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Association of Parenteral Anticoagulation Therapy With Outcomes in Chinese Patients Undergoing Percutaneous Coronary Intervention for Non–ST-Segment Elevation Acute Coronary Syndrome

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IMPORTANCE The association of parenteral anticoagulation therapy with improved outcomes in patients with non–ST-segment elevation acute coronary syndrome was previously established. This benefit has not been evaluated in the era of dual antiplatelet therapy and percutaneous coronary intervention.

OBJECTIVE To evaluate the association between parenteral anticoagulation therapy and clinical outcomes in patients with non–ST-segment elevation acute coronary syndrome undergoing percutaneous coronary intervention.

DESIGN, SETTING, AND PARTICIPANTS This cohort study included 8197 adults who underwent percutaneous coronary intervention for non–ST-segment elevation acute coronary syndrome from January 1, 2010, to December 31, 2014, at 5 medical centers in China. Patients receiving parenteral anticoagulation therapy only after percutaneous coronary intervention were excluded.

EXPOSURES Parenteral anticoagulation therapy.

MAIN OUTCOMES AND MEASURES The primary outcome was in-hospital all-cause death and in-hospital major bleeding as defined by the Bleeding Academic Research Consortium definition (grades 3-5).

RESULTS Of 6804 patients who met the final criteria, 5104 (75.0%) were male, with a mean (SD) age of 64.2 (10.4) years. The incidence of in-hospital death was not significantly different between the patients who received and did not receive parenteral anticoagulation therapy (0.3% vs 0.1%; $P = .13$) (adjusted odds ratio, 1.27; 95% CI, 0.38-4.27; $P = .70$). A similar result was found for myocardial infarction (0.3% vs 0.3%; $P = .82$) (adjusted odds ratio, 0.77; 95% CI, 0.29-2.07; $P = .61$). In-hospital major bleeding was more frequent in the parenteral anticoagulation group (2.5% vs 1.0%; $P < .001$) (adjusted odds ratio, 1.94; 95% CI, 1.24-3.03; $P = .004$). At a median (interquartile range) follow-up of 2.96 years (1.93-4.46 years), all-cause death was not significantly different between the 2 groups (adjusted hazards ratio, 0.87; 95% CI, 0.71-1.07; $P = .19$), but the incidence of major bleeding was higher in the parenteral anticoagulation group (adjusted hazards ratio, 1.43; 95% CI, 1.01-2.02; $P = .04$). The propensity score analysis confirmed these primary analyses.

CONCLUSIONS AND RELEVANCE In the patients undergoing percutaneous coronary intervention for non–ST-segment elevation acute coronary syndrome, parenteral anticoagulation therapy was not associated with a lower risk of all-cause death or myocardial infarction but was significantly associated with a higher risk of major bleeding. These findings raise important safety questions about the current practice of routine parenteral anticoagulation therapy while we await randomized trials of this practice.

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Editor's Note
Supplemental content

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Previous studies have shown that parenteral anticoagulation therapy (PACT) was associated with a lower risk of adverse cardiovascular events in patients with non–ST-segment elevation (NSTE) acute coronary syndrome (ACS).[1-3] Most of the above-cited studies were conducted before the establishment of dual antiplatelet therapy and percutaneous coronary intervention (PCI) as standards of care. The advantage of PACT was driven only by the reduction in ischemic end points, such as recurrent ischemia and emergency revascularization.[1-3] However, these end points might not be appropriate in an era when timely revascularization is recommended and widely performed to reduce the risk of ischemia. To our knowledge, controlled studies to evaluate the role of PACT among patients undergoing PCI for NSTE-ACS are lacking. This study aimed to evaluate the association between PACT and clinical outcomes in this context.

Key Points

Question Is parenteral anticoagulation therapy beneficial for patients with non–ST-segment elevation acute coronary syndrome undergoing percutaneous coronary intervention?

Findings In this multicenter cohort study that included 6804 consecutive patients from 5 centers in China, parenteral anticoagulation therapy was not associated with lower all-cause death or myocardial infarction but was significantly associated with a higher risk of major bleeding.

Meaning The findings suggest that the role of parenteral anticoagulation therapy should be reevaluated in patients undergoing percutaneous coronary intervention for non–ST-segment elevation acute coronary syndrome.

Methods

Study Design and Patients

This retrospective cohort study included 8197 consecutively enrolled patients from January 1, 2010, to December 31, 2014, at 5 hospitals in China. The study protocol was approved by the central ethics committee of the Guangdong General Hospital, Guangzhou, China, with a waiver of informed consent. Data relevant to the study were analyzed on the basis of population. Information pertaining to the specific identity of patients was strictly concealed during the study. Central ethical approval was applicable at the other collaborating hospitals as well. The definitions of unstable angina and NSTE myocardial infarction and the method to search and identify appropriate candidates are shown in eAppendix 1 in the Supplement. Patients were excluded if they were pregnant, in cardiogenic shock, required an intra-aortic balloon pump, or had other indications for anticoagulation. Patients who received PACT only after PCI were also excluded.

Data Extraction and Processing

Data were extracted from the hospital records by trained study coordinators. Data collected included patient demographics, laboratory test results, PCI procedural details, clinical events, and medical treatment. Data pertaining to antithrombotic therapy, such as PACT and dual antiplatelet therapy dosages, dates of prescriptions, and durations of therapy, were also collected.

All patients were followed up by trained nurses via telephone interviews or clinic visits from November 7, 2015, through December 30, 2016. Relevant information was also collected from the residence registration system and the clinical records for the patients who were readmitted to the hospital. For events that occurred more than once, only the index event was used for statistical analysis. All adverse clinical events were evaluated by an independent clinical events committee that was masked to the treatment details. Key variables (such as medical treatment and clinical events) were double recorded, and inconsistent data were verified by a third researcher. The remainder of the collected data was monitored by random auditing of the medical records.

Treatment and Procedure

Patients who received PACT before PCI were classified into the PACT group. Patients only receiving PACT during PCI were classified into the non-PACT group. The type and duration of non-PACT (low-molecular-weight heparin or pentasaccharide fondaparinux) was prescribed at the discretion of the clinicians. Patients received either fondaparinux, 2.5 mg, subcutaneously once daily or low-molecular-weight heparin, 1 mg/kg, subcutaneously twice daily (dosage was reduced to 1 mg/kg once daily among patients with creatinine clearance <30 mL/min [to convert creatinine clearance to mL/s/m^2, multiply by 0.0167]).[4] The dosage of low-molecular-weight heparin was also adjusted according to crossover of different anticoagulants, time of admission and discharge, and timing of PCI at the discretion of the physicians.

Unfractionated heparin was chosen as the standard PACT for PCI and was administered in a bolus dose of 70 to 100 U/kg according to current guidelines.[5] An exception was made for 3 patients who received bivalirudin at a dosage that was determined as previously described.[6] Antithrombotic therapy and other medications were administered at the discretion of the physicians.

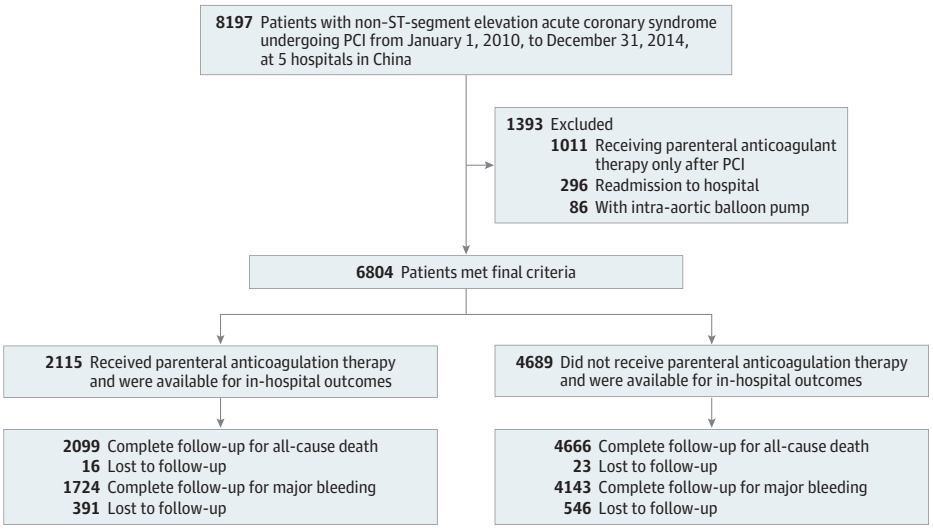
Outcomes

The primary outcome was in-hospital all-cause death and in-hospital major bleeding as defined by the Bleeding Academic Research Consortium definition (grades 3-5).[7] The prespecified secondary outcomes included the following: any bleeding as defined by the Bleeding Academic Research Consortium (grades 1-5); myocardial infarction (MI); death or MI; death, MI, or major bleeding in hospital; or death or major bleeding during follow-up. The definitions of all outcomes are detailed[8] in eAppendix 1 in the Supplement.

Statistical Analyses

The sample size calculation for in-hospital all-cause death was based on a statistical rule: the events per variable should be 10 or more. According to previous studies,[6,9] a total of 6667 patients should be included for an estimated incidence of 1.5% for all-cause death, with the expected clinically important factors included in the multivariable analysis to be no more than 10. The sample size determination for

Figure 1. Flowchart



Patients lost to follow-up were treated as censored at the time of discharge in analysis. PCIU indicates percutaneous coronary intervention.

in-hospital major bleeding was conducted based on the logistic regression of major bleeding. A sample size of 6133 patients achieves 80% power at a .05 significance level to detect a change in probability from a 1.5% in the non-PACT group to an estimated 3.0% in the PACT group. The details are given in eAppendix 1 in the Supplement.

For in-hospital outcomes, a multivariable analysis was performed using logistic regression. Potential confounders that were significant in the univariate analysis or clinically important were included in the multivariable models. All significant interactions were also examined. A 2-sided $P < .05$ was considered statistically significant. We also introduced the Global Registry of Acute Coronary Events (GRACE)[10] (scores range from 15 to 330, with higher scores indicating a higher risk of death) and Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines (CRUSADE)[11] score (scores range from 1 to 96, with higher scores indicating a higher risk of bleeding) and compared the outcomes among different risk groups. Subgroup analyses were conducted for in-hospital outcomes. For the long-term clinical outcomes, univariate analyses were performed using the log-rank test, and multivariable analyses were performed using the Cox proportional hazards regression model. An additive hazards model was used to detect time-varying associations. Factors of clinical importance were included in the Cox proportional hazards regression and additive hazards models.

Propensity score analyses were conducted to test the robustness of the results. Details of the propensity score model are shown in eAppendix 1 in the Supplement. The heterogeneity analysis between the centers was conducted using meta-analysis methods. A multivariable analysis stratified by centers and including the random associations among centers for in-hospital and follow-up outcomes was also conducted. The statistical analysis protocol is presented in eAppendix 2 in the Supplement.

Results

Baseline Characteristics

From January 1, 2010, to December 31, 2014, a total of 8197 consecutive patients with NSTE-ACS underwent PCI at 5 hospitals in China. Of 6804 patients who met the final criteria, 5104 (75.0%) were male, with a mean (SD) age of 64.2 (10.4) years. Of these patients, 3901 with NSTE myocardial infarction (57.3%) and 2903 with unstable angina (42.7%) met the inclusion criteria (**Figure 1**). Dual antiplatelet therapy was given to 6590 (96.9%) patients, among whom 6504 (98.7%) received therapy before diagnostic catheter placement. The mean (SD) GRACE score was 126.60 (28.70), and the mean (SD) CRUSADE score was 42.35 (11.97).

Baseline characteristics are presented in **Table 1**. PACT was administered to 2115 (31.1%) patients. Low-molecular-weight heparin was the most commonly used parenteral anticoagulant (79.1%), followed by fondaparinux (16.3%) and a combination of the 2 anticoagulants (4.6%). The median duration of PACT was 6 days (interquartile range, 4-9 days). Patients in the PACT group had higher mean (SD) GRACE scores (132.14 [30.23] vs 123.97 [27.56]; $P < .001$) but similar CRUSADE scores (42.39 [11.87] vs 42.34 [12.02]; $P = .87$) compared with those in the non-PACT group.

In-Hospital Outcomes

There was no significant difference in in-hospital all-cause death between the PACT and the non-PACT groups (0.3% vs 0.1%; $P = .13$) (adjusted odds ratio [OR], 1.27; 95% CI, 0.38-4.27; $P = .70$). The incidence of major bleeding in the PACT group was higher than that in the non-PACT group (2.5% vs 1.0%; $P < .001$) (adjusted OR, 1.94; 95% CI, 1.24-3.03; $P = .004$) (**Table 2** and **Figure 2**). After adjustment for the GRACE or CRUSADE score, similar results were shown (eTables 1 and 2 in the Supplement).

The incidence of MI (0.3% vs 0.3%; $P = .82$) (adjusted OR, 0.77; 95% CI, 0.29-2.07; $P = .61$), any bleeding (13.0% vs 12.9%;

Table 1. Characteristics of Patients at Index Hospitalization

Characteristic	All Patients (N = 6804)[a]			Propensity-Matched Patients			
	Non-PACT (n = 4689)	PACT (n = 2115)	*P* Value	Non-PACT (n = 997)	PACT (n = 997)	*P* Value	Standard Difference (%)
Age							
Mean (SD), y	64.01 (10.34)	64.48 (10.62)	.08	64.41 (10.63)	64.14 (10.36)	.57	2.53
≥65 y, No. (%)	2283 (48.7)	1098 (51.9)	.01	509 (51.1)	499 (50.1)	.65	NA
Female, No. (%)	1189 (25.4)	511 (24.2)	.29	225 (22.6)	243 (24.4)	.34	−4.26
Weight, mean (SD), kg	65.89 (11.53)	66.37 (11.78)	.12	66.37 (12.51)	65.95 (12.01)	.45	3.41
Heart rate, mean (SD), bpm	73.53 (10.84)	74.05 (12.40)	.10	73.56 (11.05)	74.01 (11.41)	.38	−3.93
Blood pressure, mean (SD), mm Hg							
Systolic	134.01 (19.01)	135.09 (20.33)	.04	134.82 (19.46)	134.58 (19.80)	.78	1.23
Diastolic	77.21 (11.37)	78.02 (11.94)	.01	77.65 (11.60)	77.42 (11.48)	.66	1.99
Disease type, No. (%)							
NSTEMI	2647 (56.5)	1254 (59.3)	.03	577 (57.9)	577 (57.9)	>.99	0
Unstable angina	2042 (43.5)	861 (40.7)	NA	420 (42.1)	420 (42.1)	NA	NA
Heart failure	439 (9.4)	403 (19.1)	<.001	131 (13.1)	140 (14.0)	.56	−2.63
LVEF, mean (SD), %	62.34 (10.41)	60.36 (9.62)	<.001	61.58 (10.46)	60.75 (10.66)	.12	NA
eGFR							
Mean (SD), mL/min/1.73 m^2	81.67 (24.70)	83.40 (25.91)	.01	80.87 (24.07)	81.49 (25.55)	.58	−2.49
≤60 mL/min/1.73 m^2, No. (%)	811 (17.3)	366 (17.3)	.99	164 (16.4)	175 (17.6)	.51	NA
Serum creatinine level, mean (SD), μmol/dL	1.05 (0.68)	1.03 (0.60)	.17	1.06 (0.70)	1.08 (0.78)	.71	NA
Hematocrit, mean (SD), g/L	0.40 (0.11)	0.40 (0.19)	.25	0.41 (0.22)	0.40 (0.15)	.24	−2.95
Anemia, No. (%)	1474 (31.4)	678 (32.1)	.61	314 (31.5)	325 (32.6)	.60	NA
Medical history and risk factors, No. (%)							
Current smoker	1207 (25.7)	690 (32.6)	<.001	308 (30.9)	303 (30.4)	.81	1.09
Cardiac arrest	7 (0.1)	5 (0.2)	.43	2 (0.2)	2 (0.2)	>.99	0
Myocardial infarction	661 (14.1)	394 (18.6)	<.001	170 (17.1)	175 (17.6)	.77	−1.33
Percutaneous coronary intervention	902 (19.2)	338 (16.0)	.001	172 (17.3)	162 (16.2)	.55	2.69
Coronary artery bypass surgery	61 (1.3)	16 (0.8)	.049	10 (1.0)	11 (1.1)	.83	−0.98
Stroke	301 (6.4)	167 (7.9)	.03	70 (7.0)	64 (6.4)	.59	2.40
Atrial fibrillation	121 (2.6)	108 (5.1)	<.001	40 (4.0)	31 (3.1)	.28	4.87
Hypertension	3092 (65.9)	1457 (68.9)	.02	687 (68.9)	665 (66.7)	.29	4.72
Diabetes	1434 (30.6)	678 (32.1)	.22	323 (32.4)	311 (31.2)	.56	2.58
In-hospital medication, No. (%)							
Clopidogrel or ticagrelor loading dose	2948 (62.9)	1494 (70.6)	<.001	686 (68.8)	668 (67.0)	.39	3.87
Dual antiplatelet therapy	4514 (96.3)	2076 (98.2)	<.001	970 (97.3)	968 (97.1)	.79	1.21
Clopidogrel	4514 (100)	2068 (99.6)	NA	970 (97.3)	967 (97.0)	NA	NA
Ticagrelor[b]	0	8 (0.4)	NA	0	1 (0.1)	NA	NA
Type of parenteral anticoagulant, No. (%)							
Low-molecular-weight heparin	NA	1673 (79.1)	NA	NA	744 (74.6)	NA	NA
Fondaparinux	NA	345 (16.3)	NA	NA	237 (23.8)	NA	NA
Low-molecular-weight heparin and fondaparinux	NA	97 (4.6)	NA	NA	16 (1.6)	NA	NA
Glycoprotein IIb/IIIa inhibitor	428 (9.1)	273 (12.9)	<.001	83 (8.3)	80 (8.0)	.81	1.10
Warfarin sodium	22 (0.5)	17 (0.8)	.09	11 (1.1)	6 (0.6)	.22	5.46
Statin	4588 (97.8)	2086 (98.6)	.03	980 (98.3)	980 (98.3)	>.99	0
ACE inhibitor or ARB	3594 (76.6)	1719 (81.3)	<.001	802 (80.4)	802 (80.4)	>.99	0
Calcium-channel blocker	1071 (22.8)	573 (27.1)	<.001	248 (24.9)	243 (24.4)	.80	1.16
β-Blocker	3886 (82.9)	1787 (84.5)	.10	836 (83.9)	835 (83.8)	.95	0.27

(continued)

Table 1. Characteristics of Patients at Index Hospitalization (continued)

Characteristic	All Patients (N = 6804)[a]			Propensity-Matched Patients			
	Non-PACT (n = 4689)	PACT (n = 2115)	*P* Value	Non-PACT (n = 997)	PACT (n = 997)	*P* Value	Standard Difference (%)
Procedure characteristic, No. (%)							
Radial access	4172 (89.0)	1710 (80.9)	<.001	880 (88.3)	880 (88.3)	>.99	0
Coronary anatomy							
Any left main disease	570 (12.2)	246 (11.6)		132 (13.2)	123 (12.3)		2.70
Multivessel disease	2898 (61.8)	1445 (68.3)	<.001	634 (63.6)	640 (64.2)	.83	−1.25
Other	1221 (26.0)	424 (20.0)		231 (23.2)	234 (23.5)		−0.71
Treated vessel							
Any left main disease	378 (8.1)	177 (8.4)		102 (10.2)	92 (9.2)		3.38
Multivessel disease	1547 (33.0)	694 (32.8)	.91	322 (32.3)	348 (34.9)	.42	−5.52
Other	2764 (58.9)	1244 (58.8)		573 (57.5)	557 (55.9)		3.24
Stent type, No. (%)							
Drug eluting stent	4681 (99.8)	2091 (98.9)		994 (99.7)	996 (99.9)		−4.48
First generation	2447 (52.2)	1128 (53.3)		503 (50.5)	546 (54.8)		NA
Second generation	2234 (47.6)	963 (45.5)	<.001	491 (49.2)	449 (45.0)	.32	NA
Bare metal stent, No. (%)	3 (0.1)	1 (0.0)		0	0		0
PTCA or aspiration only, No. (%)	5 (0.1)	23 (1.1)		3 (0.3)	1 (0.1)		4.48
Stents, No. (IQR)	2 (1-3)	2 (1-3)	.33	2 (1-3)	2 (1-3)	.51	−3.24
Total length of stents, mm	41 (24-66)	44 (25-69)	.03	42 (24-71)	43 (28-71)	.73	−2.23
Thrombus aspiration, No. (%)	47 (1.0)	24 (1.1)	.62	13 (1.3)	10 (1.0)	.53	2.82
Time to procedure							
Median (IQR), d	1 (1-3)	3 (2-5)	<.001	2 (1-4)	2 (1-4)	.35	NA
<24 d, No. (%)	2511 (53.6)	440 (20.8)		330 (33.1)	322 (32.3)		1.71
24-72 d, No. (%)	1417 (30.2)	720 (34.0)	<.001	353 (35.4)	365 (36.6)	.85	−2.51
>72 d, No. (%)	761 (16.2)	955 (45.2)		314 (31.5)	310 (31.1)		0.87

Abbreviations: ACE, angiostensin-converting enzyme; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LVEF, left ventricular ejection fraction; NA, not applicable; NSTEMI, non–ST-segment elevation myocardial infarction; PACT, parenteral anticoagulation therapy; PTCA, percutaneous transluminal coronary angioplasty.

[a] Data were missing for the following categories: current smoker (n = 22), LVEF (n = 1210), hematocrit (n = 138), weight (n = 177), and eGFR (n = 79).

[b] Ticagrelor was available in only 1 of the 5 centers until late 2014.

P = .91) (adjusted OR, 0.92; 95% CI, 0.78-1.10; *P* = .35), and the composite end point of death or MI (0.6% vs 0.4%; *P* = .37) (adjusted OR, 0.82; 95% CI, 0.38-1.78; *P* = .61) were not significantly different between the 2 groups. However, the incidence of the composite end point of death, MI, or major bleeding was higher in the PACT group than in the non-PACT group (3.0% vs 1.4%; *P* < .001) (adjusted OR, 1.54; 95% CI, 1.04-2.30; *P* = .03) (Table 2 and Figure 2).

Long-term Outcomes

Complete follow-up (mean [SD] period, 3.25 [1.56] years; median [interquartile range], 2.96 years [1.93-4.46 years]) for all-cause death was achieved for 6765 patients (99.4%) and for major bleeding was achieved for 5867 patients (86.2%). All-cause death was not significantly different between the PACT and the non-PACT groups (adjusted hazard ratio [HR], 0.87; 95% CI, 0.71-1.07; *P* = .19) (Table 2 and Figure 2 and **Figure 3**A). However, patients in the PACT group tended to have higher risk of major bleeding (adjusted HR, 1.43; 95% CI, 1.01-2.02; *P* = .04). (Table 2 and Figure 2 and Figure 3B). The bleeding episodes in the PACT group mostly occurred in the first 30 days, and no further difference in new bleeding events between the groups was found in long-term follow-up (Figure 3C and D and eFigure 1 in the Supplement). The additive hazards model confirmed these results (eFigures 2 and 3 in the Supplement). The incidence of the composite end point of death or major bleeding did not differ between the 2 groups (adjusted HR, 1.03; 95% CI, 0.86-1.24; *P* = .74) (Figure 2 and eFigure 4 in the Supplement).

Subgroup Analyses

The association of PACT with all-cause mortality, MI, and major bleeding was not significantly different among patients with different GRACE or CRUSADE scores (low, medium, or high risk) (eFigure 5 in the Supplement). Other subgroup analyses did not identify any significant difference in all-cause death or in the composite outcomes of death or MI (eFigures 6 and 7 in the Supplement). The higher incidence of major bleeding associated with PACT was consistent across all the subgroups with the exception of patients with NSTEMI. Major bleeding

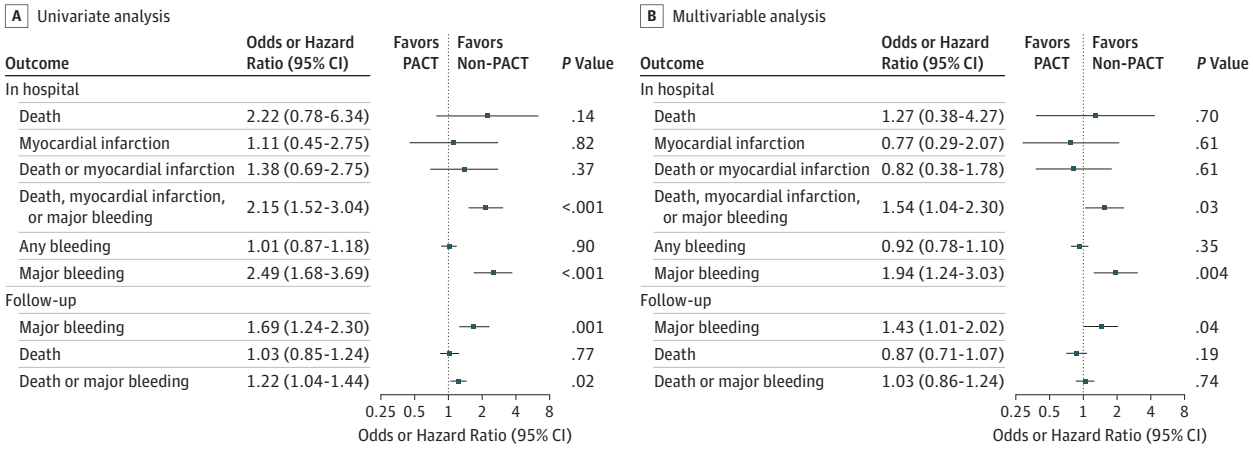
Table 2. In-Hospital and Long-Term Clinical Outcomes

Outcome	No. (%) Non-PACT (N = 4689)	PACT (N = 2115)	*P* Value
In-hospital outcome			
Death[a]	7 (0.1)	7 (0.3)	.13
Myocardial infarction	14 (0.3)	7 (0.3)	.82
Death or myocardial infarction	21 (0.4)	13 (0.6)	.37
Major bleeding	48 (1.0)	53 (2.5)	<.001
Any bleeding	607 (12.9)	276 (13.0)	.91
Death, myocardial infarction, or major bleeding	67 (1.4)	64 (3.0)	<.001
Long-term outcome			
30 d			
Death	13 (0.3)	10 (0.5)	.20
Major bleeding	48 (1.0)	53 (2.5)	<.001
Death or major bleeding	59 (1.3)	61 (2.9)	<.001
1 y			
Death	91 (1.9)	39 (1.8)	.79
Major bleeding	61 (1.3)	58 (2.7)	<.001
Death or major bleeding	146 (3.1)	93 (4.4)	.01
3 y			
Death	227 (4.8)	111 (5.2)	.47
Major bleeding	91 (1.9)	68 (3.2)	.001
Death or major bleeding	310 (6.6)	169 (8.0)	.04

Abbreviation: PACT, parenteral anticoagulant therapy.

[a] All-cause death.

Figure 2. Univariate and Multivariable Logistic or Cox Proportional Hazards Regression Analyses for Clinical Outcomes



PACT indicates parenteral anticoagulant therapy.

appeared to be more pronounced in the subgroup without anemia or heart failure (eFigure 8 in the Supplement).

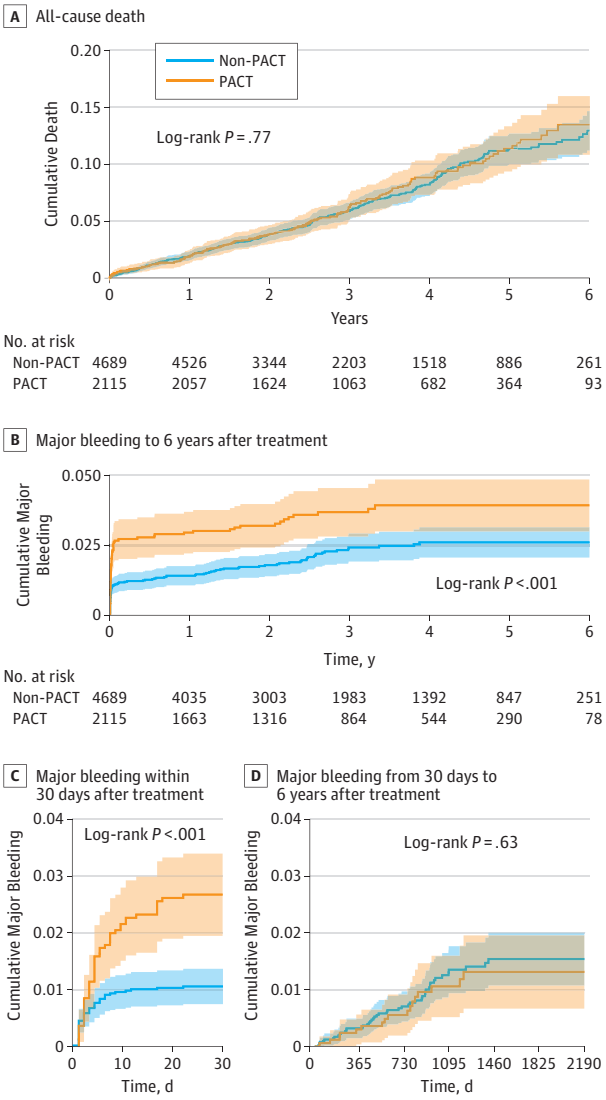
Propensity Score Analyses

We matched 997 patients receiving PACT to those receiving non-PACT in a 1:1 ratio (Table 1 and eTable 3 and eFigure 9 in the Supplement). The propensity-matched results showed an absence of a significant difference in all-cause death between the PACT and non-PACT groups (in-hospital OR, 1.33; 95% CI, 0.30-5.98; long-term HR, 0.97; 95% CI, 0.67-1.39). PACT was associated with a higher risk of major bleeding during the hospital stay (OR, 2.33; 95% CI, 1.07-5.09), and a similar result was found at follow-up, although it was not statistically significant (HR, 1.47; 95% CI, 0.82-2.64) (eTable 4 in the Supplement). A similar result was also found in the covariate adjustment using the propensity score and after stratification of the quintiles of the propensity score (eTables 3 and 4 and eFigure 10 in the Supplement).

Heterogeneity Analyses Between Centers

The heterogeneity analyses showed low heterogeneity for in-hospital and long-term outcomes among the centers ($I^2 \leq 30\%$, where I^2 indicates the percentage of variation across centers that is the result of heterogeneity) (eFigures 11 and 12 in the Supplement). Furthermore, consistent results

Figure 3. Kaplan-Meier Estimated Event Rates of All-Cause Death and Major Bleeding



PACT indicates parenteral anticoagulation therapy.

were found in the multivariable analyses stratified by centers and including the random association of the centers (eTable 5 in the Supplement).

Discussion

This study, to our knowledge, is the first to evaluate the association between PACT and clinical outcomes in patients undergoing PCI for NSTE-ACS. Our results showed that PACT was not associated with a lower risk of in-hospital death or MI or long-term death but was associated with a higher risk of major bleeding.

Unfractionated heparin has been previously proven to lower the risk of adverse cardiovascular events in patients with NSTE-ACS.[1] Newer PACT, such as low-molecular-weight heparin and fondaparinux, is considered to be superior to unfractionated heparin.[2,4,12,13] Although recommended for all patients with NSTE-ACS, PACT was reportedly used in 72.7% of patients with NSTE-ACS in China.[14] It is difficult to determine the reason behind the variety of management. A possible explanation could be that physicians in PCI centers are reluctant to administer PACT before the procedure because of concern for bleeding attributable to aggressive antithrombotic treatment and the crossover between different anticoagulants. Although anticoagulation therapy has been proven to be beneficial among patients with NSTE-ACS, all studies comparing PACT with placebo or control were conducted more than 20 years ago,[2,3] when neither dual antiplatelet therapy nor PCI was commonly used. Contrary to the previous findings, our study found no significant difference in effectiveness outcomes between the PACT and non-PACT groups. The difference in the findings may be explained by the difference in the end points over time and the changes in clinical practice. In previous studies, the benefit of PACT was mainly attributed to a reduction in recurrent angina and emergency revascularization.[1-3] The PCI is now being widely accepted as an important measure to effectively prevent ischemic events, particularly in high-risk groups.[15-18] Therefore, the protective effect of PACT might become less significant.

Conversely, our results reinforce the findings of previous studies,[1-3,19] wherein no significant difference of mortality between the 2 groups was identified. Moreover, the results of previous studies were inconsistent even with respect to the composite end points, with some of them finding no protective effect of PACT in patients with NSTE-ACS.[20-23] It could be argued that the efficacy of PACT might have been underestimated because fondaparinux, which has been found to be superior to enoxaparin because of fewer bleeding events,[4] was used in less than 20% of patients in our study. Fondaparinux, enoxaparin, and bivalirudin have shown superiority compared with the older anticoagulants. However, studies comparing these agents with placebo are still lacking.[14-16,24] Our results are hypothesis generating, and further studies are needed to evaluate the role of PACT in patients with NSTE-ACS for whom invasive management is planned.

An assessment of the role of PACT in patients with NSTE-ACS also requires consideration of antiplatelet therapy. Antiplatelet agents are the core of medical management in patients with ACS owing to their ability to prevent acute coronary events. Dual antiplatelet therapy consisting of aspirin and clopidogrel has been proven to improve patient prognoses and is recommended for patients with NSTE-ACS.[25-27] Another study[28] showed that ticagrelor was associated with further reduction in adverse events compared with clopidogrel, especially in those undergoing PCI. The $P2Y_{12}$ inhibitors were not used in any of the previous studies that have shown the advantage of PACT over placebo.[1-3] In our study, more than 96% of patients were prescribed $P2Y_{12}$ inhibitors (96.4% of clopidogrel and 0.4% of ticagrelor) in addition to aspirin, with more than 62% receiving a loading dose of $P2Y_{12}$ inhibitors before PCI. When platelet function is fundamentally inhibited by more aggressive antiplatelet therapy, the association of PACT might be attenuated.

Although the association between PACT and increased bleeding has been well established,[29] it is possible that, in our study,

more major bleeding in the anticoagulation group occurred because of an imbalance of the baseline characteristics. The association between PACT and major bleeding remained significant in both the logistic regression analyses and the propensity analyses. Moreover, the difference between the groups was based on mainly more major bleeding episodes within 30 days in the PACT group, and after 30 days, a similar incidence of new bleeding was observed. This finding suggests that the difference in management rather than an imbalance of baseline characteristics could be the main reason for higher bleeding in the PACT group. Conversely, excessive anticoagulation resulting from a crossover between different anticoagulants could not be ruled out as a contributing factor owing to the routine use of unfractionated heparin (99.9%) in our study for procedures in catheter laboratories regardless of the choice of preprocedure anticoagulation. A Korean study[9] reported no extra bleeding events among patients who were routinely given unfractionated heparin in the catheter laboratory when low-molecular-weight heparin was administered before PCI. The incidence of major bleeding in the anticoagulation group was comparable to that in a previous study without crossover anticoagulation therapy.[30] Therefore, anticoagulation itself rather than crossover anticoagulation therapy may have been the main cause of more major bleeding in the PACT group.

Limitations

Although many measures were taken to control inherent bias in this retrospective study, residual confounders secondary to unmeasured variables were possible. Bleeding events could not be determined in 13.8% of the study population during follow-up. However, our finding that PACT was not associated with long-term bleeding after hospital discharge is similar to previous studies, implying that the missing follow-up data were unlikely to change the results.[4,31] Most of the patients were classified as low-moderate risk, which might underestimate the efficacy of PACT among patients with NSTE-ACS. However, the neutral effect of PACT in this study is still relevant to clinical practice because PACT is recommended in all patients with NSTE-ACS by current guidelines regardless of risk stratification. The low event rate means that our study had insufficient power to exclude a substantial associated increase in the risk of death or MI, which justifies further studies to determine the efficacy of PACT. Finally, because we only included patients undergoing PCI, the findings could not be generalized to all patients with NSTE-ACS.

Conclusions

In patients undergoing PCI for NSTE-ACS, PACT was not associated with lower risk of all-cause death or MI but was significantly associated with higher risk of major bleeding. Further studies are warranted to determine the role of PACT in this context.

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