



Postprocedure Anticoagulation in Patients With Acute ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention

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ABSTRACT

OBJECTIVES This study sought to assess the association between postprocedural anticoagulation (PPAC) use and several clinical outcomes.

BACKGROUND PPAC after primary percutaneous coronary intervention (pPCI) in patients with ST-segment elevation myocardial infarction (STEMI) may prevent recurrent ischemic events but may increase the risk of bleeding. No consensus has been reached on PPAC use.

METHODS Using data from the Improving Care for Cardiovascular Disease in China–Acute Coronary Syndrome registry, conducted between 2014 and 2019, we stratified all STEMI patients who underwent pPCI according to the use of PPAC or not. Inverse probability of treatment weighting and a Cox proportional hazards model with hospital as random effect were used to analyze differences in in-hospital clinical outcomes: the primary efficacy endpoint was mortality and the primary safety endpoint was major bleeding.

RESULTS Of 34,826 evaluable patients, 26,272 (75.4%) were treated with PPAC and were on average younger, more stable at admission with lower bleeding risk score, more likely to have comorbidities and multivessel disease, and more often treated within 12 hours of symptom onset than those without PPAC. After inverse probability of treatment weighting adjustment for baseline differences, PPAC was associated with significantly reduced risk of in-hospital mortality (0.9% vs 1.8%; HR: 0.62; 95% CI: 0.43–0.89; $P < 0.001$) and a nonsignificant difference in risk of in-hospital major bleeding (2.5% vs 2.2%; HR: 1.05; 95% CI: 0.83–1.32; $P = 0.14$).

CONCLUSIONS PPAC in STEMI patients after pPCI was associated with reduced mortality without increasing major bleeding complications. Dedicated randomized trials with contemporary STEMI management are needed to confirm these findings. (J Am Coll Cardiol Intv 2022;15:251–263) © 2022 by the American College of Cardiology Foundation.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

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**ABBREVIATIONS
AND ACRONYMS****ACS** = acute coronary syndrome**CS** = cardiogenic shock**DAPT** = dual antiplatelet therapy**IPTW** = inverse probability of treatment weighting**LMWH** = low-molecular-weight heparin**MACE** = major adverse cardiovascular event(s)**NACE** = net adverse cardiovascular event(s)**PCI** = percutaneous coronary intervention**PPAC** = postprocedural anticoagulation**pPCI** = primary percutaneous coronary intervention**STEMI** = ST-segment elevation myocardial infarction**UFH** = unfractionated heparin

Anticoagulant therapy in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (pPCI) can effectively prevent thrombotic complications and is recommended by the American College of Cardiology/American Heart Association and European Society of Cardiology guidelines.^{1,2} However, no consensus has been reached on whether anticoagulation should be continued after pPCI, when STEMI patients remain at risk for major adverse cardiovascular events (MACE), especially within the first 48 hours, but the rate of major bleeding events increases steadily.³ The decision to continue prescribing an anticoagulant can involve a difficult balance between benefit and risk; in real-life clinical practice, it is often a matter of physician's choice, depending on patient complications and hospital- or clinic-specific prescribing patterns, rather than on any accepted recommendations.^{4,5}

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The effect of postprocedural anticoagulation (PPAC) on reducing mortality and clinically relevant complications, including bleeding, in STEMI patients has been evaluated in randomized clinical trials^{6,7}; however, neither of these studies reached adequate statistical power. The pooled analysis of the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) and EUROMAX (European Ambulance Acute Coronary Syndrome Angiography) trials failed to demonstrate that routine use of PPAC (bivalirudin or unfractionated heparin [UFH], with or without a glycoprotein IIb/IIIa inhibitor) had beneficial effects on ischemic outcomes, and there were higher rates of both protocol-defined bleeding and Thrombolysis In Myocardial Infarction (TIMI) major and minor bleeding.⁶ In the present study, we aimed to explore the association of PPAC use with in-hospital mortality and bleeding rates using a nationwide, real-world registry of patients with acute coronary syndrome (ACS).

METHODS

STUDY DESIGN AND PATIENT SELECTION. Data from the prospective CCC-ACS (Improving Care for Cardiovascular Disease in China-Acute Coronary Syndrome) database were used in the study. Launched in 2014, the CCC-ACS project (NCT02306616) is a

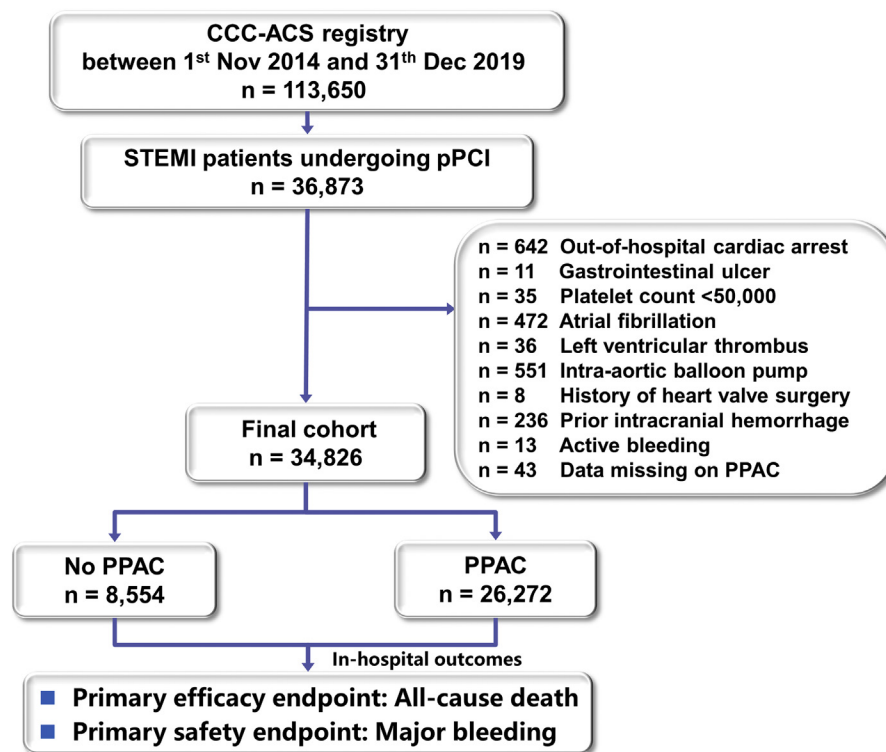
nationwide registry involving 159 tertiary and 82 secondary hospitals across China, and completed in December 2020 with 124,363 participants. The registry is a collaborative program of the American Heart Association and the Chinese Society of Cardiology, focusing on quality improvement efforts for ACS care and modeled in part on the American Heart Association Get With The Guidelines program.⁸ Details of the rationale and design of the CCC-ACS project have been reported previously.⁹ Briefly, in every month, the first 20 to 30 consecutive ACS patients were recruited in tertiary and 10 to 20 in secondary hospital. Patient were eligible for enrollment with a principal discharge diagnosis of ACS, including STEMI, non-STEMI, and unstable angina pectoris. The protocol was approved by the Ethics Committee of Beijing Anzhen Hospital, Capital Medical University.

Patient demographics, medical history, symptoms at admission, in-hospital treatment and procedures, and in-hospital outcomes were collected via an electronic data capture platform. All consecutive patients with STEMI at admission who underwent pPCI during hospitalization in the CCC-ACS registry between November 1, 2014, and December 31, 2019, were included in this study. Patients who had an indication for anticoagulation (eg, atrial fibrillation, left ventricular thrombus) or a bleeding complication (eg, active bleeding) prior to PCI were excluded from the analysis.

DEFINITIONS OF VARIABLES. Medical history and periprocedural details were obtained from patients' medical charts and entered into the database by trained data abstractors. Standardized definitions were utilized across all hospitals for variable collection. STEMI was defined in accordance with the guidelines published by the Chinese Society of Cardiology and extracted from the patient's original medical records.¹⁰ Patients were considered to have comorbidities, such as diabetes, hypertension, or hyperlipidemia, if those had been documented in admission. Renal insufficiency was defined as an estimated glomerular filtration rate of lower than 60 mL/min/1.73 m².¹¹ Patients were classified as having PPAC if they had received anticoagulation therapy with UFH, low-molecular-weight heparin (LMWH), fondaparinux, or other anticoagulants after the procedure. Patients who did not receive any anticoagulant after pPCI were defined as "no PPAC."

ENDPOINTS. The primary efficacy endpoint was in-hospital mortality. The secondary efficacy endpoint was MACE, defined as any occurrence of cardiovascular death, myocardial infarction (MI), stent thrombosis, or stroke during hospitalization. The primary

FIGURE 1 Study Flow Chart



Out of 36,873 ST-segment elevation myocardial infarction (STEMI) patients who underwent primary percutaneous coronary intervention (pPCI) during the study period, 34,826 evaluable patients were included in the study: 26,272 (75.4%) were treated with postprocedural anti-coagulation (PPAC) and 8,554 (24.6%) were not. CCC-ACS = Care for Cardiovascular Disease in China-Acute Coronary Syndromes; PPAC = postprocedural anticoagulation; pPCI = primary percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

safety endpoint was in-hospital major bleeding, including any of the following events: fatal bleeding, intracranial bleeding, retroperitoneal bleeding, drop in hemoglobin ≥ 40 g/L during hospitalization, transfusion with overt bleeding, or bleeding requiring surgical intervention.

Stent thrombosis was defined as an acute or sub-acute stent occlusion after the procedure. MI as an in-hospital event refers to a reinfarction during hospitalization for the index MI. Stroke was defined as a new neurologic deficit during the index event hospitalization. Cardiac arrest was defined in accordance with the Chinese cardiopulmonary resuscitation expert consensus.¹² Fatal bleeding was defined as any death occurring within 1 week of a major bleeding. A net adverse cardiovascular event (NACE) was defined as a composite of all-cause death, MI, stroke, or major bleeding during hospital stay for the index event. All of these endpoints were reported by clinical doctors and documented in medical records during hospitalization.

STATISTICAL ANALYSIS. Baseline characteristics and procedural details of STEMI patients are described. Continuous variables are presented as mean $\pm$ SD if a normal distribution and as median (IQR) if skewed. Categorical variables are presented as frequency and percentage. A *t* test or Kruskal-Wallis test for continuous variables and a chi-square test for categorical variables were used to test for statistically significant differences between the PPAC and no PPAC groups. Kaplan-Meier methods were used to estimate 15-day event rates for each endpoint, and comparisons between the study groups were performed using the log-rank test.

To consolidate the findings, we also carried out inverse probability of treatment weighting (IPTW) using the propensity score method in the study cohort and compared differences between the PPAC and no PPAC groups. A logistic regression was performed to estimate propensity score, adjusting for the following variables: age, sex, previous disease history (MI, PCI, coronary artery bypass grafting,

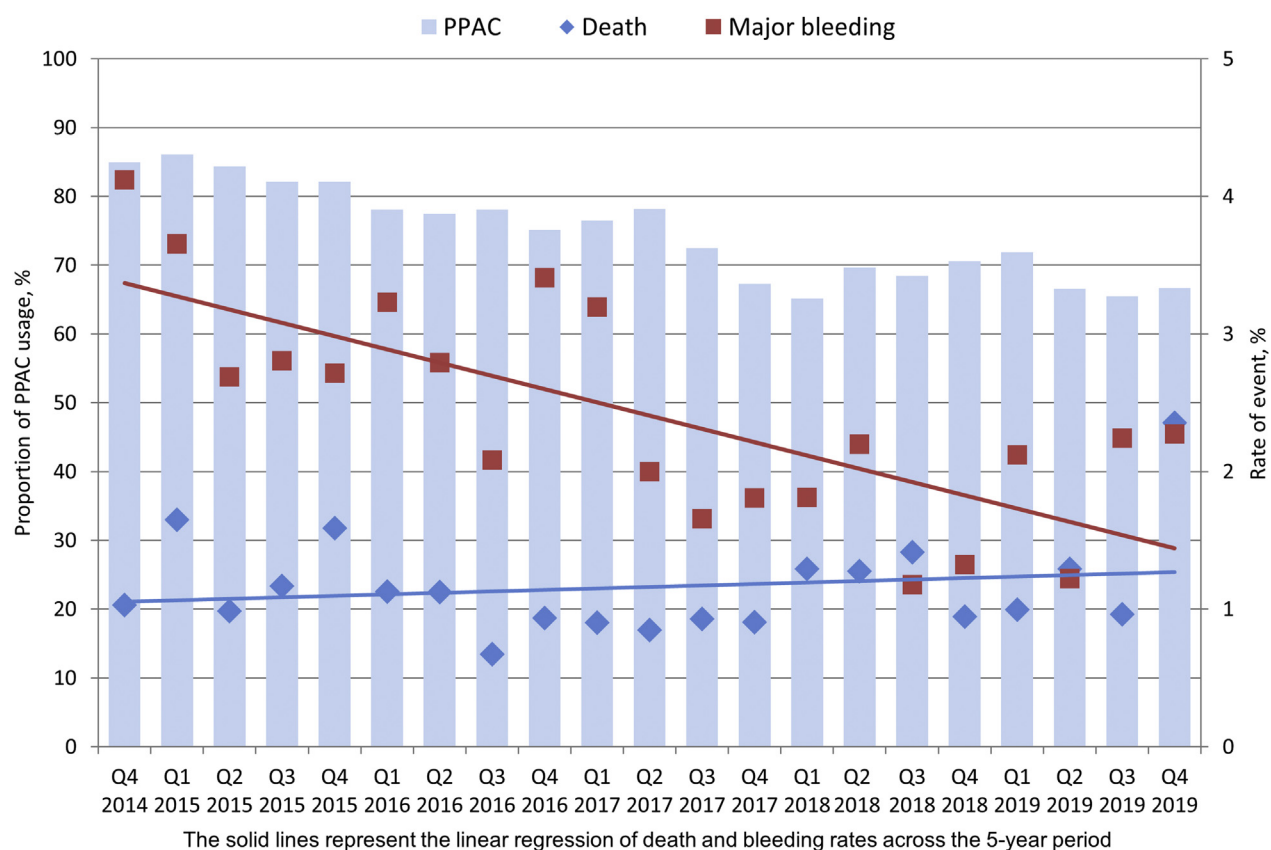
TABLE 1 Baseline Characteristics

	Unweighted Population			IPTW Population		
	PPAC (n = 26,272)	No PPAC (n = 8,554)	P Value	PPAC (n = 26,272)	No PPAC (n = 8,554)	P Value
Sociodemographics						
Age, y	60.7 ± 12.4	61.8 ± 12.6	<0.001	61.0 ± 12.2	61.1 ± 13.2	0.44
Age ≥75 y	3,691 (14.1)	1,402 (16.4)	<0.001	3,691 (14.6)	1,402 (14.7)	0.85
Female	5,232 (19.9)	1,788 (20.9)	0.05	5,232 (20.0)	1,788 (20.3)	0.67
Medical history and risk factors						
Previous MI	1,173 (4.5)	396 (4.6)	0.52	1,173 (4.7)	396 (4.8)	0.83
Previous PCI	1,258 (4.8)	403 (4.7)	0.77	1,258 (5.1)	403 (5.2)	0.84
Previous CABG	37 (0.1)	13 (0.2)	0.81	37 (0.2)	13 (0.2)	0.94
Hypertension	12,663 (48.2)	3,971 (46.4)	<0.001	12,663 (49.1)	3,971 (49.5)	0.67
Dyslipidemia	1,581 (6.0)	431 (5.0)	<0.001	1,581 (6.2)	431 (6.3)	0.63
Diabetes mellitus	5,042 (19.2)	1,652 (19.3)	0.81	5,042 (19.9)	1,652 (20.3)	0.54
Renal failure history	181 (0.7)	80 (0.9)	0.02	181 (0.8)	80 (0.8)	0.98
Heart failure history	92 (0.4)	22 (0.3)	0.19	92 (0.3)	22 (0.3)	0.69
Peripheral artery disease	157 (0.6)	31 (0.4)	0.01	157 (0.6)	31 (0.6)	0.82
Ischemic stroke	1,670 (6.4)	392 (4.6)	<0.001	1,670 (6.4)	392 (6.7)	0.37
Current smoker	13,010 (49.5)	4,024 (47.0)	<0.001	13,010 (50.0)	4,024 (49.8)	0.80
Clinical status at admission						
Cardiogenic shock	707 (2.7)	223 (2.6)	0.68	707 (2.6)	223 (2.6)	0.91
Heart rate, beats/min	77.5 ± 15.7	78.5 ± 15.8	<0.001	77.6 ± 15.6	78.4 ± 16.3	<0.001
SBP, mm Hg	128.0 ± 23.5	126.6 ± 23.4	<0.001	127.8 ± 23.1	127.6 ± 24.7	0.64
Killip class						
I	20,365 (77.5)	6,190 (72.4)	<0.001	20,365 (78.8)	6,190 (78.5)	0.92
II or III	5,020 (19.1)	2,057 (24.1)		5,020 (18.0)	2,057 (18.1)	
IV	887 (3.4)	307 (3.6)		887 (3.3)	307 (3.4)	
Anterior ^a	4,395 (44.1)	1,962 (43.2)	0.35	4,395 (43.7)	1,962 (43.9)	0.79
TIMI risk score	2.9 ± 1.6	3.6 ± 2.0	0.05	2.9 ± 1.5	3.4 ± 2.1	0.27
CRUSADE	20.2 ± 12.1	21.4 ± 12.7	<0.001	20.5 ± 11.8	20.3 ± 12.4	0.29
High bleeding risk	9,822 (37.4)	3,545 (41.4)	<0.001	9,822 (38.2)	3,545 (38.5)	0.63
Hemoglobin, g/L	141.1 ± 19.5	138.9 ± 19.8	<0.001	140.9 ± 19.1	140.8 ± 20.1	0.67
Platelet count, 10 ⁹ /L ^a	221.6 ± 65.2	219.2 ± 65.3	0.04	221.5 ± 64.2	221.2 ± 67.4	0.85
Renal insufficiency	2,735 (10.4)	1,191 (13.92)	<0.001	2,735 (10.7)	1,191 (10.7)	0.97
TnT or TnI	24,478 (93.2)	7,774 (90.9)	<0.001	24,478 (100)	7,774 (100)	
5-fold elevated TnT or TnI	17,386 (66.2)	5,138 (60.1)	<0.001	17,386 (84.2)	5,138 (83.8)	0.39
ST-segment elevation in ECG	23,582 (89.8)	7,650 (89.4)	0.38	23,582 (89.6)	7,650 (89.3)	0.50
LVEF, %	54.9 ± 10.2	53.9 ± 9.3	<0.001	54.9 ± 10.1	54.8 ± 9.5	0.25
Procedural details						
pPCI <12 h of symptom onset	22,599 (86.0)	7,247 (84.7)	<0.001	22,599 (86.1)	7,247 (86.1)	0.92
pPCI ≥12 h but <24 h after symptom onset	3,673 (14.0)	1,307 (15.3)		3,673 (14.0)	1,307 (13.9)	
Radial access	24,150 (91.9)	7,864 (91.9)	0.97	24,150 (92.8)	7,864 (92.5)	0.46
Multivessel ^b	7,089 (71.1)	3,125 (68.9)	0.01	7,089 (72.3)	3,125 (69.2)	<0.001
Number of stents implanted	1 (1-2)	1 (1-2)	0.39	1 (1-2)	1 (1-2)	0.39
Drug-eluting stent implanted	23,129 (88.0)	7,429 (86.9)	<0.001	23,129 (89.0)	7,429 (89.1)	0.85
Duration of hospitalization, d	8 (7-11)	7 (6-10)	<0.001	9 (7-11)	7 (6-9)	<0.001

Values are mean ± SD, n (%), or median (IQR). Percentages may not sum to 100 caused by rounding. ^aCalculated for 14,512 patients with available data since August 1, 2017.

CABG = coronary artery bypass grafting; CRUSADE = Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the American College of Cardiology/American Heart Association guidelines; ECG = electrocardiography; IPTW = inverse probability of treatment weighting; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; PPAC = postprocedural anticoagulation; pPCI = primary percutaneous coronary intervention; SBP = systolic blood pressure; TIMI = Thrombolysis In Myocardial Infarction; Tn = troponin.

FIGURE 2 Proportion of Patients Treated With PPAC and Event Rates Over Quarters During the Study Period



The proportion of patients treated with postprocedural anticoagulation (PPAC) decreased over 5 years, from 85% at the end of 2014 to <70% at the end of 2019. The incidence of in-hospital death increased slightly over time, while in-hospital bleeding rates declined. PPAC = postprocedural anticoagulation; Q = quarter.

hypertension, dyslipidemia, diabetes, renal failure history, heart failure history, peripheral artery disease, ischemic stroke), current smoker, cardiogenic shock, Killip class, systolic blood pressure, high bleeding risk, CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the American College of Cardiology/American Heart Association guidelines) score, ST-segment elevation on electrocardiography, left ventricular ejection fraction, dual antiplatelet therapy (DAPT) and glycoprotein IIb/IIIa inhibitor at arrival, elevated troponin T or troponin I, hemoglobin, renal insufficiency, PCI access, and drug-eluting stent (Supplemental Table 1). Imputation was performed for variables with missing data with the sequential regression multiple imputation method by IVEware software version 0.2 (Survey Research Center, University of Michigan). IPTW was calculated by each individual based on his or her propensity score (PS). Each case from the PPAC group

was given a weight of Pt/PS , and each case from the no PPAC group was given a weight of $(1-Pt)/(1-PS)$, where Pt refers to the proportion of patients receiving any anticoagulant after pPCI among the whole cohort. By this means we obtained a stabilized weight for each case of the study cohort, avoiding any extreme values that may result in unreliable outcomes.

Cox proportional hazards models were used to analyze the effects of PPAC on each endpoint, and HRs and 95% CIs were reported. Three models were applied to explore the association between PPAC use and each of the endpoints: 1) an unadjusted model; 2) an adjusted model controlling prespecified variables with impact of in-hospital outcomes (age, sex, medical history, current smoking, cardiogenic shock, Killip class, elevated troponin T or troponin I, ST-segment elevation in electrocardiography, year of enrollment, and hospital type); and 3) a further adjusted model, with the study site as random effect. Additional Cox analysis among 14 subgroups, selected based on

TABLE 2 Incidence of In-Hospital Clinical Outcomes, and Risk of PPAC Treatment

	Study Group		P Value	HR (95% CI)		
	PPAC (n = 26,272)	No PPAC (n = 8,554)		Unadjusted	Adjusted Cox Model with IPTW ^a	Adjusted Cox Model With Random Effect With IPTW ^b
Death	245 (0.9)	159 (1.9)	<0.001	0.50 (0.41-0.61)	0.59 (0.42-0.82)	0.62 (0.43-0.89)
Cardiovascular death	242 (0.9)	156 (1.8)	<0.001	0.50 (0.41-0.61)	0.59 (0.42-0.82)	0.62 (0.43-0.90)
Myocardial infarction	61 (0.2)	27 (0.3)	0.18	0.74 (0.47-1.16)	1.27 (0.62-2.60)	1.25 (0.61-2.56)
Stent thrombosis	58 (0.2)	13 (0.2)	0.22	1.45 (0.80-2.65)	1.59 (0.70-3.61)	1.37 (0.59-3.16)
Stroke	88 (0.3)	29 (0.3)	0.95	0.99 (0.65-1.50)	1.42 (0.77-2.62)	1.62 (0.86-3.07)
Cardiac arrest	228 (0.9)	100 (1.2)	0.01	0.74 (0.59-0.94)	0.95 (0.66-1.35)	0.84 (0.58-1.24)
Major bleeding	662 (2.5)	191 (2.2)	0.14	1.13 (0.96-1.33)	1.15 (0.94-1.42)	1.05 (0.83-1.32)
Bleeding	934 (3.6)	252 (3.0)	0.01	1.21 (1.05-1.39)	1.20 (1.01-1.42)	0.92 (0.76-1.13)
Fatal bleeding	18 (0.1)	12 (0.1)	0.05	0.49 (0.24-1.01)	0.89 (0.28-2.77)	0.74 (0.01-77.36)
MACE	405 (1.5)	204 (2.4)	<0.001	0.64 (0.54-0.76)	0.85 (0.65-1.11)	0.89 (0.67-1.19)
NACE	946 (3.6)	358 (4.2)	0.01	0.86 (0.76-0.97)	1.03 (0.87-1.22)	0.94 (0.77-1.14)

Values are n (%), unless otherwise indicated. ^aAdjusting for age, sex, previous disease history (myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, hypertension, dyslipidemia, diabetes, renal failure, heart failure, peripheral artery disease), current smoking, cardiogenic shock, Killip class, elevated troponin T or troponin I, ST-segment elevation in electrocardiography, enrollment year, and hospital type. ^bFurther adjusting the study site as random effect.

MACE = major adverse cardiovascular event(s); NACE = net adverse cardiovascular event(s); other abbreviations as in Table 1.

clinical experience, was performed to assess the consistency of treatment effects on the primary efficacy endpoint and safety endpoint. To consolidate the stability of the multivariate-adjusted model, we used MACE as an endpoint to estimate the effect size by including the variables listed above.

Finally, we also conducted sensitivity analyses using an adjusted Cox model in a propensity score-matched cohort and an adjusted Cox model with propensity score treated as a covariate together with the variables listed previously.

No PPAC was used as the reference in all analyses. All tests were 2-sided, and a *P* value of <0.05 was considered to indicate statistical significance. All analyses were performed using SAS version 9.3 (SAS Institute).

RESULTS

PATIENT CHARACTERISTICS AND TREATMENTS.

Up to December 31, 2019, a total of 113,650 patients with cleaned data were enrolled in the study. Based on the principal discharge diagnosis, 36,873 STEMI patients who underwent pPCI during the study period were identified (Figure 1). After excluding patients with an indication for anticoagulation or a bleeding complication, or who had missing data, 34,826 patients were included in the study, of whom 26,272 (75.4%) were treated with PPAC.

Patient baseline characteristics and management are shown in Table 1. Patients receiving PPAC were on average younger, were more stable at admission, had a lower bleeding risk score, and were more often treated

within 12 hours of symptom onset. They were also more likely to have comorbidities and multivessel disease. The PPAC group had a longer median duration of hospital stay than the no PPAC group (8 days vs 7 days; *P* < 0.001). The most frequently used anticoagulant for PPAC was LMWH (91.8%), with rare cross-over to another anticoagulant (3%). After adjustment using the IPTW and propensity score-matched methods, baseline characteristics were well balanced (Table 1, Supplemental Table 2). The distribution of patients receiving PPAC and the primary event rates per quarter over the 5-year study period are shown in Figure 2.

CLINICAL OUTCOMES AND ASSOCIATION WITH PPAC. Primary efficacy endpoint: In-hospital mortality. Table 2 and the Central Illustration show in-hospital mortality in the 2 groups. In-hospital mortality before discharge was lower in patients on PPAC compared with no PPAC (0.9% vs 1.9%; *P* < 0.001), with an adjusted HR of 0.62 (95% CI: 0.43-0.89). Similar results were found in the sensitivity analyses (Supplemental Table 3).

Primary safety endpoint: In-hospital major bleeding. The overall incidence of in-hospital major bleeding after pPCI was 2.5% (853 cases). After adjusting for patient characteristics and hospital effect using the Cox model, no statistically significant difference was found in patients with and without PPAC treatment (2.5% vs 2.2%; adjusted HR: 1.05; 95% CI: 0.83-1.32) (Table 2, Central Illustration). Similar results were observed with the sensitivity analyses (Supplemental Table 3).

Other in-hospital events. In-hospital cardiovascular death occurred in 398 (1.1%) patients. After adjustment, the incidence of cardiovascular death was lower in patients with PPAC (0.9% vs 1.8%; $P < 0.001$; adjusted HR: 0.62; 95% CI: 0.43–0.90), as was the incidence of MACE (1.5% vs 2.4%; $P < 0.001$) and cardiac arrest during hospitalization (0.9% vs 1.2%; $P = 0.01$). In the multivariate analysis, however, PPAC was not associated with lower risk of in-hospital MACE (adjusted HR: 0.89; 95% CI: 0.67–1.19) or NACE (adjusted HR: 0.94; 95% CI: 0.77–1.14) (Table 2, Central Illustration). The incidence of other in-hospital events was similar in the 2 groups, including MI (0.2% vs 0.3%; $P = 0.18$), stent thrombosis (0.2% vs 0.2%; $P = 0.22$), and stroke (0.3% vs 0.3%; $P = 0.95$) (Table 2, with sensitivity analysis results shown in Supplemental Tables 3 and 4). The coefficients of MACE risk factors were stable in the multivariate-adjusted models, with or without adjusting for hospital effect (Supplemental Figure 1).

Higher rates of any bleeding were observed in the PPAC group than in the no PPAC group in the overall population (3.6% vs 3.0%; $P = 0.01$), whereas the incidence of fatal bleeding was no significant difference between 2 groups (0.1% vs 0.1%; $P = 0.05$). However, following adjustment, the estimated risk did not differ between the 2 groups either for any bleeding (adjusted HR: 0.92; 95% CI: 0.76–1.13) or for fatal bleeding (adjusted HR: 0.74; 95% CI: 0.01–77.36) (Table 2). The location of and interventions for bleeding are shown in Table 3. Subcutaneous hemorrhage was reported more frequently in the PPAC group (0.3% vs 0.1%; $P < 0.001$), whereas patients with no PPAC experienced more retroperitoneal bleeding (0% vs 0.1%; $P < 0.001$). There were no statistically significant differences between the groups in terms of intracranial, gastrointestinal, or access site bleeding.

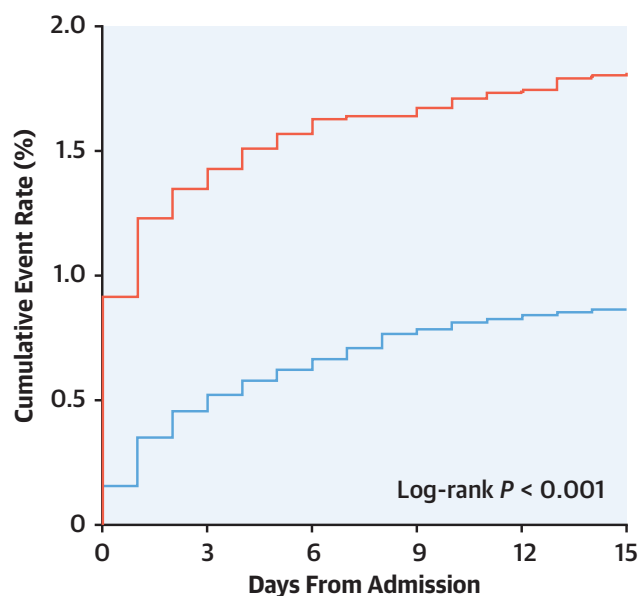
SUBGROUP ANALYSIS. We also conducted analyses in 14 subgroups based on important baseline information in the whole study population (Figure 3). The results showed that PPAC was associated with a decreased risk of mortality without an increased risk of major bleeding, which was consistent with the main results. With the exception of smoking, cardiogenic shock, early revascularization, and multivessel disease, there were no significant interactions with baseline or procedural variables.

DISCUSSION

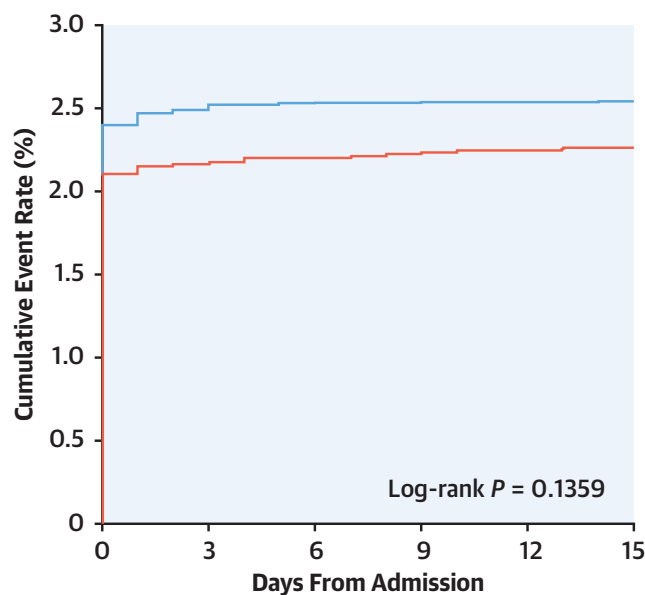
Among 34,826 patients undergoing pPCI for STEMI in the CCC-ACS registry who were analyzed in this

study, PPAC was associated with improved survival without an increased risk of bleeding complications. Furthermore, no differences were found between PPAC and no PPAC patients with regard to the risk of in-hospital MI, stent thrombosis, stroke, or cardiac arrest.

Whereas the American College of Cardiology/American Heart Association guidelines make no mention of PPAC treatment in STEMI, the European Society of Cardiology guidelines current during the study period stated a preference for no routine use of PPAC unless there is a specific indication for anticoagulation therapy, without reference to level of evidence or classification.^{2,13} In our study, not surprisingly, there was an observed decrease in mortality and bleeding risk over time, representing recent progress in medical therapies.¹⁴ When looking at time trends, the decline in proportion of PPAC usage was notable, which is likely related to the publication of more recent guidelines and studies. With the use of more effective and timely reperfusion therapies, the frequency of acute thrombotic complications has decreased, and low-risk patients may be discharged very early after pPCI.¹⁵ However, the average length of hospital stay has been documented as 3 days or more, with some geographic differences.¹⁶ During the acute phase of STEMI, there may be angiographically detected coronary thrombi, which is a well-known negative prognostic factor with the potential for further thrombotic complications.¹⁷ Pharmacodynamic studies have proved that PPAC can provide sustained anticoagulation effects following pPCI.^{18,19} In addition, data from the ATLAS ACS 2-TIMI 51 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 51) study demonstrated that rivaroxaban reduced the risk of stent thrombosis when given on top of DAPT in ACS patients who had undergone recent stent placement.²⁰ Post hoc analysis from the MATRIX (Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX) study also showed that full-dose bivalirudin given post-PCI was associated with the lowest risk of ischemic and bleeding events compared with no or low-dose bivalirudin or heparin.²¹ Furthermore, PPAC has been proven an efficient therapeutic strategy to reverse poor prognosis in patients with left ventricular thrombus and venous thromboembolism, which are common, potentially lethal conditions with acute morbidity.²² The lower incidence of cardiovascular death and cardiac arrest was observed in the PPAC group, which highlights the complexity surrounding the prognostication

CENTRAL ILLUSTRATION In-Hospital Clinical Outcomes (Unadjusted Analysis)**A Mortality****No. at risk:**

— Postprocedural Anticoagulation	26,231	26,135	26,097	26,066	26,051	26,043
— No Postprocedural Anticoagulation	8,476	8,432	8,415	8,411	8,405	8,399

B Major Bleeding**No. at risk:**

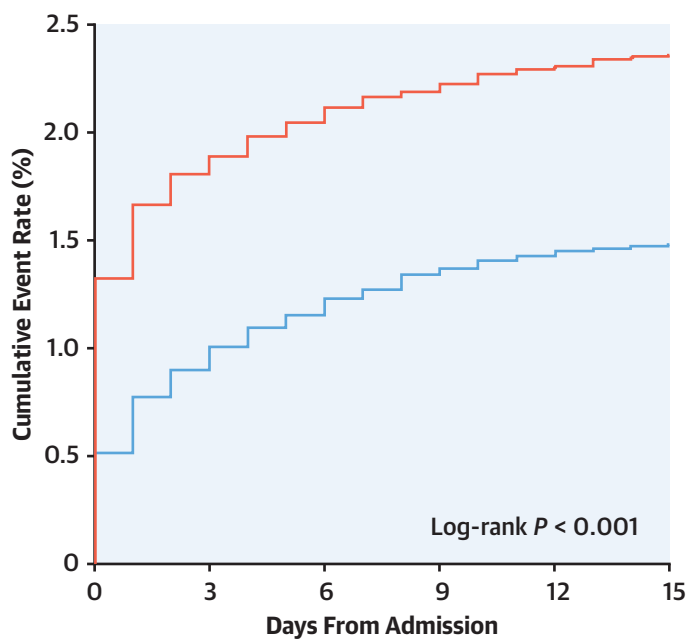
— Postprocedural Anticoagulation	25,608	25,480	25,439	25,407	25,392	25,383
— No Postprocedural Anticoagulation	8,298	8,248	8,229	8,222	8,215	8,208

Yan, Y. et al. *J Am Coll Cardiol Interv.* 2022;15(3):251-263.

Cumulative Kaplan-Meier curve estimates of effectiveness outcomes during the 15-day in-hospital period in the whole study population: **(A)** mortality, **(B)** major bleeding, **(C)** major adverse cardiovascular event (MACE), and **(D)** net adverse cardiovascular event (NACE). In-hospital mortality was significantly lower in patients treated with postprocedural anticoagulation (PPAC) compared with those who were not. The overall incidence of in-hospital major bleeding after primary percutaneous coronary intervention was 2.5%; after adjustment for patient characters and hospital effects (Cox model), there was no statistically significant difference between patients with or without PPAC treatment.

CENTRAL ILLUSTRATION Continued

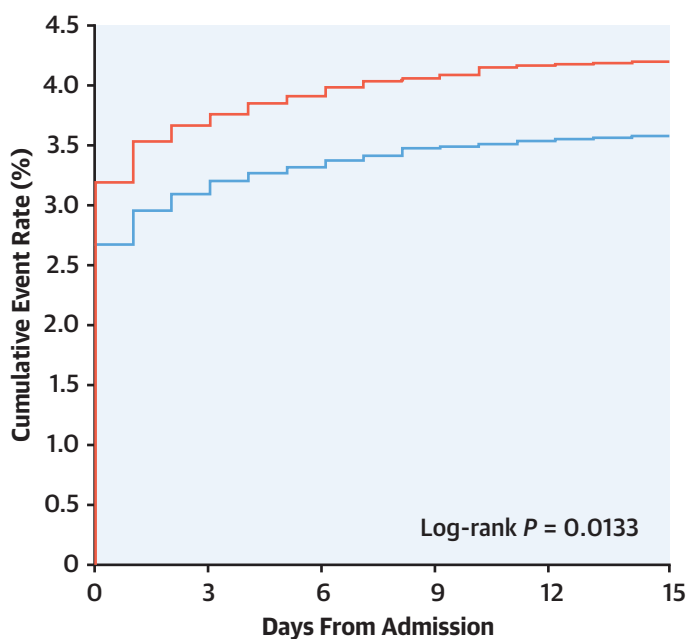
C MACE



No. at risk:

— Postprocedural Anticoagulation	26,097	25,873	25,778	25,694	25,675	25,657
— No Postprocedural Anticoagulation	8,364	8,272	8,236	8,216	8,210	8,199

D NACE



No. at risk:

— Postprocedural Anticoagulation	25,536	25,304	25,220	25,160	25,129	25,112
— No Postprocedural Anticoagulation	8,206	8,114	8,078	8,065	8,052	8,043

TABLE 3 Location of and Interventions for Bleeding

	Total (N = 34,826)	PPAC (n = 26,272)	No PPAC (n = 8,554)	P Value
Intracranial bleeding	72 (0.2)	54 (0.2)	18 (0.2)	0.93
Gastrointestinal bleeding	273 (0.8)	197 (0.8)	76 (0.9)	0.21
Subcutaneous hemorrhage	85 (0.2)	76 (0.3)	9 (0.1)	<0.001
Access site bleeding/hematoma ^a	38 (0.2)	35 (0.2)	3 (0.1)	0.07
Retroperitoneal bleeding ^a	3 (0.01)	0 (0)	3 (0.1)	<0.001
Bleeding requiring surgical intervention	74 (0.2)	49 (0.2)	25 (0.3)	0.07
Blood transfusion	106 (0.3)	75 (0.3)	31 (0.4)	0.26

Values are n (%). ^aCalculated for 20,314 patients with available data from November 2014 to July 2017.
PPAC = postprocedural anticoagulation.

following STEMI and demonstrates that other mechanisms other than stent thrombosis contribute to the high mortality associated with no PPAC in the acute phase after procedural.²³ As an observational study, our data might be influenced by potentially unmeasured confounding variables. Further studies, especially the ongoing RIGHT (Randomized Comparison of Anticoagulation after Primary Percutaneous Coronary Intervention Using Enoxaparin, ACT Guided Unfractionated Heparin or Bivalirudin Prolongation vs no Anticoagulation To Improve Clinical Outcome) trial (NCT03664180), should shed light on this important remark.²⁴

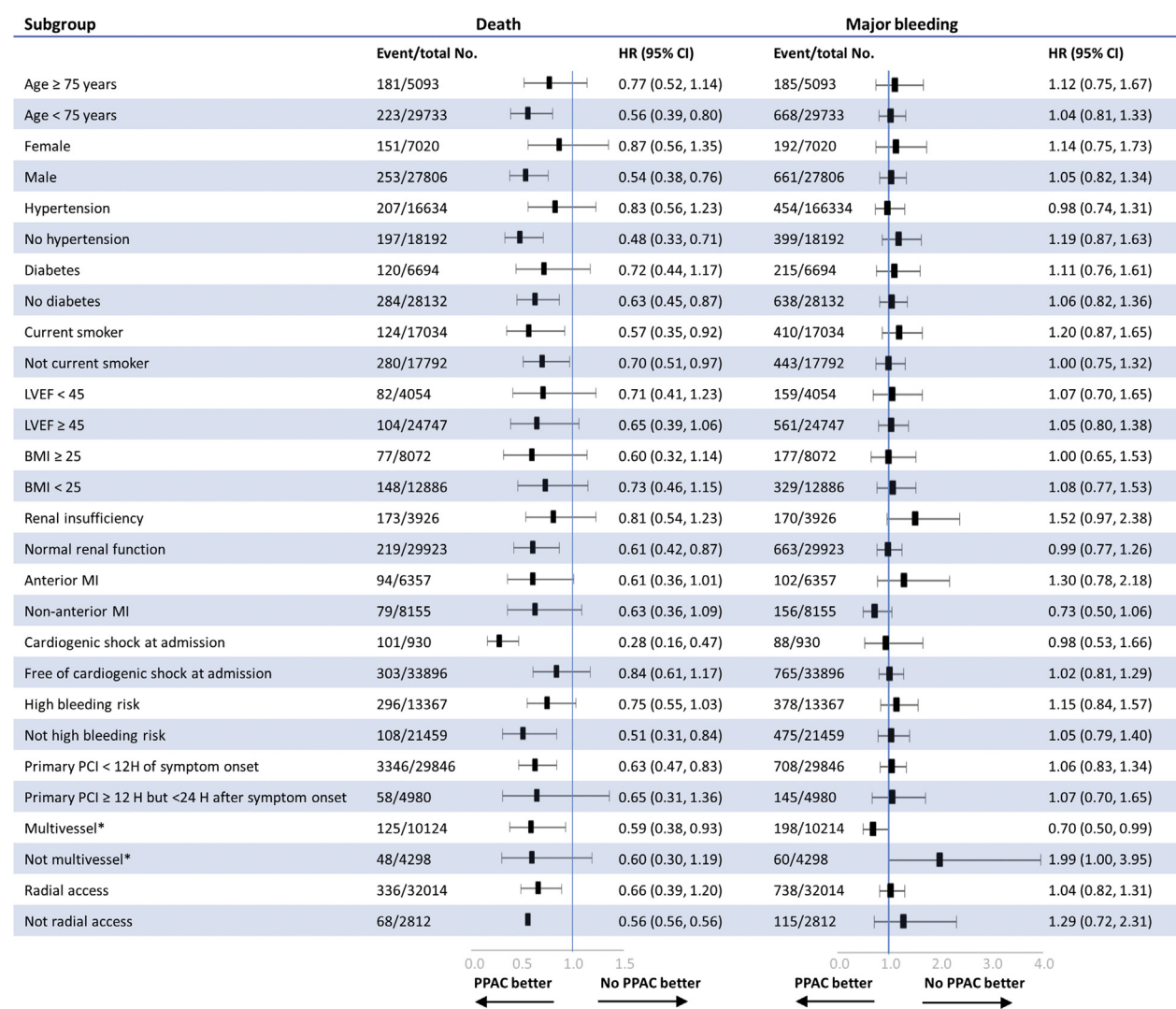
There has been no randomized clinical trial directly addressing the potential benefits of prolongation of anticoagulant beyond in-hospital administration in patients with STEMI who have undergone pPCI. Thus, there is limited and conflicting information on this topic. In the post-randomization subgroup analysis of STEMI patients in the HORIZONS-AMI and EUROMAX trials, mortality was low and was not significantly different between the PPAC and no PPAC groups at 30 days, and the rate of MACE was also similar.⁶ However, a higher rate of protocol-defined major bleeding was observed in the PPAC vs no PPAC group. The ATLAS ACS 2-TIMI 51 randomized trial evaluated the strategy of concomitant use of rivaroxaban during the long-term DAPT in stented ACS patients.²⁰ Among 15,526 enrolled patients without an anticoagulation indication, compared with placebo, rivaroxaban reduced the incidence of ischemic events, with increased risk of major bleeding and intracranial hemorrhage, but the incidence of fatal bleeding did not differ between groups.²⁵ In the MATRIX trial of 7,213 patients with ACS, post-PCI bivalirudin did not improve clinical outcomes compared with no prolongation of anticoagulation.³ In our study, PPAC

reduced the risk of in-hospital mortality or cardiovascular death without the cost of increased risk of bleeding complications. A priori, it may have been hypothesized that PPAC would reduce the rate of acute thrombotic complications after pPCI, which is driven by the delayed effect of oral P2Y₁₂ inhibitors and residual risk of post-stent thrombosis, especially in the STEMI population with higher ischemic risk.^{26,27} The ongoing RIGHT trial will provide firmer information on this question.

In our study, the benefit of PPAC was observed consistently irrespective of smoking, cardiogenic shock (CS), early revascularization, and multivessel disease. Advances in timely revascularization therapy have been associated with improvements in survival for STEMI patients, but CS remains a feared complication associated with a high risk of life-threatening end-organ hypoperfusion and hypoxia, and subsequent mortality.²⁸ In the American Heart Association scientific statement and European Society of Cardiology position paper for CS, UFH is recommended as the anticoagulant of choice for PPAC in consideration of the high prevalence of acute renal and liver injury in this population.²⁹ However, there are limited data to support the use of anticoagulant agents in this setting, including UFH. There are no clinical studies assessing the effect of heparin or heparin type on outcomes in CS. In the CULPRIT-SHOCK (Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock) trial, the choice of anticoagulant was left to the investigator's discretion, and UFH was used in over 80% of patients, while 14% received LMWH and 5% received bivalirudin.³⁰ In this study of data from the CCC-ACS registry, patients experiencing out-of-hospital cardiac arrest or receiving mechanical circulatory support, indicating a group of patients with severe degree of shock, were excluded from the analysis. We included variables such as age, sex, CS, timely revascularization, and multivessel disease in the adjusted analyses. As previous studies have reported differences in revascularization strategy for CS and non-CS patients with STEMI undergoing pPCI,²⁸ PPAC may also differ in this special population. Our findings should be considered as the basis of a hypothesis for further investigation.

STUDY LIMITATIONS. As an observational study, selection bias and residual confounding exist, and the results must be interpreted as hypothesis-generating. Nevertheless, the study provides real-world data from the CCC-ACS registry, a nationwide cohort with over 110,000 patients, including complete coverage of STEMI patients who underwent pPCI in China. Second, we do not have data on indication, type of drug,

FIGURE 3 Subgroup Analysis



Analysis of 14 subgroups based on baseline information showed that postprocedural anticoagulation (PPAC) was associated with a decreased risk of mortality without an increased risk of major bleeding, consistent with the main results. With the exceptions of smoking, cardiogenic shock, early revascularization, and multivessel disease, there were no significant interactions between event rates and either baseline or procedural variables. BMI = body mass index; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention;

and dose of these drugs used for anticoagulation, which may represent a potential bias of the main objective of our study. However, well-known anticoagulation indications, such as atrial fibrillation or left ventricular thrombus, were included among the exclusion criteria in order to minimize their confounding effect. In addition, the choice of anticoagulant is not standardized, and the proportion of

patients treated with PPAC decreased over time. However, although the CCC-ACS registry does not collect data on the exact dosage and duration of PPAC, over 90% of patients were prescribed LMWH at least once during the acute phase after pPCI. Furthermore, changes in clinical practice over time were accounted for as a covariate in the statistical models. Despite the limitations, this is the largest

pool of data describing the utility of PPAC after pPCI for STEMI patients in the contemporary era.

CONCLUSIONS

Among patients undergoing pPCI for STEMI in the CCC-ACS registry between 2014 and 2019, PPAC was associated with a decreased risk of in-hospital mortality without increasing bleeding complications. Dedicated randomized studies are awaited to assess the value of PPAC with modern anticoagulants.

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PERSPECTIVES

WHAT IS KNOWN? There is currently a lack of consensus on the use of PPAC in STEMI patients who have undergone pPCI, with concerns that the potential bleeding risk may outweigh any benefit in terms of cardiovascular event reduction.

WHAT IS NEW? Of 34,826 evaluable STEMI patients who underwent pPCI and were included in the CCC-ACS registry in China (2014-2019), 75.4% were treated with PPAC. After adjustment for baseline differences, PPAC was associated with a significantly reduced risk of in-hospital mortality (0.9% vs 1.8%; $P < 0.001$) and no significant difference in risk of in-hospital major bleeding (2.5% vs 2.2%; $P = 0.14$). The benefit of PPAC was observed consistently in 14 subgroups of interest.

WHAT IS NEXT? This analysis of data—excluding patients with an established indication for anticoagulation or a recent bleeding complication—provides evidence that PPAC may indeed reduce in-hospital mortality after primary PCI for STEMI, without an increase in major bleeding, after adjustment for key baseline characteristics. The results of this analysis provide the basis for further investigation on the use of PPAC in STEMI patients, with ongoing randomized clinical trials (eg, RIGHT trial).

REFERENCES

1. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J*. 2019;40:87-165.
2. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American college of cardiology foundation/American heart association task force on practice guidelines. *J Am Coll Cardiol*. 2013;61:e78-e140.
3. Valgimigli M, Frigoli E, Leonardi S, et al. Bivalirudin or unfractionated heparin in acute coronary syndromes. *N Engl J Med*. 2015;373:997-1009.
4. De Luca L, Musumeci G, Leonardi S, et al. Antithrombotic strategies in the catheterization laboratory for patients with acute coronary syndromes undergoing percutaneous coronary interventions: insights from the employed antithrombotic therapies in patients with acute coronary syndromes hospitalized in Italian cardiac care units registry. *J Cardiovasc Med*. 2017;18:580-589.
5. Wayankar SA, Bangalore S, McCoy LA, et al. Temporal trends and outcomes of patients undergoing percutaneous coronary interventions for cardiogenic shock in the setting of acute myocardial infarction: a report from the CathPCI registry. *J Am Coll Cardiol Interv*. 2016;9:341-351.
6. Ducrocq G, Steg PG, Van't Hof A, et al. Utility of post-procedural anticoagulation after primary PCI

for STEMI: insights from a pooled analysis of the HORIZONS-AMI and EUROMAX trials. *Eur Heart J Acute Cardiovasc Care*. 2017;6:659–665.

7. Madhavan MV, Genereux P, Kirtane AJ, et al. Is routine post-procedural anticoagulation warranted after primary percutaneous coronary intervention in ST-segment elevation myocardial infarction? Insights from the HORIZONS-AMI trial. *Eur Heart J Acute Cardiovasc Care*. 2017;6:650–658.

8. Smaha LA, American Heart Association. The American Heart Association Get With the Guidelines program. *Am Heart J*. 2004;148(5 Suppl):S46–S48.

9. Hao Y, Liu J, Liu J, et al. Rationale and design of the improving care for cardiovascular disease in china (CCC) project: a national effort to prompt quality enhancement for acute coronary syndrome. *Am Heart J*. 2016;179:107–115.

10. China Society of Cardiology of Chinese Medical Association, Editorial Board of Chinese Journal of Cardiology. Guideline for diagnosis and treatment of patients with ST-elevation myocardial infarction. *Zhonghua Xin Xue Guan Bing Za Zhi*. 2010;38:675–690.

11. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999;130:461–470.

12. Chinese 2011 cardiopulmonary resuscitation expert consensus group. Chinese 2011 cardiopulmonary resuscitation expert Consensus. *Chin J Cardiovasc Res*. 2011;9(12):881–887.

13. Ibanez B, James S, Agewall S, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39:119–177.

14. Zhao Q, Yang Y, Chen Z, Yu H, Xu H. Changes in characteristics, risk factors, and in-hospital mortality among patients with acute myocardial infarction in the capital of china over 40 years. *Int J Cardiol*. 2018;265:30–34.

15. Gong W, Li A, Ai H, Shi H, Wang X, Nie S. Safety of early discharge after primary angioplasty in low-risk patients with ST-segment elevation myocardial infarction: a meta-analysis of randomised controlled trials. *Eur J Prev Cardiol*. 2018;25:807–815.

16. Han H, Wei X, He Q, et al. Comparison of in-hospital mortality and length of stay in acute ST-segment-elevation myocardial infarction among urban teaching hospitals in china and the united states. *J Am Heart Assoc*. 2019;8:e012054.

17. Sigirci S, Keskin K, Yildiz SS, et al. Can thrombus burden predict contrast-induced nephropathy in patients with ST-segment elevation myocardial infarction? *Angiology*. 2019;70:642–648.

18. Sumaya W, Parker WAE, Fretwell R, et al. Pharmacodynamic effects of a 6-hour regimen of enoxaparin in patients undergoing primary percutaneous coronary intervention (PENNY PCI study). *Thromb Haemost*. 2018;118:1250–1256.

19. Kikert WJ, van Nes SH, Lieve KV, et al. Prognostic value of post-procedural APTT in patients with ST-elevation myocardial infarction treated with primary PCI. *Thromb Haemost*. 2013;109:961–970.

20. Gibson CM, Chakrabarti AK, Mega J, et al. Reduction of stent thrombosis in patients with acute coronary syndromes treated with rivaroxaban in ATLAS-ACS 2 TIMI 51. *J Am Coll Cardiol*. 2013;62:286–290.

21. Gargiulo G, Carrara G, Frigoli E, et al. Post-procedural bivalirudin infusion at full or low regimen in patients with acute coronary syndrome. *J Am Coll Cardiol*. 2019;73:758–774.

22. Lattuca B, Bouziri N, Kerneis M, et al. Antithrombotic therapy for patients with left ventricular mural thrombus. *J Am Coll Cardiol*. 2020;75:1676–1685.

23. Romanov A, Martinek M, Pürerfellner H, et al. Incidence of atrial fibrillation detected by continuous rhythm monitoring after acute myocardial infarction in patients with preserved left ventricular ejection fraction: results of the ARREST study. *Europace*. 2018;20:263–270.

24. Yan Y, Wang X, Guo J, et al. Rationale and design of the RIGHT trial: A multicenter, randomized, double-blind, placebo-controlled trial of anticoagulation prolongation versus no anti-

coagulation after primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. *Am Heart J*. 2020;227:19–30.

25. Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med*. 2012;366:9–19.

26. Higuma T, Soeda T, Yamada M, et al. Does residual thrombus after aspiration thrombectomy affect the outcome of primary PCI in patients with ST-segment elevation myocardial infarction?: an optical coherence tomography study. *J Am Coll Cardiol Interv*. 2016;9:2002–2011.

27. Franchi F, Rollini F, Rivas A, et al. Platelet inhibition with cangrelor and crushed ticagrelor in patients with ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Circulation*. 2019;139:1661–1670.

28. Marquis-Gravel G, Zeitouni M, Kochar A, et al. Technical consideration in acute myocardial infarction with cardiogenic shock: a review of antithrombotic and PCI therapies. *Catheter Cardiovasc Interv*. 2020;95:924–931.

29. Gorog DA, Price S, Sibbing D, et al. Antithrombotic therapy in patients with acute coronary syndrome complicated by cardiogenic shock or out-of-hospital cardiac arrest: a joint position paper from the European Society of Cardiology (ESC) Working Group on Thrombosis, in association with the Acute Cardiovascular Care Association (ACCA) and European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J Cardiovasc Pharmacother*. 2021;7(2):125–140.

30. Thiele H, Akin I, Sandri M, et al. PCI strategies in patients with acute myocardial infarction and cardiogenic shock. *N Engl J Med*. 2017;377:2419–2432.

KEY WORDS postprocedural anticoagulation, primary PCI, real-world registry, STEMI

APPENDIX For an expanded Methods section and supplemental tables and a figure, please see the online version of this paper.