) without replacement. The inverse probability treatment-weighting analyses were performed based on propensity scores. Propensity score matching (PSM) yielded 503 patients in the clopidogrel group and 503 patients in the potent $P2Y_{12}$ inhibitor group. Residual differences between the two groups after PSM or IPTW adjustment were assessed by calculating absolute standardized mean differences. Absolute standardized mean differences were < 0.1 across all matched covariates (age, sex, presentation with STEMI, previous MI, previous cerebrovascular accident, heart failure, atrial fibrillation, diabetes mellitus, hypertension, current smoking, three-vessel disease, acute renal failure during hospitalization, oral anticoagulant use, use of VA-ECMO and intra-aortic balloon pump, and use of drug-eluting stent), indicating successful balance achievement between the two groups (Supplemental Fig. 1 and Supplemental Table 1). Third, subgroup analysis of primary and major secondary outcomes was performed according to clinical and procedural factors of interest between the two groups. The interaction between treatment effect and the covariables was evaluated by a Cox proportional hazard regression model.

All probability values were 2-sided, and P values < 0.05 were considered statistically significant. Statistical analyses were performed using R version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

Baseline clinical and procedural characteristics are summarized in Table 1. Among the total population, 537 patients (36.2%) received potent $P2Y_{12}$ inhibitors, including ticagrelor or prasugrel, and 945 patients (63.8%) received clopidogrel. Patients receiving potent $P2Y_{12}$ inhibitors were younger and more likely to be male compared with patients in the clopidogrel group. A greater proportion of patients in the potent $P2Y_{12}$ inhibitors group presented with STEMI than in the clopidogrel group (84.0% versus 70.8%; $P < 0.001$). Use of VA-ECMO during hospitalization was not significantly different between the two groups (6.3% versus 7.7%; $P = 0.372$). The rates of complete revascularization during index hospitalization were comparable between the two groups (60.1% versus 60.9%; $P = 0.811$). During the procedure, DES was more frequently used in the potent $P2Y_{12}$ inhibitors group compared with the clopidogrel group (97.1% versus 91.8%; $P < 0.001$) and the use of thrombus aspiration or glycoprotein IIb/IIIa inhibitor were not significantly different between the two groups. The relatively low rates of radial access were observed in both groups (Table 1).

Clinical outcomes according to use of potent $P2Y_{12}$ inhibitors

Comparisons of clinical outcomes between the potent $P2Y_{12}$ inhibitors and the clopidogrel groups are presented in Table 2 and Fig. 2. The risk of MACE was significantly lower in the potent $P2Y_{12}$ inhibitors group than in the clopidogrel group (16.6% versus 24.7%; adjusted hazard ratio [HR], 0.76 [95% CI 0.59–0.99]; $P = 0.046$). This was mainly driven by significantly lower risk of cardiac death in the potent $P2Y_{12}$ inhibitors group (11.2% versus 24.8%; adjusted HR, 0.60 [95% CI 0.42–0.85]; $P = 0.004$). There was no significant difference in the risk of BARC type 2 or greater bleeding between the two groups (12.5% versus 10.7%; adjusted HR, 1.36 [95% CI 0.98–1.88]; $P = 0.064$). Sensitivity analyses using PSM, and IPTW adjustment showed consistent results with multivariable adjusted analysis (Table 2 and Fig. 3).

The clinical outcomes at 30 days also showed a significantly lower risk of MACE in the potent $P2Y_{12}$ inhibitors group than the clopidogrel group (7.4% versus 13.5%; adjusted HR, 0.63 [95% CI 0.43–0.93]; $P = 0.019$) and comparable risk of BARC type 2 or greater bleeding between the two groups (9.3% versus 7.6%; adjusted HR, 1.46 [95% CI 0.99–2.14]; $P = 0.052$) (Supplemental Table 2). The results comparing ticagrelor and prasugrel individually to clopidogrel are also presented in Supplemental Table 3.

Subgroup analysis

The prognostic impact of potent $P2Y_{12}$ inhibitors among the various subgroups is presented in Fig. 4. Regarding the risk of MACE, significant interaction was observed between potent $P2Y_{12}$ inhibitors and the use of VA-ECMO. Among patients without the use of VA-ECMO, there was a significantly lower risk of MACE following potent $P2Y_{12}$ inhibitors than clopidogrel (HR, 0.56 [95% CI 0.42–0.74]). Conversely,

Table 1 Baseline characteristics of patients with AMI and Cardiogenic shock according to potent $P2Y_{12}$ inhibitors

Characteristics	Total (n = 1,482)	Potent $P2Y_{12}$i (n = 537)	Clopidogrel (n = 945)	*P* Value
Demographics				
Age, years	66.1 ± 12.4	62.4 ± 11.5	68.2 ± 12.4	< 0.001
Male, no. (%)	1116 (75.3)	447 (83.2)	669 (70.8)	< 0.001
Body mass index, kg/m^2	23.6 ± 3.5	23.9 ± 3.4	23.4 ± 3.5	0.004
Initial presentation, no. (%)				< 0.001
ST-segment elevation MI	1134 (76.5)	451 (84.0)	683 (72.3)	
Non-ST-segment elevation MI	348 (23.5)	86 (16.0)	262 (27.7)	
Anterior MI	514 (36.2)	192 (36.0)	322 (36.3)	0.928
Hemodynamic data				
Systolic blood pressure, mmHg	85.7 ± 32.6	86.5 ± 31.4	85.2 ± 33.3	0.496
Diastolic blood pressure, mmHg	52.5 ± 21.7	53.7 ± 21.1	51.9 ± 22.0	0.159
Heart rate, beats/min	71.4 ± 30.8	67.6 ± 27.8	73.5 ± 32.1	< 0.001
Medical history, no. (%)				
Hypertension	760 (51.3)	232 (43.2)	528 (55.9)	< 0.001
Diabetes mellitus	448 (30.2)	136 (25.3)	312 (33.0)	0.002
Dyslipidemia	164 (11.1)	56 (10.4)	108 (11.4)	0.614
Current smoking	571 (40.1)	264 (50.7)	307 (34.0)	< 0.001
Cerebrovascular accident	125 (8.5)	27 (5.0)	98 (10.4)	< 0.001
Heart failure	35 (2.4)	5 (0.9)	30 (3.2)	0.011
Previous MI	110 (7.4)	25 (4.7)	85 (9.0)	0.003
Atrial fibrillation	174 (11.9)	49 (9.2)	125 (13.4)	0.023
LVEF, %	48.9 ± 12.7	50.8 ± 11.6	47.7 ± 13.1	< 0.001
Arteries with stenosis, no. (%)				
1	629 (42.9)	220 (41.0)	409 (44.0)	0.278
2	493 (33.6)	186 (34.6)	307 (33.0)	0.573
3	329 (22.4)	131 (24.4)	198 (21.3)	0.194
Laboratory data				
Hemoglobin, g/dL	13.1 ± 2.2	13.8 ± 1.9	12.8 ± 2.3	< 0.001
Cr, mg/dL	1.4 ± 1.2	1.2 ± 0.6	1.5 ± 1.5	< 0.001
Glycated hemoglobin, %	6.5 ± 1.5	6.5 ± 1.6	6.5 ± 1.4	0.714
Total cholesterol, mg/dL	160.7 ± 45.6	166.9 ± 45.4	157.4 ± 45.3	< 0.001
HDL-cholesterol, mg/dL	69.1 ± 40.8	62.4 ± 39.6	73.1 ± 41.0	< 0.001
LDL-cholesterol, mg/dL	70.9 ± 47.4	85.6 ± 46.4	62.4 ± 45.9	< 0.001
Discharge medication, no. (%)				
Aspirin	1478 (99.7)	537 (100.0)	941 (99.6)	0.323
RASi	947 (63.9)	346 (64.4)	601 (63.6)	0.791
Beta blocker	989 (66.7)	384 (71.5)	605 (64.0)	0.004
Calcium channel blocker	71 (4.8)	14 (2.6)	57 (6.0)	0.005
Oral anticoagulants	71 (4.8)	9 (1.7)	62 (6.6)	< 0.001
Statin	1235 (83.3)	481 (89.6)	754 (79.8)	< 0.001
Procedural Characteristics				
Culprit-only PCI on index procedure, no. (%)	1147 (80.9)	419 (78.6)	728 (82.3)	0.105
Multivessel PCI on index procedure, no. (%)	271 (19.1)	114 (21.4)	157 (17.7)	0.105
Complete revascularization during index hospitalization, no. (%)	860 (60.6)	321 (60.1)	539 (60.9)	0.811
Radial access, no. (%)	316 (22.3)	156 (29.2)	160 (18.1)	< 0.001
Thrombus aspiration, no. (%)	353 (24.9)	121 (22.7)	232 (26.2)	0.151
GPIIbIIIa inhibitor use, no. (%)	250 (17.6)	105 (19.7)	145 (16.4)	0.134
Treatment method, no. (%)				
Drug-eluting stent	1296 (93.8)	506 (97.1)	790 (91.8)	< 0.001

Table 1 (continued)

Characteristics	Total (n = 1,482)	Potent $P2Y_{12}$i (n = 537)	Clopidogrel (n = 945)	*P* Value
Intravascular imaging used, no. (%)	300 (21.1)	134 (25.1)	166 (18.8)	0.006
Mean no. of stents used per patient	1.2 ± 0.8	1.4 ± 0.8	1.2 ± 0.9	0.003
Total length of stents, mm	30.5 ± 14.5	31.7 ± 14.5	29.7 ± 14.4	0.014
Procedural success, no. (%)	1402 (98.8)	527 (98.7)	875 (98.9)	0.959
Use of VA-ECMO, no. (%)	107 (7.2)	34 (6.3)	73 (7.7)	0.372
Use of IABP, no. (%)	170 (11.5)	37 (6.9)	133 (14.1)	< 0.001
Acute renal failure during hospitalization, no. (%)	62 (4.2)	38 (4.0)	24 (4.5)	0.780
CPR during hospitalization, no. (%)	406 (27.4)	129 (24.0)	277 (29.3)	0.033
Ventricular tachycardia during hospitalization, no. (%)	177 (11.9)	60 (11.2)	117 (12.4)	0.545

Cr, creatinine; CPR, cardiopulmonary resuscitation; HDL, high density lipoprotein; LDL, low density lipoprotein; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; RASi, renin-angiotensin-system inhibitor; VA-ECMO, venoarterial extracorporeal membrane oxygenation

Table 2 Clinical outcomes according to use of potent $P2Y_{12}$ inhibitors

	Potent $P2Y_{12}$i (n = 537)	Clopidogrel (n = 945)	Unadjusted HR (95% CI)	Adjusted HR† (95% CI)	*P* value	PSM-adjusted‡ HR (95% CI)	*P* value	IPTW-adjusted‡ HR (95% CI)	*P* value
MACE*	89 (16.6%)	233 (24.7%)	0.62 (0.49–0.80)	0.76 (0.59–0.99)	0.046	0.74 (0.55–0.98)	0.036	0.73 (0.56–0.95)	0.018
Secondary outcomes									
Death	60 (11.2%)	234 (24.8%)	0.42 (0.32–0.56)	0.56 (0.41–0.76)	< 0.001	0.54 (0.39–0.76)	< 0.001	0.60 (0.44–0.82)	0.001
Cardiac death	47 (8.8%)	175 (18.5%)	0.44 (0.32–0.61)	0.60 (0.42–0.85)	0.004	0.58 (0.40–0.84)	0.004	0.63 (0.44–0.89)	0.009
MI	9 (1.7%)	17 (1.8%)	0.86 (0.38–1.93)	1.11 (0.45–2.77)	0.823	1.29 (0.45–3.72)	0.635	0.97 (0.42–2.23)	0.947
Repeat revascularization	38 (7.1%)	58 (6.1%)	1.03 (0.68–1.54)	1.03 (0.66–1.61)	0.901	0.97 (0.61–1.53)	0.883	0.86 (0.56–1.31)	0.473
Stent thrombosis	3 (0.6%)	4 (0.4%)	1.19 (0.27–5.3)	1.30 (0.27–6.21)	0.744	0.95 (0.13–6.77)	0.963	1.31 (0.28–6.13)	0.732
Cerebrovascular event	9 (1.7%)	10 (1.1%)	1.45 (0.59–3.56)	2.04 (0.73–5.67)	0.172	1.43 (0.51–4.01)	0.499	2.81 (1.04–7.64)	0.043
BARC ≥ 2 bleeding	67 (12.5%)	101 (10.7%)	1.11 (0.82–1.52)	1.36 (0.98–1.88)	0.064	1.28 (0.89–1.85)	0.189	1.27 (0.91–1.79)	0.164

*MACE was a composite of cardiac death, MI, repeat revascularization, and definite stent thrombosis at 2 years of follow-up

† Adjusted for variables of age, sex, presented with STEMI, previous MI, previous cerebrovascular accident, heart failure, atrial fibrillation, diabetes mellitus, hypertension, current smoking, three-vessel disease, acute renal failure during hospitalization, oral anticoagulant use and use of venoarterial extracorporeal membrane oxygenation and intra-aortic balloon pump

‡ For propensity score-matching and inverse probability treatment-weighting analysis, the logistic regression model for use of $P2Y_{12}$ inhibitors was used to calculate propensity scores. Patients with clopidogrel were matched 1:1 with patients with potent $P2Y_{12}$ inhibitors by "nearest-neighbor matching" (a greedy match) without replacement. The inverse probability treatment-weighting analyses were performed based on propensity scores. Residual differences in characteristics between matched cohorts were assessed by calculating the absolute standardized mean differences. Absolute standardized mean differences were < 0.1 across all matched covariates (age, sex, presentation with STEMI, previous MI, previous cerebrovascular accident, heart failure, atrial fibrillation, diabetes mellitus, hypertension, current smoking, three-vessel disease, acute renal failure during hospitalization, oral anticoagulant use, use of venoarterial extracorporeal membrane oxygenation and intra-aortic balloon pump, and use of drug-eluting stent), indicating successful balance achievement between the two groups (Supplemental Fig. 1 and Supplemental Table 1)

Abbreviations: BARC, Bleeding Academic Research Consortium; CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; MACE, major adverse cardiovascular events; MI, myocardial infarction; PSM, propensity score matching

patients who required VA-ECMO during hospitalization showed lack of benefit following potent $P2Y_{12}$ inhibitors than clopidogrel (HR, 1.10 [95% CI 0.67–1.80]) (interaction $P = 0.022$). In terms of BARC type 2 or greater bleeding, patients aged ≥ 75 years and the use of VA-ECMO were associated with the increased risk of BARC type 2 or greater bleeding following potent $P2Y_{12}$ inhibitors than clopidogrel (interaction $P = 0.021$ and 0.015, respectively).

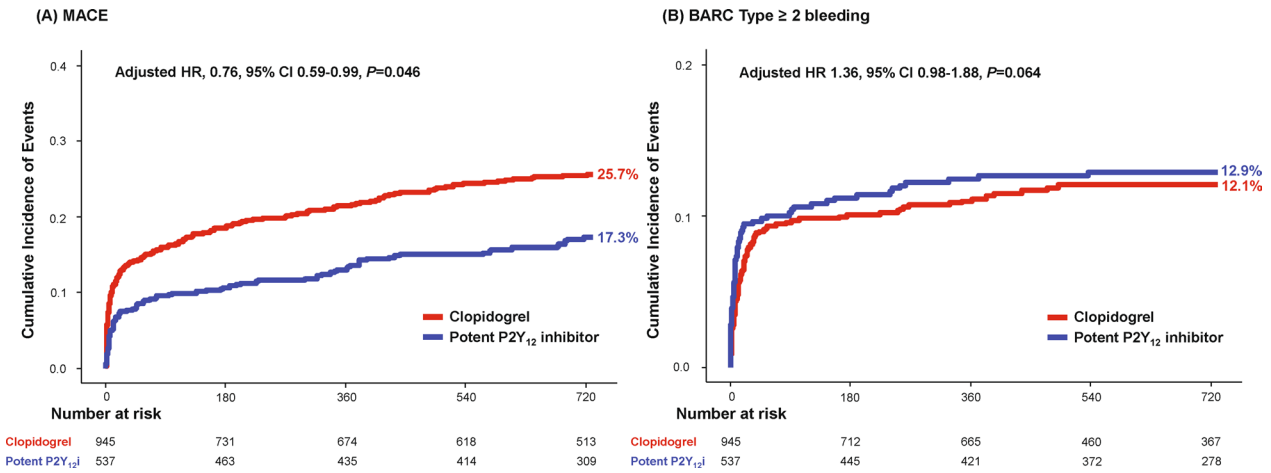


Fig. 2 Primary and Major Secondary Outcomes in AMI patients with Cardiogenic Shock According to Use of Potent $P2Y_{12}$ Inhibitors. Kaplan–Meier curves with cumulative incidence of (**A**) MACE and (**B**) BARC type 2 or greater bleeding according to use of potent $P2Y_{12}$ inhibitors are shown. Abbreviations: AMI, acute myocardial infarction; BARC, Bleeding Academic Research Consortium; CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events

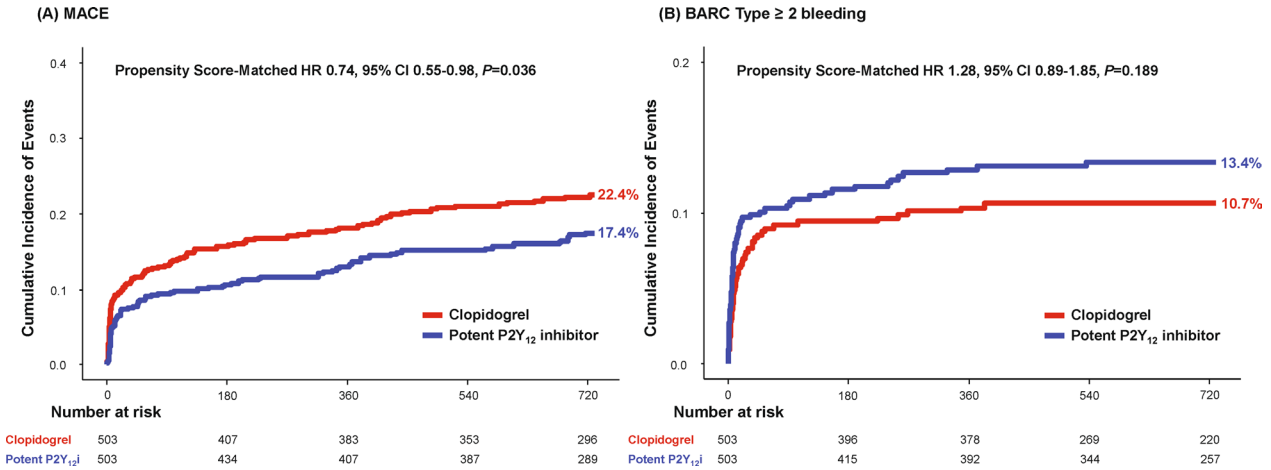


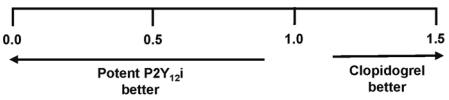
Fig. 3 Primary and Major Secondary Outcomes in AMI patients with Cardiogenic Shock According to Use of Potent $P2Y_{12}$ Inhibitors Among Propensity Score-Matched Population. Kaplan–Meier curves with cumulative incidence of (**A**) MACE and (**B**) BARC type 2 or greater bleeding according to use of potent $P2Y_{12}$ inhibitors among propensity score-matched populations are shown. Abbreviations: AMI, acute myocardial infarction; BARC, Bleeding Academic Research Consortium; CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events

Discussion

The current study evaluated 2-year clinical outcomes between potent $P2Y_{12}$ inhibitors and clopidogrel in patients with AMI and cardiogenic shock using nationwide, multicenter, prospective AMI registries. Main findings were as follows. First, potent $P2Y_{12}$ inhibitors showed a significantly lower risk of MACE than clopidogrel after PCI in patients with AMI and cardiogenic shock. Multiple sensitivity analysis including PSM and IPTW adjustment showed consistent results. Second, there was no significant difference in the risk of BARC type 2 or greater bleeding between potent $P2Y_{12}$ inhibitors and clopidogrel. Third, there was a significant interaction between the treatment effect of $P2Y_{12}$ inhibitors and prespecified subgroups who required ECMO during hospitalization or were 75 years of age or older for significantly increased risk of BARC type 2 or greater bleeding following the use of potent $P2Y_{12}$ inhibitors than clopidogrel.

(A) MACE

Subgroup		Event number / Patient number		Hazard ratio (95% CI)	Interaction *P*
		Potent $P2Y_{12}i$	Clopidogrel		
Age ≥ 75 years	No	71/451	125/601	0.72(0.54-0.96)	0.586
	Yes	18/86	108/344	0.61(0.37-1.01)	
Sex	Female	20/90	75/276	0.78(0.48-1.28)	0.385
	Male	69/447	158/669	0.60(0.46-0.80)	
Clinical presentation	NSTEMI	22/86	68/262	0.98(0.61-1.59)	0.057
	STEMI	67/451	165/683	0.56(0.42-0.75)	
Diabetes mellitus	No	63/401	144/633	0.65(0.48-0.87)	0.811
	Yes	26/136	89/312	0.61(0.39-0.94)	
Multi-vessel disease	No	24/220	79/424	0.55(0.35-0.86)	0.497
	Yes	65/317	145/505	0.66(0.49-0.88)	
Use of ECMO	No	65/503	187/872	0.56(0.42-0.74)	0.022
	Yes	24/34	46/73	1.10(0.67-1.80)	



(B) BARC Type ≥ 2 bleeding

Subgroup		Event number / Patient number		Hazard ratio (95% CI)	Interaction *P*
		Potent $P2Y_{12}i$	Clopidogrel		
Age ≥ 75 years	No	50/451	69/601	0.93(0.64-1.33)	0.021
	Yes	17/86	32/344	2.14(1.19-3.86)	
Sex	Female	17/90	30/276	1.74(0.96-3.15)	0.126
	Male	50/447	71/669	1.00(0.70-1.44)	
Clinical presentation	NSTEMI	12/86	31/262	1.20(0.61-2.33)	0.859
	STEMI	55/451	70/683	1.12(0.79-1.59)	
Diabetes mellitus	No	48/401	63/633	1.14(0.79-1.66)	0.939
	Yes	19/136	38/312	1.11(0.64-1.93)	
Multi-vessel disease	No	28/220	40/424	1.30(0.80-2.10)	0.390
	Yes	39/317	60/505	0.98(0.66-1.47)	
Use of ECMO	No	46/503	77/872	0.98(0.68-1.41)	0.015
	Yes	21/34	24/73	2.32(1.29-4.16)	

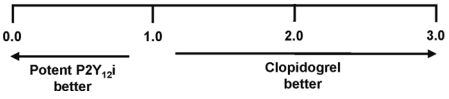


Fig. 4 Subgroup Analysis Regarding Primary and Major Secondary Outcomes. The effects of potent $P2Y_{12}$ inhibitors on the risk of (**A**) MACE and (**B**) BARC type 2 or greater bleeding are shown across various subgroups. Abbreviations: BARC, Bleeding Academic Research Consortium; CI, confidence interval; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; VA-ECMO, venoarterial extracorporeal membrane oxygenation

Limited evidence regarding use of potent $P2Y_{12}$ inhibitors in patients with AMI and cardiogenic shock

Nearly 10% of patients with AMI were complicated by cardiogenic shock [4]. Given the high thrombotic and bleeding risks in patients with AMI and cardiogenic shock, proper antithrombotic therapy is critical to preventing ischemic complication while minimizing bleeding events [1, 4, 5]. Although superior efficacy of potent $P2Y_{12}$ inhibitors than clopidogrel has been supported by landmark trials [2, 3], it should be noted that both TRITON-TIMI 38 and PLATO trials excluded patients with AMI complicated by cardiogenic shock. Furthermore, there were no sufficiently powered randomized controlled trials to evaluate the efficacy and safety of antiplatelet therapies based on potent $P2Y_{12}$ inhibitors in the setting of AMI complicated by cardiogenic shock.

There have been only a few observational studies with inconclusive results. In the pooled sub-analysis of the Intraaortic Balloon Pump in Cardiogenic shock II (IABP-SHOCK II) and Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic shock (CULPRIT-SHOCK) trial which included 856 patients with AMI and cardiogenic shock, there was no significant difference in 1-year mortality rate between potent $P2Y_{12}$ inhibitors and clopidogrel [9]. In the meta-analysis of 1100 patients with AMI complicated by cardiac arrest and/or cardiogenic shock, patients receiving potent $P2Y_{12}$ inhibitors had lower risk of 1-year mortality compared with those receiving clopidogrel [8]. However, the results from the study-level meta-analysis should be interpreted with caution, given the substantial heterogeneity among the study designs and insufficient consideration of potential confounding by patient and clinical variables [8]. As a result, there have been no specific recommendations about selection of the $P2Y_{12}$ inhibitors for patients with AMI and cardiogenic shock in contemporary guidelines [16, 17].

Potent $P2Y_{12}$ inhibitors in patients with AMI and cardiogenic shock

Theoretically, achieving effective platelet inhibition in the setting of AMI improves prognosis by lowering the risk of ischemic complications at the expense of bleeding risk [18]. Potent $P2Y_{12}$ inhibitors, such as prasugrel and ticagrelor, more rapidly and effectively inhibit platelet activity than clopidogrel [2, 3, 19, 20]. Furthermore, previous studies presented that potent $P2Y_{12}$ inhibitors are also more effective for platelet inhibition in the setting of cardiogenic shock compared with clopidogrel [7, 21]. However, the potential benefit of these agents has never been tested by randomized controlled trials, and previous observational studies showed inconclusive results in patients with AMI and cardiogenic shock where both thrombotic and bleeding risk are elevated.

Given the lack of robust evidence supporting the use of potent $P2Y_{12}$ inhibitors in patients with AMI and cardiogenic shock, the current study evaluated the largest number of patients with AMI and cardiogenic shock using nationwide registries. The current study observed that potent $P2Y_{12}$ inhibitors showed consistently lower risk of MACE without increased bleeding than clopidogrel after PCI in patients with AMI and cardiogenic shock. This was mainly driven lower risk of cardiac death within 30 days from the index procedure. These findings support the importance of effective platelet inhibition in preventing thrombotic complications in patients with AMI and cardiogenic shock as well as patients without cardiogenic shock.

Interestingly, the clinical benefit of potent $P2Y_{12}$ inhibitors was reduced in specific subgroups who required VA-ECMO during hospitalization or were 75 years of age or older. These two subgroups showed significantly increased risk of bleeding without reduced risk of MACE following the use of potent $P2Y_{12}$ inhibitors than clopidogrel. These two subgroups have a high risk of bleeding in common. Multiple observational studies have demonstrated an increased risk of bleeding after VA-ECMO support due to several factors, including the use of anticoagulants and the VA-ECMO procedure itself [22, 23]. Furthermore, bleeding events are also significantly associated with an increased risk of in-hospital mortality in patients with VA-ECMO support [22, 23]. In elderly patients with acute coronary syndrome, potent $P2Y_{12}$ inhibitors have been associated with a higher risk of bleeding events in previous randomized controlled trials compared to clopidogrel [2, 3, 24]. Frailty and a higher prevalence of comorbidities and concomitant medications may contribute to an elevated risk of bleeding in elderly patients [24]. Consequently, high bleeding risk in these two subgroups may result in less clinical benefit derived from the use of potent $P2Y_{12}$ inhibitors than the overall cohort. Although the subgroup analysis, particularly for patients requiring VA-ECMO, might be underpowered due to the limited sample size, these results imply that caution is needed in using potent $P2Y_{12}$ inhibitors in these subgroups, and the strategy of antiplatelet agent use should be individualized, according to the inherent risk of bleeding.

Future research

Considering the high mortality rate of patients with cardiogenic shock and the crucial role of antiplatelet therapy in AMI after PCI, dedicated randomized trials for patients with AMI and cardiogenic shock are required to validate and clarify the current observations. In addition, given the significant differences in the management of cardiogenic shock depending on whether mechanical circulatory support devices are used, it is imperative to further evaluate the antiplatelet strategy for patients who require mechanical circulatory support.

Study limitations

Some limitations should be acknowledged. First, this study has an inherent limitation regarding its observational nature with registry data. As the KAMIR registries primarily focus on AMI patients, the use of inotropes and vasopressors, management of noncardiac organ failure including mechanical ventilation and renal replacement therapy and detailed hemodynamic parameters were not systematically collected. Consequently, these variables could not be incorporated within the scope of this study. However, a large sample size was analyzed in this study and with the extensive sensitivity analyses, most of the clinically important confounding factors were adjusted to minimize the bias from different baseline characteristics. Nevertheless, it should be noted that unmeasured confounders including secular trends of changes and advances in treatments could not be adjusted. Second, although all patients were recommended to take DAPT at least for 12 months after index PCI unless there was an undisputed reason for discontinuing antiplatelet agents, the precise duration of DAPT was not available from the registry data. Thus, the clinical impact of the duration of DAPT could not be analyzed. However, considering that the clinical benefit of potent $P2Y_{12}$ inhibitors over clopidogrel was observed at a very early time point in this study, the duration of DAPT may not have a significant impact on our results. Third, this cohort was composed of East Asian patients in whom there were significant differences in the incidence of thrombotic and bleeding complications after PCI, and the pharmacokinetic and pharmacodynamics profiles of antiplatelet drugs compared to Caucasian patients [25]. Further investigation of the clinical impact of potent $P2Y_{12}$ inhibitors for patients with AMI and cardiogenic shock in the Western population is still needed to generalize our findings.

Conclusion

In patients with AMI complicated by cardiogenic shock, the use of potent $P2Y_{12}$ inhibitors was associated with a lower risk of MACE compared with clopidogrel, without an increased risk of BARC type 2 or greater bleeding. The current data supports the use of potent $P2Y_{12}$ inhibitors in patients with AMI and cardiogenic shock, except in patients aged ≥ 75 years or receiving VA-ECMO support.

Abbreviations

AMI	Acute myocardial infarction
BARC	Bleeding Academic Research Consortium
CI	Confidence interval
DAPT	Dual antiplatelet therapy
DES	Drug-eluting stent
HR	Hazard ratio
IPTW	Inverse probability of treatment weighting
KAMIR	Korea Acute Myocardial Infarction Registry
MACE	Major adverse cardiovascular event
PCI	Percutaneous coronary intervention

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-025-05277-y.

Additional file 1.

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None.

Author contributions

Jinhwan Jo and Seung Hun Lee equally contributed to this study as first authors. Joo Myung Lee contributed to conception, design, data acquisition, interpretation, and critical revision and take responsibility for the integrity of study. All other authors contributed to data acquisition, interpretation, and revision.

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Availability of data and materials

Data will be shared on reasonable request to the corresponding author, if required.

Declarations

Ethics approval and consent to participate

The protocol of the KAMIR-NIH and KAMIR-V registries were approved by the ethics committee at each participating center, and all patients provided written informed consent. The registry protocols were conducted according to the principles of the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

Dr. Seung Hun Lee received an Institutional Research Grant from Abbott Vascular and Boston Scientific. Prof. Joo-Yong Hahn received an Institutional Research Grant from National Evidence-based Healthcare Collaborating Agency, Ministry of Health & Welfare, Korea, Abbott Vascular, Biosensors, Boston Scientific, Daiichi Sankyo, Donga-ST, Hanmi Pharmaceutical, and Medtronic Inc. Prof. Hyeon-Cheol Gwon received an Institutional Research Grant from Boston Scientific, Genoss, and Medtronic Inc. Dr. Joo Myung Lee received an Institutional Research Grant from Abbott Vascular, Boston Scientific, Philips Volcano, Terumo Corporation, Zoll Medical, Donga-ST, and Yuhan Pharmaceutical. All other authors declare that there are no competing interests to declare.

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