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ORIGINAL ARTICLE

Ticagrelor vs clopidogrel when coadministered with bivalirudin in patients with acute coronary syndrome undergoing percutaneous coronary intervention

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Abstract

Background: The optimal perioperative antithrombotic strategy for patients with acute coronary syndrome (ACS) during percutaneous coronary intervention (PCI) remains controversial.

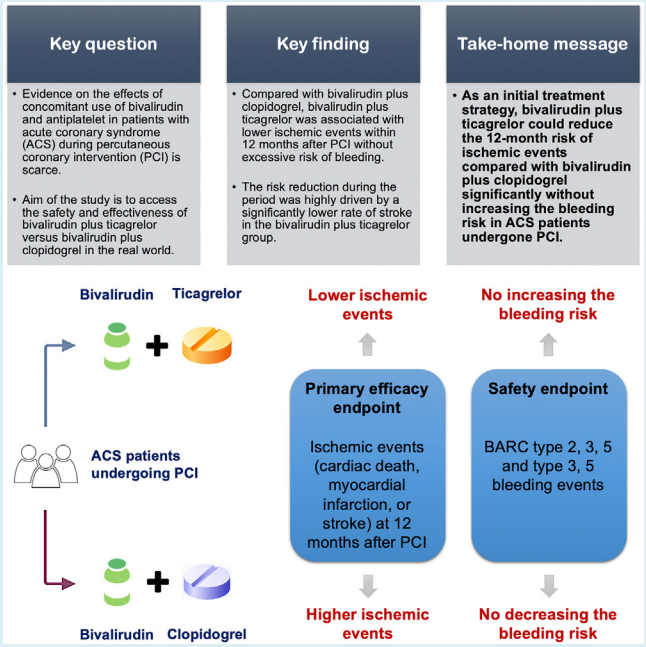
Objectives: To determine the safety and effectiveness of bivalirudin plus ticagrelor vs bivalirudin plus clopidogrel in patients with ACS undergoing PCI in the real world.

Methods: Between March 2016 and March 2019, 7234 patients with ACS who had undergone PCI, received bivalirudin periprocedurally, and were prescribed ticagrelor or clopidogrel were enrolled in a single-center, all-comer, modern, retrospective cohort study. Incidence rates of 12-month ischemia (cardiac death, myocardial infarction, or stroke), all-cause death, Bleeding Academic Research Consortium (BARC) type 2,3,5 bleeding, and BARC type 3,5 bleeding were compared between different groups.

Results: In total, 4960 patients received bivalirudin plus clopidogrel and 2274 patients received bivalirudin plus ticagrelor. Compared with bivalirudin plus clopidogrel, bivalirudin plus ticagrelor was associated with lower ischemic events (1.74% vs 2.84%; relative risk, 0.61; 95% CI, 0.41-0.91; $P = .02$) and stroke (0.05% vs 1.01%, $P < .001$) within 12 months after PCI without excessive risk of bleeding (BARC type 2,3,5 bleeding: 4.49% vs 3.76%, $P = .22$; BARC type 3,5 bleeding: 2.84% vs 2.02%, $P = .08$). The beneficial effects of bivalirudin plus ticagrelor were consistent among subgroups.

Conclusion: As an initial treatment strategy, bivalirudin plus ticagrelor could reduce the 12-month risk of ischemic events compared with bivalirudin plus clopidogrel significantly without increasing the bleeding risk in ACS patients undergoing PCI.

Yang Li, Yi Li, and Miaohan Qiu contributed equally to this study.



KEYWORDS
acute coronary syndrome, antithrombotic therapy, bivalirudin, clopidogrel, percutaneous coronary intervention, ticagrelor

Essentials

- How to combine bivalirudin and antiplatelet drugs is an important decision.
- We compared bivalirudin plus ticagrelor with bivalirudin plus clopidogrel in the real world.
- Bivalirudin plus ticagrelor was associated with lower ischemic events.
- The risk reduction was highly driven by a significantly lower rate of stroke.

1 | INTRODUCTION

The optimal periprocedural antithrombotic strategy in patients with acute coronary syndrome (ACS) treated with current practice has always been a hotspot problem and remains strongly debated [1]. Consequently, a fast-acting, safe, and efficacious antithrombotic option in this setting to balance bleeding and ischemic risks is needed. Ticagrelor, a direct-acting oral antagonist of $P2Y_{12}$ inhibition with a more potent and rapid onset of action compared with clopidogrel and without catabolite activation, is now the standard of care for percutaneous coronary intervention (PCI) in patients with ACS [2,3]. However, concerns about the increased risk of bleeding associated with more effective antiplatelet strategies have posed challenges in balancing ischemic and bleeding events.

Indeed, bivalirudin, a reversible and direct thrombin inhibitor, possesses several potential advantages, such as a short half-life with low risk of bleeding, linear kinetics with a predictable anticoagulant response, and low immunogenic profile without induction of heparin-induced thrombocytopenia [4]. Moreover, previous randomized trials suggest that bivalirudin determines superiority, especially in terms of decreased bleeding compared with unfractionated heparin, despite its concern about stent thrombosis [5]. In this study, we sought to evaluate the relative safety and efficacy of bivalirudin combined with ticagrelor vs the use of bivalirudin combined with clopidogrel for ACS patients undergoing PCI in the real world.

2 | METHODS

2.1 | Study population and data source

We completed a single-center, all-comer, retrospective cohort study that enrolled consecutive patients hospitalized for ACS managed with successful PCI who received bivalirudin periprocedurally and were prescribed ticagrelor or clopidogrel at the General Hospital of Northern Theater Command from March 2016 through March 2019. In our study,

the inclusion criteria included patients with ACS ≥ 18 years of age, undergoing PCI with at least 1 stent implanted, receiving treatment with bivalirudin, and receiving ticagrelor- or clopidogrel-based dual antiplatelet therapy. Major exclusion criteria included active or recent major bleeding or bleeding tendency, allergy to bivalirudin or hirudin, cardiogenic shock, receiving heparin monotherapy, receiving planned long-term tirofiban infusions, and switching between ticagrelor and clopidogrel during hospitalization. The Global Registry of Acute Coronary Events (GRACE) score was calculated according to age, heart rate, systolic blood pressure, Killip class, creatinine and cardiac enzyme levels, ST-segment deviation on the electrocardiogram, and cardiac arrest at admission [6]. The 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 was based on 8 variables, 4 dichotomous (female sex, heart failure signs, diabetes, and peripheral artery disease) and 4 semiquantitative (baseline hematocrit, creatinine clearance, heart rate, and systolic blood pressure, all analyzed as ordinal categories) [7]. The study was approved by the hospital's research ethics committee, which agreed to exempt the written informed consent. The study complied with the Declaration of Helsinki. A standard web-based data collection platform (CV-NET system of Crealife Technology) was used.

2.2 | Anticoagulant and antiplatelet strategy

Intravenous (i.v.) injection of 0.75 mg/kg of bivalirudin was followed by i.v. infusion of 1.75 mg/kg/h during the procedure and for at least 30 minutes but no more than 4 hours thereafter. After that, physicians could decide whether to reduce the infusion dose (0.2 mg/kg/h) for up to 20 hours or not. After 5 minutes of i.v. injection of bivalirudin, activated coagulation time (ACT, measured using the Hematec assay) was required to be detected; if ACT was less than 225 seconds, an additional 0.3 mg/kg of bivalirudin should be injected intravenously. For patients with a creatinine clearance rate below 30 mL/min, the infusion rate of bivalirudin decreases to 1 mg/kg/h. For hemodialysis patients, the infusion rate decreases to 0.25 mg/kg/h.

The choice of antiplatelet strategy was left at the physician's discretion. Before PCI, all participants were given antiplatelet therapy within the recommended standard dose range (a loading dose of 300 mg of aspirin in combination with 180 mg of ticagrelor or 300-600 mg of clopidogrel). After discharge, all participants were prescribed aspirin (100 mg daily) and ticagrelor (90 mg twice daily) or clopidogrel (75 mg daily) for at least 12 months. Other pharmacologic therapy was according to the current guidelines.

2.3 | Outcomes and definitions

The primary efficacy end point was the occurrence of ischemic events at 12 months after PCI, defined as a composite of cardiac death, myocardial infarction (MI), and stroke. Secondary efficacy end points included each individual component of the primary end point, all-cause death, and net adverse clinical events (defined as a composite of all-cause death, MI, stroke, and Bleeding Academic Research Consortium [BARC] type 3,5 bleeding events). The safety end point was BARC type 2,3,5 and type 3,5 bleeding events. The definition of MI was based on the Third Universal Definition of Myocardial Infarction Guidelines. According to clinicians or imaging investigations, stroke was defined as a neurologic loss caused by ischemic attacks that persist for at least 24 hours or lead to death. The definition of all-cause death was based on the Academic Research Consortium criteria. Clinical follow-up was performed through phone calls, outpatient visits, or readmission at 1, 6, and 12 months. All clinical events were examined by a clinical event committee.

2.4 | Statistical analysis

Categorical variables were summarized by frequencies and percentages and compared using the chi-squared or Fisher exact test. Continuous variables with normal distribution were reported as mean and SD, and nonnormally distributed variables were reported with median and IQR. Continuous variables were compared using the independent *t*-test or nonparametric test. Propensity score matching was used to match the baseline demographic, clinical, and angiographic variables (Table 1) well between ticagrelor group and clopidogrel group. A greedy matching protocol (1:1 matching without replacement) with a caliper width of 0.1 was used for matching [8]. We measured the absolute standardized differences for all covariates before and after matching, and a standardized difference of <10% for a given covariate indicated adequate matching (Supplementary Figure S1). Results are presented as crude incidences with 95% CIs. Subgroups were classified by age < 65 years vs age ≥ 65 years, male vs female, diabetes vs no diabetes, previous MI vs no previous MI, previous stroke vs no previous stroke, estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 vs eGFR ≥ 60 mL/min/1.73 m^2, ST-segment–elevation MI vs non–ST-segment–elevation ACS, glycoprotein IIb/IIIa receptor inhibitor during PCI vs no glycoprotein IIb/IIIa receptor inhibitor during PCI, CRUSADE score > 30 vs CRUSADE score ≤ 30, and activated clotting time ≤ 360 seconds vs activated clotting time > 360 seconds. All statistical analyses were performed with SPSS version 26.0 (SPSS Inc), and a 2-sided *P* value of <.05 was considered to indicate statistical significance.

3 | RESULTS

3.1 | Patient characteristics and treatments

During the study period, of the 22,445 patients who underwent PCI at our center, 7234 met the inclusion criteria (Figure 1). In the unmatched cohort, 4960 (68.6%) patients received bivalirudin plus clopidogrel and 2274 (31.4%) patients received bivalirudin plus ticagrelor. The matched cohort consisted of 2182 patients receiving bivalirudin plus clopidogrel and 2182 patients receiving bivalirudin

TABLE 1 Baseline clinical characteristics and medication after discharge before and after propensity score matching.

Characteristic	All patients			Propensity-matched patients		
	Bivalirudin plus clopidogrel (*N* = 4960)	Bivalirudin plus ticagrelor (*N* = 2274)	*P* value	Bivalirudin plus clopidogrel (*N* = 2182)	Bivalirudin plus ticagrelor (*N* = 2182)	*P* value
Age (y)	64.74 ± 10.47	59.38 ± 9.36	<.0001	59.82 ± 10.10	59.69 ± 9.08	.66
Male sex. no. (%)	3347 (67.48%)	1762 (77.48%)	<.0001	1689 (77.41%)	1681 (77.04%)	.77
Hypertension, no. (%)	3213 (64.90%)	1402 (61.76%)	.01	1359 (62.28%)	1348 (61.78%)	.73
Diabetes mellitus, no. (%)	1605 (32.44%)	781 (34.48%)	.09	724 (33.18%)	751 (34.42%)	.39
History of stroke, no. (%)	987 (19.96%)	253 (11.17%)	<.0001	261 (11.96%)	244 (11.18%)	.42
Peripheral vascular disease	73 (1.47%)	17 (0.75%)	.0098	17 (0.78%)	15 (0.69%)	.72
Prior MI, no. (%)	862 (17.45%)	455 (20.05%)	.008	428 (19.62%)	436 (19.98%)	.76
Prior PCI, no. (%)	1258 (25.41%)	638 (28.09%)	.02	595 (27.27%)	609 (27.91%)	.63
Prior CABG, no. (%)	77 (1.55%)	29 (1.28%)	.36	26 (1.19%)	28 (1.28%)	.78
Family history of CAD, no. (%)	404 (8.18%)	252 (11.16%)	<.001	217 (9.98%)	238 (10.93%)	.31
Smoking, no. (%)			<.0001			.62
No	2374 (48.07%)	881 (38.98%)		877 (40.19%)	860 (39.41%)	
Current smoker	1819 (36.83%)	1030 (45.58%)		955 (43.77%)	986 (45.19%)	
Former smoker	746 (15.10%)	349 (15.44%)		350 (16.04%)	336 (15.40%)	
Clinical presentation, no. (%)			.05			.94
Unstable angina	2977 (60.02%)	1302 (57.26%)		1242 (56.92%)	1252 (57.38%)	
NSTEMI	866 (17.46%)	406 (17.85%)		398 (18.24%)	390 (17.87%)	
STEMI	1117 (22.52%)	566 (24.89%)		542 (24.84%)	540 (24.75%)	
eGFR (mL/min/1.73 m^2)	88.89 ± 26.83	93.97 ± 24.48	<.0001	92.36 ± 26.05	93.81 ± 24.53	.07
Ejection fraction, %	58.17 ± 8.88	57.79 ± 8.78	.12	57.87 ± 8.90	57.83 ± 8.73	.90
LDL-C (mmol/L)	2.31 ± 0.81	2.31 ± 0.85	.97	2.30 ± 0.82	2.31 ± 0.84	.80
GRACE score	129.57 ± 34.58	121.46 ± 30.14	<.0001	122.83 ± 33.38	122.09 ± 29.80	.54
CRUSADE score	25.17 ± 12.56	21.82 ± 11.15	<.0001	22.45 ± 12.17	21.90 ± 11.14	.13
Medications at discharge						
Aspirin	4844 (97.66%)	2228 (97.98%)	.40	2140 (98.08%)	2138 (97.98%)	.83
Statins	4601 (92.76%)	2085 (91.69%)	.11	2012 (92.21%)	2005 (91.89%)	.70
ACEI/ARB	3182 (64.15%)	1506 (66.23%)	.09	1430 (65.54%)	1436 (65.81%)	.85
β-blockers	3314 (66.81%)	1597 (70.23%)	.004	1518 (69.57%)	1535 (70.35%)	.58
Proton pump inhibitors	1867 (37.64%)	715 (31.44%)	<.0001	695 (31.85%)	692 (31.71%)	.92

Values are *n* (%) or mean ± SD.

ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin II receptor blocker; CABG, coronary artery bypass graft; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction.

plus ticagrelor. Baseline patients' characteristics and medications at discharge of unmatched and matched cohorts are presented in Table 1, and procedure-related details are presented in Table 2. No statistically significant difference in patients' demographics, comorbidities, procedures, and medications was observed after propensity score matching. In addition, adherence to antiplatelet therapy among patients during 1 year was optimal (Supplementary Table S1).

3.2 | Clinical outcome

The adjusted analysis showed a reduction in the primary effectiveness end point of cardiac death/MI/stroke at 12 months for patients treated with bivalirudin plus ticagrelor compared with bivalirudin plus clopidogrel (1.74% vs 2.84%; relative risk, 0.61; 95% CI, 0.41-0.91; *P* = .02; Figure 2). Of note, the risk reduction during the period was highly driven

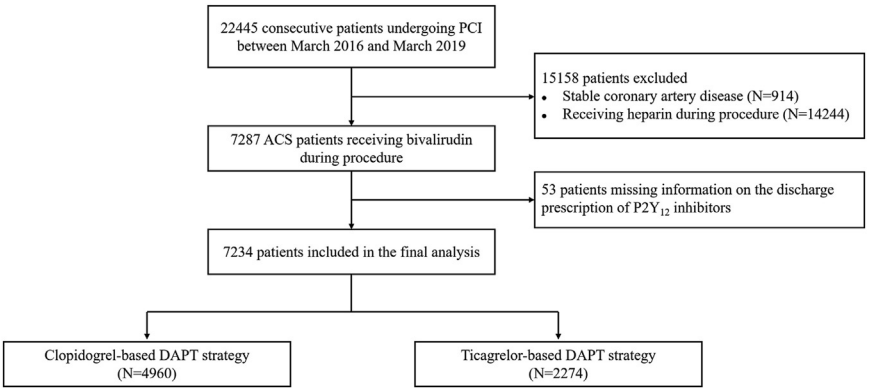


FIGURE 1 Flow chart of the study population.

by a significantly lower rate of stroke in the bivalirudin plus ticagrelor group (0.05% vs 1.01%; $P < .001$; Table 3). The event rate of all-cause mortality was 1.79% in bivalirudin plus clopidogrel group and 1.28% in bivalirudin plus ticagrelor group at 12 months ($P = .18$; Figure 2). There were also similar risks of the safety end point of BARC 2,3,5 bleeding (4.49% vs 3.76%; $P = .22$; Figure 2) and BARC 3,5 bleeding (2.84% vs 2.02%; $P = .08$; Figure 2) in the bivalirudin plus ticagrelor and bivalirudin plus clopidogrel groups after propensity score matching. Supplementary Figure S2 showed Kaplan–Meier cumulative event curves for a 12-month period for patients treated with bivalirudin plus clopidogrel or bivalirudin plus ticagrelor before propensity score matching. Results from Cox regression models with various event outcomes are shown in Table 3. Subgroup analyses showed no considerable heterogeneity for the treatment effects of bivalirudin plus clopidogrel or bivalirudin plus ticagrelor on the primary ischemic end point (Figure 3) and BARC 2,3,5 bleeding (Figure 4).

TABLE 2 Baseline procedural characteristics before and after propensity score matching.

	All patients			Propensity-matched patients		
Characteristic	Bivalirudin plus clopidogrel (*N* = 4960)	Bivalirudin plus ticagrelor (*N* = 2274)	*P* value	Bivalirudin plus clopidogrel (*N* = 2182)	Bivalirudin plus ticagrelor (*N* = 2182)	*P* value
Radial access, no. (%)	4537 (91.47%)	2103 (92.48%)	.15	2019 (92.53%)	2017 (92.44%)	.91
Target lesion location, no. (%)						
LMCA	217 (4.38%)	152 (6.68%)	<.0001	130 (5.96%)	139 (6.37%)	.57
LAD	2650 (53.43%)	1277 (56.16%)	.03	1205 (55.22%)	1220 (55.91%)	.65
LCX	1178 (23.75%)	592 (26.03%)	.04	563 (25.80%)	564 (25.85%)	.97
RCA	1890 (38.10%)	789 (34.70%)	.005	765 (35.06%)	757 (34.69%)	.80
Complex lesion type, no. (%)						
Bifurcation	417 (8.41%)	252 (11.08%)	.0003	228 (10.45%)	236 (10.82%)	.70
Ostial	291 (5.87%)	136 (5.98%)	.85	133 (6.10%)	130 (5.96%)	.85
Total occlusion	1489 (30.02%)	817 (35.93%)	<.0001	749 (34.33%)	771 (35.33%)	.49
Calcification	1020 (20.56%)	490 (21.55%)	.34	446 (20.44%)	467 (21.40%)	.44
Thrombus	405 (8.17%)	226 (9.94%)	.01	205 (9.40%)	215 (9.85%)	.61
Diffuse	794 (16.01%)	428 (18.82%)	.003	388 (17.78%)	398 (18.24%)	.69
No. of stents per subject	1.52 ± 0.85	1.70 ± 0.94	<.0001	1.64 ± 0.89	1.68 ± 0.93	.19
Total stent length (mm)	39.84 ± 25.58	45.79 ± 28.46	<.0001	43.73 ± 27.30	45.04 ± 27.97	.12
Average stent diameter (mm)	3.02 ± 0.76	3.08 ± 1.10	.047	3.06 ± 0.99	3.08 ± 1.12	.54
SYNTAX score	14.81 ± 8.65	16.08 ± 9.15	<.0001	15.62 ± 8.88	15.91 ± 9.03	.30

Values are *n* (%) or mean ± SD.

LMCA, left main coronary artery; LAD, left anterior descending branch; LCX, left circumflex artery; RCA, right coronary artery; SYNTAX, synergy between PCI with TAXUS and cardiac surgery.

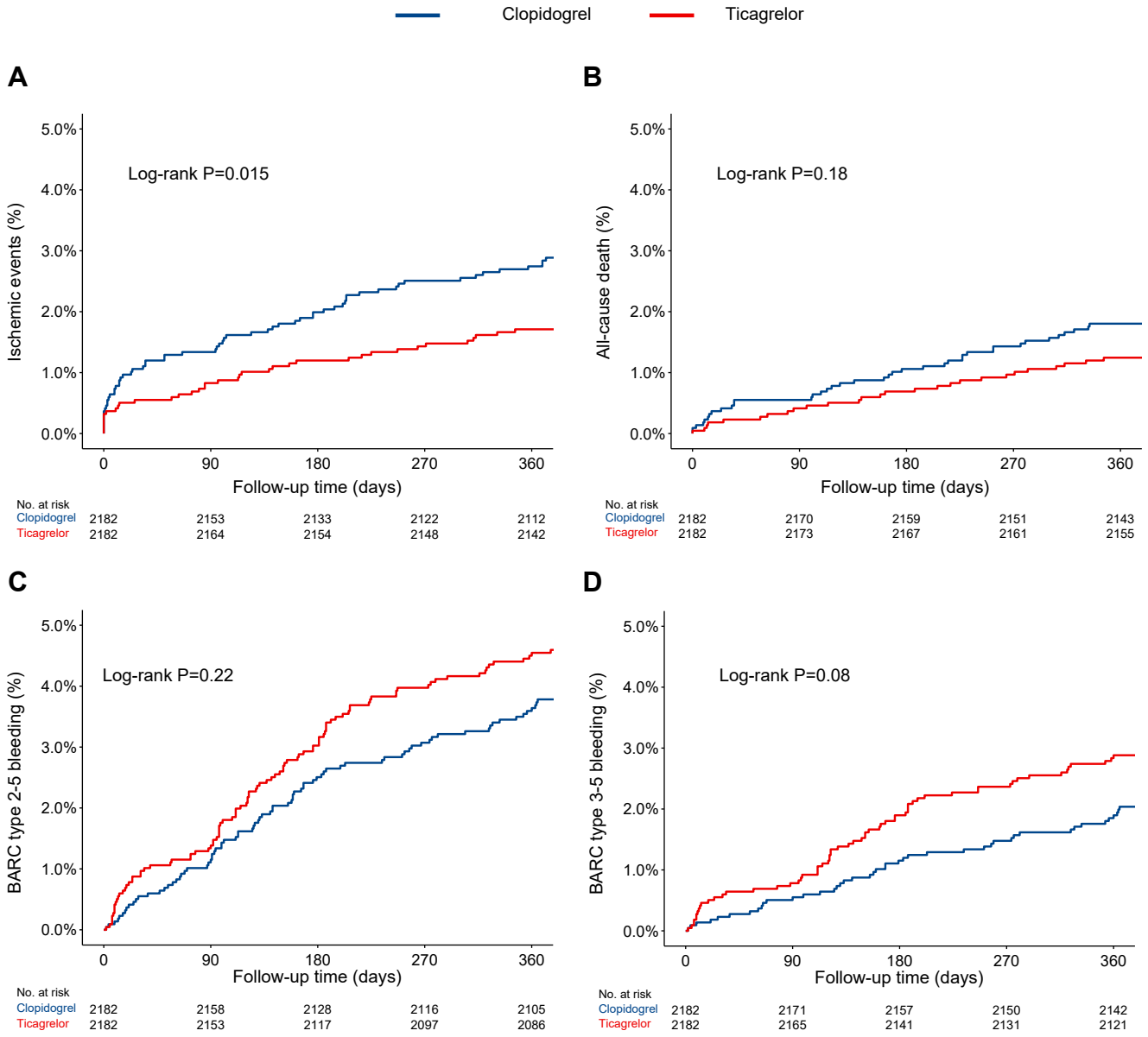


FIGURE 2 Kaplan–Meier cumulative event curves for (A) a 12-month primary end point, ischemic events, (B) all-cause death, (C) BARC 2,3,5 bleeding, and (D) BARC 3,5 bleeding after propensity score matching. Ischemic events are defined as a composite of cardiac death, myocardial infarction, and stroke. BARC, Bleeding Academic Research Consortium.

4 | DISCUSSION

To our knowledge, no study has evaluated the association between use of bivalirudin plus ticagrelor compared with bivalirudin plus clopidogrel and ischemic and hemorrhagic outcomes. In this single-center, all-comer, modern, retrospective cohort study targeting ACS patients undergoing PCI, we summarize the 12-month clinical outcomes of the 2 different pharmacologic strategies. The main results showed that bivalirudin plus ticagrelor could reduce the 12-month risk of ischemic events compared with bivalirudin plus clopidogrel significantly without increasing the risk of bleeding. The results were consistent in all major subgroups, regardless of baseline clinical or angiographic characteristics.

Balancing the risk of bleeding against the benefits of using antithrombotic drugs is always a challenge in daily PCI practice [5]. Bivalirudin exhibits several potential pharmacodynamic and pharmacokinetic advantages compared with unfractionated heparin, and a net clinical benefit of bivalirudin compared with unfractionated heparin with and without glycoprotein IIb/IIIa inhibitors has been repeatedly shown due to a reduction in bleedings; some studies even suggested a decrease in cardiovascular and all-cause mortality in several large randomized clinical trials including Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS AMI) [9], The European Ambulance Acute Coronary Syndrome Angiography (EuroMax) [10], The Bivalirudin in Acute Myocardial

TABLE 3 Clinical outcomes over 12 months between bivalirudin plus clopidogrel and bivalirudin plus ticagrelor in the high-risk groups before and after propensity score matching.

	All patients			Propensity-matched patients		
Characteristic	Bivalirudin plus clopidogrel (*N* = 4960)	Bivalirudin plus ticagrelor (*N* = 2274)	*P* value	Bivalirudin plus clopidogrel (*N* = 2182)	Bivalirudin plus ticagrelor (*N* = 2182)	*P* value
Ischemic events	140 (2.82%)	43 (1.89%)	.02	62 (2.84%)	38 (1.74%)	.02
Cardiac death	72 (1.45%)	26 (1.14%)	.29	26 (1.19%)	25 (1.15%)	.89
MI	27 (0.54%)	18 (0.79%)	.21	16 (0.73%)	15 (0.69%)	.86
Stroke	46 (0.93%)	2 (0.09%)	<.0001	22 (1.01%)	1 (0.05%)	<.0001
All-cause death	108 (2.18%)	29 (1.28%)	.009	39 (1.79%)	28 (1.28%)	.18
BARC 2,3,5 bleeding events	201 (4.05%)	103 (4.53%)	.35	82 (3.76%)	98 (4.49%)	.22
BARC 3,5 bleeding events	124 (2.50%)	65 (2.86%)	.38	44 (2.02%)	62 (2.84%)	.08

Values are *n* (%). *P* values were calculated using the log-rank test based on all available follow-up data. Ischemic events, defined as a composite of cardiac death, MI, or stroke.

MI, myocardial infarction; BARC, Bleeding Academic Research Consortium.

Infarction vs Heparin and GPI Plus Heparin Trial (BRIGHT) [11], and Bivalirudin or unfractionated heparin in patients with acute coronary syndromes managed invasively with and without ST elevation (MATRIX). However, bivalirudin has caused an increase in the rate of acute (<24 hours) stent thrombosis (possibly due to its short half-life when suddenly discontinued after PCI), which has raised concerns. The BRIGHT, the MATRIX, and the Bivalirudin versus heparin in non-ST and ST-segment elevation myocardial infarction-a registry-based randomized clinical trial in the SWEDEHEART registry (VALIDATE-SWEDEHEART) studies [12] proposed the concept of the empty window of antithrombotic therapy in primary PCI, which clarified that high-dose infusion of bivalirudin after PCI overcomes the increased risk of acute stent thrombosis. Thus, compared with unfractionated heparin, perioperative use of bivalirudin can reduce the risk of bleeding events, thereby reducing all-cause mortality and cardiovascular mortality.

Meanwhile, current clinical practice guidelines recommend the newer and more potent $P2Y_{12}$ inhibitors (prasugrel and ticagrelor) over clopidogrel in ACS patients undergoing PCI [3,13], while the proportion of patients who received ticagrelor was not high in the previous randomized trials on bivalirudin. In the EuroMax study [10], ticagrelor was used in 26.9% of patients in the bivalirudin group and 26.7% of patients in the heparin group and prasugrel was used in 33.5% of patients in the bivalirudin group and 30.8% of patients in the heparin group. In the MATRIX study [14], ticagrelor or prasugrel was administered in 1314 patients (36.5%) in the bivalirudin group and 1320 patients (36.6%) in the unfractionated heparin group. Unlike earlier trials, patients participating in the VALIDATE-SWEDEHEART study received prasugrel, ticagrelor, or cangrelor [12]. However, no randomized controlled trial compared contemporary $P2Y_{12}$ inhibitors with clopidogrel when coadministered with bivalirudin in patients with ACS treated with PCI. In this study, we investigated the relative safety and effectiveness of bivalirudin plus ticagrelor vs bivalirudin plus clopidogrel for patients with ACS who were undergoing PCI in the real world. Before propensity score matching, patients treated with ticagrelor were younger than those who received clopidogrel. There were significantly higher percentages of male gender, hypertension, peripheral vascular disease, low eGFR, previous stroke, and high GRACE and CRUSADE scores in the clopidogrel group than in the ticagrelor group, indicating that among all patients receiving bivalirudin treatment, the bleeding risk in patients receiving clopidogrel is lower than that in those receiving ticagrelor in real-world clinical practice. After propensity score matching, patients' characteristics were comparable between 2 groups. The key findings of our study showed that the treatment with bivalirudin plus ticagrelor reduced the risk of ischemic events compared with bivalirudin plus clopidogrel without increasing bleeding risk during the 12 months following PCI. Similar to our findings, a previous comparative study that enrolled 168 patients with acute ST-segment–elevation MI demonstrated that the cumulative incidence of primary end point occurred (cardiac death, thrombosis, MI, or nonfatal cerebrovascular accident at 30 days) in 5.7% of the patients in the bivalirudin plus clopidogrel group and in 0.0% in the bivalirudin plus prasugrel group (P = .04) without increasing major bleeding complications following primary angioplasty [15]. These findings indicate that the application of bivalirudin plus potent $P2Y_{12}$ inhibitors was superior to bivalirudin plus clopidogrel in ACS patients treated with PCI.

Guideline recommendation on ticagrelor is primarily based on the PLATelet inhibition and patient Outcomes (PLATO) trial in which ACS patients treated with ticagrelor had a 16% relative risk reduction at 12 months in a composite of death from vascular causes, MI, or stroke compared with those treated with clopidogrel [16], which was mainly driven by a reduction in the rate of all-cause death and MI. Meanwhile, there was no significant difference in the incidence of stroke between the 2 treatment groups. However, ticagrelor was associated with an increased incidence of major bleeding not related to coronary artery bypass grafting compared with clopidogrel. Additionally, the results of the M Safety and Efficacy of Ticagrelor Versus Clopidogrel

	Ischemic Events - Events/Total (%)			Relative Risk (95%CI)	P For Interaction
	Ticagrelor	Clopidogrel	P value		
Age ≥65 yrs					0.22
Yes	10/689(1.5)	24/703(3.4)	0.02	0.43 (0.20-0.88)	
No	28/1493(1.9)	38/1479(2.6)	0.20	0.73 (0.45-1.18)	
Male					0.16
Yes	25/1681(1.5)	49/1689(2.9)	0.01	0.51 (0.32-0.83)	
No	13/501(2.6)	13/493(2.6)	0.97	0.98 (0.46-2.10)	
Diabetes Mellitus					0.14
Yes	19/751(2.5)	21/724(2.9)	0.66	0.87 (0.47-1.61)	
No	19/1431(1.3)	41/1458(2.8)	0.01	0.47 (0.28-0.81)	
Previous MI					0.79
Yes	9/436(2.1)	13/428(3.0)	0.36	0.68 (0.29-1.57)	
No	29/1746(1.7)	49/1754(2.8)	0.02	0.59 (0.38-0.94)	
Previous stroke					0.16
Yes	4/244(1.6)	14/261(5.4)	0.02	0.31 (0.10-0.92)	
No	34/1938(1.8)	48/1921(2.5)	0.11	0.70 (0.45-1.08)	
eGFR <60 ml/min/1.73 m^2					0.68
Yes	6/163(3.7)	13/195(6.7)	0.21	0.55 (0.21-1.42)	
No	30/1856(1.6)	44/1842(2.4)	0.09	0.68 (0.43-1.07)	
Type of ACS					0.10
STEMI	11/540(2.0)	28/542(5.2)	0.01	0.39 (0.20-0.78)	
NSTE-ACS	27/1642(1.6)	34/1640(2.1)	0.36	0.79 (0.48-1.31)	
SYNTAX score ≥13					0.52
Yes	29/1286(2.3)	43/1262(3.4)	0.08	0.66 (0.42-1.05)	
No	9/896(1.0)	19/920(2.1)	0.07	0.49 (0.22-1.07)	
GPI during PCI					0.93
Yes	1/47(2.1)	2/52(3.8)	0.62	0.50 (0.24-1.04)	
No	37/2135(1.7)	60/2130(2.8)	0.02	0.62 (0.41-0.92)	
GRACE score ≥88					0.13
Yes	17/773(2.2)	35/755(4.6)	0.01	0.47 (0.27-0.84)	
No	19/1245(1.5)	22/1282(1.7)	0.71	0.89 (0.48-1.63)	
CRUSADE score >30					0.40
Yes	10/415(2.4)	21/432(4.9)	0.06	0.50 (0.24-1.04)	
No	26/1603(1.6)	36/1604(2.2)	0.20	0.72 (0.44-1.19)	
Activated clotting time					0.78
≤ 360s	10/805(1.2)	21/803(2.6)	0.05	0.48 (0.23-1.00)	
> 360s	12/779(1.5)	30/806(3.7)	0.01	0.41 (0.21-0.80)	

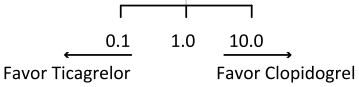


FIGURE 3 Subgroup analysis of the primary end point ischemic events after propensity score matching. Ischemic events are defined as a composite of cardiac death, myocardial infarction, and stroke. ACS, acute coronary syndrome; eGFR, estimated glomerular filtration rate; GPI, glycoprotein IIb/IIIa receptor inhibitor; NSTE-ACS, non–ST-segment–elevation ACS; PCI, percutaneous coronary intervention.

	BARC type 2-5 bleeding - Events/Total (%)			Relative Risk (95%CI)	P For Interaction
	Ticagrelor	Clopidogrel	P value		
Age ≥ 65 yrs					0.72
Yes	34/689(4.9)	27/703(3.8)	0.32	1.28 (0.78-2.11)	
No	64/1493(4.3)	55/1479(3.7)	0.43	1.15 (0.81-1.64)	
Male					0.82
Yes	76/1681(4.5)	65/1689(3.8)	0.33	1.17 (0.85-1.62)	
No	22/501(4.4)	17/493(3.4)	0.44	1.27 (0.68-2.37)	
Diabetes Mellitus					0.80
Yes	34/751(4.5)	26/724(3.6)	0.36	1.26 (0.76-2.08)	
No	64/1431(4.5)	56/1458(3.8)	0.40	1.16 (0.82-1.65)	
Previous MI					0.08
Yes	29/436(6.7)	15/428(3.5)	0.04	1.90 (1.03-3.49)	
No	69/1746(4.0)	67/1754(3.8)	0.84	1.03 (0.74-1.44)	
Previous stroke					0.75
Yes	13/244(5.3)	13/261(5.0)	0.86	1.07 (0.51-2.26)	
No	85/1938(4.4)	69/1921(3.6)	0.21	1.22 (0.89-1.67)	
eGFR <60 ml/min/1.73 m^2					0.58
Yes	11/163(6.7)	9/195(4.6)	0.38	1.46 (0.62-3.44)	
No	80/1856(4.3)	70/1842(3.8)	0.43	1.13 (0.83-1.55)	
Type of ACS					0.43
STEMI	17/540(3.1)	18/542(3.3)	0.87	0.95 (0.49-1.82)	
NSTE-ACS	81/1642(4.9)	64/1640(3.9)	0.15	1.26 (0.92-1.74)	
SYNTAX score ≥13					0.13
Yes	55/1286(4.3)	54/1262(4.3)	1.00	1.00 (0.69-1.44)	
No	43/896(4.8)	28/920(3.0)	0.05	1.58 (0.99-2.52)	
GPI during PCI					0.36
Yes	3/47(6.4)	1/52(1.9)	0.26	3.32 (0.36-30.82)	
No	95/2135(4.4)	81/2130(3.8)	0.29	1.17 (0.88-1.56)	
GRACE score ≥88					0.91
Yes	43/773(5.6)	37/755(4.9)	0.56	1.14 (0.74-1.74)	
No	48/1245(3.9)	42/1282(3.3)	0.43	1.18 (0.78-1.77)	
CRUSADE score >30					0.55
Yes	20/415(4.8)	21/432(4.9)	0.98	0.99 (0.55-1.80)	
No	71/1603(4.4)	58/1604(3.6)	0.24	1.22 (0.87-1.72)	
Activated clotting time					0.43
≤ 360s	43/805(5.3)	26/803(3.2)	0.04	1.65 (1.02-2.66)	
> 360s	39/779(5.0)	32/806(4.0)	0.32	1.26 (0.80-1.99)	

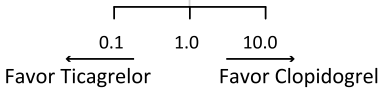


FIGURE 4 Subgroup analysis of the BARC 2,3,5 bleeding events after propensity score matching. ACS, acute coronary syndrome; BARC, Bleeding Academic Research Consortium; eGFR, estimated glomerular filtration rate; GPI, glycoprotein IIb/IIIa receptor inhibitor; MI, myocardial infarction; NSTE-ACS, non–ST-segment–elevation ACS; PCI, percutaneous coronary intervention; ST-segment–elevation myocardial infarction.

in Asian/KOREAn Patients with Acute Coronary Syndromes Intended for Invasive anagement (TICA-KOREA) [17] and Ticagrelor vs. clopidogrel in Japanese, Korean and Taiwanese patients with acute coronary syndrome (PHILO) [18] trials showed an increased risk of bleeding with ticagrelor compared with clopidogrel, but it has no protective effect on reducing ischemic events in ACS patients undergoing PCI in South Korea, Japan, and Taiwan. Also, recent observational studies have provided similar results [19,20]. Our findings differ from prior randomized trials and registry studies on this topic. In our study, bivalirudin plus ticagrelor was associated with a lower ischemic risk, which was mainly driven by a reduction in the rate of stroke; however, it was not associated with more bleeding. This might be explained by the differences in geography and ethnicity, patient populations and progresses in interventional cardiology. PLATO trial enrolled all ACS subtypes regardless of planned invasive management, in whom Asian subgroup represented only 6% and PCI was performed predominantly using bare-metal stents and first-generation drug-eluting stents. And, each of the observational studies was confined to a single country and produced without assessment of residual bias by using falsification end points. Importantly, the proportion of patients with hypertension (62.5%), diabetes (33.8%), history of stroke (11.6%), prior MI (19.8%), and prior PCI (27.6%) was high in our study, indicating the patients were at high risk of ischemic events. Consistent with our results, a previous study from our group demonstrated that ticagrelor showed a lower ischemic events compared with clopidogrel within 12 months after PCI without increasing bleeding risk in patients with CHA_2DS_2-VASc scores ≥ 3 but showed poor safety in patients with CHA_2DS_2-VASc scores < 3 for excessive bleeding [21].

Aspirin, clopidogrel and ticagrelor have been proven effective in the secondary prevention of stroke. A meta-analysis including 12 randomized controlled trials with 105,654 patients showed that ticagrelor compared with clopidogrel or aspirin provided more favorable outcomes for all stroke (odds ratio [OR], 0.84; 95% CI, 0.78-0.90; $P < .001$), ischemic stroke (OR, 0.83; 95% CI, 0.77-0.90; $P < .001$), and transient ischemic attack prevention (OR, 0.78; 95% CI, 0.62-0.97; $P = .03$) in patients with vascular high-risk factors. Ideally, ticagrelor can attenuate ischemia reperfusion injury possibly via phosphorylation of endothelial nitric oxide synthase and extracellular signal-regulated kinase 1/2 in endothelial cells and reduce microglial activation and chemotaxis after permanent middle cerebral artery occlusion in rats (oral treatment 10 minutes, 22 hours, and 36 hours after occlusion). This suggests that ticagrelor has neuroprotective effects via mechanisms other than its antiplatelet action.

5 | LIMITATIONS

We acknowledge the potential limitations of the study. Conclusions drawn from observational studies have inherent limitations, and the conclusion of this study can only prove associations, not causality. First, the design of observational studies only adjusts for various known clinical, angiographic, and laboratory variables, but there is still a possibility of residual unmeasured confounding, which is a potential source of error known in registry studies [22]. Accordingly, the results should not be interpreted as providing precise measurements of therapeutic efficacy. Second, propensity score adjustment can eliminate more than 90% of treatment bias, but observational studies still have residual and unmeasured confounding bias [23]. In our study, body mass index, H2-receptor antagonists, blood pressure control, diabetes control, liver disease, alcohol use, and social determinants of health were not collected routinely. The lack of adjustment for severity of comorbidities is also acknowledged. In the present study, we enrolled only East Asian ACS patients. The effects of bivalirudin plus ticagrelor need to be studied in other races and ethnicities. Interestingly, subgroup analyses from How Effective are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention Study (HEAT-PPCT) study (96% enrolled patients were White) showed a reduction in the primary outcome (a composite of all-cause mortality, cerebrovascular accident, reinfarction, or unplanned target lesion revascularization) at 28 days for the patients received bivalirudin plus ticagrelor compared with bivalirudin plus clopidogrel (8.7% vs 10.3%). Nevertheless, further research is needed to determine whether bivalirudin plus ticagrelor is more effective than bivalirudin plus clopidogrel in ACS patients undergoing PCI. Third, the choice of periprocedural antithrombotic was decided by physicians, which might limit the clinical value. In this study, most of patients (68.6%) received bivalirudin plus clopidogrel before propensity score matching analysis. Bivalirudin plus clopidogrel treated patients were older with more comorbidities and had higher GRACE score and CRUSADE score. This may be due to operators' selection based on the patients' clinical condition and difference in treatment strategy over the study period. To account for differences in patient baseline between the bivalirudin plus clopidogrel group and the bivalirudin plus ticagrelor group, we adjusted all analysis for age, comorbidities and GRACE score and CRUSADE score. Fourth, the observational data may not always able to estimate the short-term effect of intervention measures or the impact on results that are not regularly collected [24].

6 | CONCLUSION

Among ACS patients who underwent PCI, bivalirudin plus ticagrelor compared with bivalirudin plus clopidogrel was associated with lower ischemic events and no excessive bleeding within 12 months. Since the possibility of unmeasured confounding factors cannot be excluded, further research is needed to determine whether bivalirudin plus ticagrelor is more effective than bivalirudin plus clopidogrel in this setting.

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AUTHOR CONTRIBUTIONS

Y.L. and M.H.Q. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Y.L., Y.L., and Y.L.H. conceptualized and designed the study. Y.L., Y.L., M.H.Q., Y.X., and Y.L.H. acquired, analyzed, or interpreted the data. Y.L. drafted the manuscript. All authors critically revised the manuscript. M.H.Q. performed the statistical analysis. Y.L. obtaining funding.

RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author, Yaling Han (hanyaling@163.net), upon reasonable request.

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SUPPLEMENTARY MATERIAL

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