Comparison of net adverse clinical events between bivalirudin and heparin as anticoagulants for percutaneous coronary intervention in Chinese patients

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Abstract. Bivalirudin, as a direct thrombin inhibitor, is considered to be safer compared with other anticoagulants, such as heparin; however, relevant data in China are unclear. The present study aimed to compare the safety of bivalirudin and heparin as anticoagulants in Chinese patients who underwent percutaneous coronary intervention (PCI). In the present study, 2,377 patients with ST-segment elevation myocardial infarction (STEMI), unstable angina, non-STEMI or stable coronary artery disease who underwent primary PCI while receiving bivalirudin or heparin (low molecular weight heparin or unfractionated heparin) were reviewed, and then analyzed as the bivalirudin group (n=944) and heparin group (n=1,433). The net adverse clinical events (NACEs) within 30 days were obtained, which were defined as major adverse cardiac and cerebral events (MACCEs) + Bleeding Academic Research Consortium (BARC) grade 2-5 bleeding events. Compared with the heparin group, the incidence of NACEs was reduced in the bivalirudin group (9.3 vs. 13.4%; P=0.003). However, no discrepancy was found in the incidence of MACCEs between the groups (5.9 vs. 7.6%; P=0.116). Moreover, the incidences of BARC 2-5 (4.8 vs. 8.7%; P<0.001) and BARC 3-5 bleeding events (1.9 vs. 4.4%; P=0.001) were decreased in the bivalirudin group compared with the heparin group. Following adjustment using multivariate logistic regression analysis, bivalirudin treatment (vs. heparin treatment) was independently associated with lower risks of NACEs [odds ratio (OR), 0.587; P<0.001], MACCEs (OR, 0.689; P=0.041) and BARC 2-5 (OR, 0.459; P<0.001) and 3-5 bleeding events (OR, 0.386; P=0.002). Overall, the present study demonstrated that bivalirudin decreased the risks of NACEs and bleeding events compared with heparin in Chinese patients who undergo PCI. However, further validation is required.

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Introduction

Percutaneous coronary intervention (PCI) alleviates coronary artery stenosis or occlusion and restores blood flow by implanting stents; this has been one of the key methods used in the treatment of coronary artery diseases (1,2). Notably, patients who undergo PCI exhibit an unstable hypercoagulable state in their blood, resulting in a high risk of thrombosis (3-5). In order to prevent the occurrence of thrombosis, treatment with anticoagulants is also usually applied simultaneously in patients who undergo PCI, (6,7). However, bleeding and even mortality may occur during or after receiving anticoagulants in patients who undergo PCI (8,9). Therefore, it is critical to select appropriate anticoagulants in order to both effectively prevent thrombosis and minimize the risk of bleeding events.

Generally, bivalirudin, unfractionated heparin, enoxaparin and fondaparinux are the most commonly applied anticoagulant drugs used during PCI (10). Bivalirudin, as a direct thrombin inhibitor with a rapid onset and a short half-life, has been reported to be safer for use compared with heparin in several previous studies (11-14). For example, a previous study demonstrated that bivalirudin decreases the incidence of net adverse clinical events (NACEs) and major bleeding within 1 year compared with heparin plus a glycoprotein IIb/IIIa inhibitor (GPI) in patients with ST-segment elevation myocardial infarction (STEMI) who undergo primary PCI (13). Moreover, another study indicated that in patients with coronary artery disease complicated with diabetes who undergo PCI, bivalirudin decreases the risk of 30-day major adverse cardiac and cerebral events (MACCEs) compared with heparin (14). In addition, another study demonstrated

that compared with heparin alone and heparin plus tirofiban, bivalirudin achieves a reduction in bleeding event rates in patients with acute myocardial infarction who undergo primary PCI (15). However, the aforementioned studies were both conducted in countries other than China. Due to the short time period since bivalirudin has begun to be been marketed in China, the safety of the use of bivalirudin among Chinese patients who undergo PCI remains unclear; thus, this is a key issue which needs to be resolved.

Therefore, the present study aimed to compare the incidences of NACEs, MACCEs and bleeding events between the use of bivalirudin and heparin in Chinese patients who underwent PCI.

Patients and methods

Patients. The present cohort study reviewed 2,377 patients [mean age: 64.8±11.3 years; males: 1,644 (69.2%)] who underwent primary PCI and received bivalirudin or heparin as anticoagulants in HanDan Central hospital (Handan, China) between December, 2017 and February, 2022. The screening criteria were as follows: i) An age >18 years; ii) patients who underwent primary PCI; iii) patients who had the clinical manifestation of STEMI, unstable angina (UA), non-STEMI (NSTEMI) or stable coronary artery disease (SCAD); and iv) patients who received bivalirudin or heparin [low molecular weight heparin (LMWH) or unfractionated heparin (UFH)] as anticoagulants. Patients who had the following conditions were ineligible: i) Had incomplete clinical data for study use; ii) were complicated with cancers or severe hematological diseases; and iii) women who were pregnant or breastfeeding. The present study was approved by the Ethics Committee of HanDan Central Hospital (Handan, China; approval no. 20230816001). Patients or their families provided written informed consent. Clinical characteristics of patients are given in Table I.

Treatment. Bivalirudin or heparin (LMWH or UFH) were administered to the eligible patients for anticoagulant treatment. The treatment was not intervened with in the present study; the appropriate medication was selected was based on the actual clinical status of the patient. Furthermore, there were no restrictions on the addition of GPIs. As a result, patients who received bivalirudin were considered as the bivalirudin group (n=944) and patients who received LMWH or UFH were considered as the heparin group (n=1,433). The detailed regimens of bivalirudin and heparin were the same as those described in a previous study (16).

Data collection and assessment. Demographics, comorbidities, disease features and treatment-related information were obtained for analysis. The Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA guidelines (CRUSADE) score was evaluated based on 8 predictors and ranged from 1-100 points (17). Patients were classified into 5 categories of bleeding risk based on CRUSADE score: Very low, ≤20 points; low, 21-30 points; moderate, 31-40 points; high, 41-50 points; and very high risk, ≤51 points (17). Additionally, within 30 days after PCI, NACEs, MACCEs, Bleeding Academic Research Consortium grades 2-5 (BARC 2-5) bleeding events and BARC 3-5 bleeding events were assessed. NACEs was defined as the composite of MACCEs and BARC 2-5 bleeding events (18). MACCEs was defined as the composite of all-cause death, cardiac mortality, recurrent myocardial infarction, ischemia-driven target vessel revascularization and stroke (18). BARC 2-5 bleeding events and BARC 3-5 bleeding events were assessed according to BARC criteria (19).

Statistical analysis. Statistical analysis was carried out using SPSS V22.0 software (IBM Corp.). Graph plotting was performed using GraphPad Prism V6.1 software (GraphPad Software Inc.). Comparisons between the two groups were performed using the unpaired Student's t-test, χ^2 test or Wilcoxon rank sum test. Factors associated with NACEs, MACCEs, BARC 2-5 bleeding events or BARC 3-5 bleeding events were assessed using logistic regression analysis, and all factors analyzed in the univariate logistic regression analysis were included in the multivariate logistic regression analysis with the forward stepwise mode. A value of $P<0.05$ was considered to indicate a statistically significant difference.

Results

Clinical features. The heparin group included 458 (32.0%) females and 975 (68.0%) males with a mean age of 65.1±11.3 years. Moreover, the bivalirudin group included 275 (29.1%) females and 669 (70.9%) males with a mean age of 64.4±11.3 years. The median value [interquartile range (IQR)] of the CRUSADE score in the bivalirudin group was lower compared with that in the heparin group [27.0 (20.0-36.0) vs. 28.0 (21.0-38.0); P=0.019]. Moreover, the bleeding risk stratified by the CRUSADE score revealed a significant difference between the bivalirudin and heparin groups (P=0.013). In terms of demographics, comorbidities, other disease features and treatment-related information, there were no significant differences between the groups (all P>0.05). The detailed clinical features of the patients are presented in Table I.

Incidences of NACEs, MACCEs, BARC 2-5 bleeding events and BARC 3-5 bleeding events. The incidence of NACEs in the bivalirudin group was significantly lower compared with that in the heparin group (9.3 vs. 13.4%; P=0.003). Moreover, no significant difference was found in the incidence of MACCEs between the bivalirudin and heparin groups (5.9 vs. 7.6%; P=0.116). Furthermore, among the MACCEs, the incidences of all-cause mortality (3.7 vs. 4.5%; P=0.325), cardiac mortality (3.0 vs. 3.4%; P=0.541), recurrent myocardial infarction (1.6 vs. 2.0%; P=0.442), ischemia-driven revascularization (1.9 vs. 1.3%; P=0.263) and stroke (1.6 vs. 1.5%; P=0.809) did not vary significantly between the groups. Of note, the incidences of BARC 2-5 bleeding events (4.8 vs. 8.7%; P<0.001) and BARC 3-5 bleeding events (1.9 vs. 4.4%; P=0.001) in the bivalirudin group were lower compared with those in the heparin group (Table II).

Independent factors for NACEs. Univariate logistics regression analysis revealed that bivalirudin treatment (vs. heparin treatment; P=0.003) predicted a lower risk of NACEs. Age (≥65 years vs. <65 years; P=0.017), a history of hypertension

Table I. Clinical characteristics of patients.

Items	Heparin group (n=1433)	Bivalirudin group (n=944)	P-value
Demographics			
Age (years), mean ± SD	65.1±11.3	64.4±11.3	0.122
Sex, n (%)			0.144
Female	458 (32.0)	275 (29.1)	
Male	975 (68.0)	669 (70.9)	
BMI (kg/m^2), mean ± SD	24.0±3.1	24.1±3.1	0.435
Comorbidities			
History of hypertension, n (%)			0.277
No	488 (34.1)	342 (36.2)	
Yes	945 (65.9)	602 (63.8)	
History of diabetes mellitus, n (%)			0.721
No	1070 (74.7)	711 (75.3)	
Yes	363 (25.3)	233 (24.7)	
History of cardiac surgery, n (%)			0.292
No	1310 (91.4)	851 (90.1)	
Yes	123 (8.6)	93 (9.9)	
Disease features			
Clinical manifestation, n (%)			0.577
STEMI	608 (42.4)	402 (42.6)	
UA	467 (32.6)	309 (32.7)	
NSTEMI	188 (13.1)	136 (14.4)	
SCAD	170 (11.9)	97 (10.3)	
CRUSADE score, median (IQR)	28.0 (21.0-38.0)	27.0 (20.0-36.0)	0.019
Bleeding risk, n (%)			0.013
Very low risk (CRUSADE score ≤20)	313 (21.8)	248 (26.3)	
Low risk (CRUSADE score 21-30)	488 (34.1)	312 (33.1)	
Moderate risk (CRUSADE score 31-40)	336 (23.4)	219 (23.2)	
High risk (CRUSADE score 41-50)	175 (12.2)	98 (10.4)	
Very high risk (CRUSADE score ≥51)	105 (7.3)	58 (6.1)	
Unknown	16 (1.1)	9 (1.0)	
Operative timing, n (%)			0.464
Elective operation	787 (54.9)	504 (53.4)	
Emergency operation	646 (45.1)	440 (46.6)	
Lesional vessel, No. (%)			0.605
Single	1136 (79.3)	740 (78.4)	
Multiple	297 (20.7)	204 (21.6)	
Treatment-related information			
PCI type, n (%)			0.408
Balloon	61 (4.3)	47 (5.0)	
Stent	1372 (95.7)	897 (95.0)	
Stent diameter (mm), median (IQR)	3.0 (3.0-3.5)	3.0 (2.8-3.5)	0.239
Total stent length (mm), median (IQR)	33.0 (23.0-38.0)	33.0 (23.0-38.0)	0.819

SD, standard deviation; BMI, body mass index; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina; NSTEMI, non-ST-segment elevation myocardial infarction; SCAD, stable coronary artery disease; CRUSADE, Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA guidelines; IQR, interquartile range; PCI, percutaneous coronary intervention.

(yes vs. no; P=0.013), clinical manifestation of SCAD (vs. UA; P<0.001), NSTEMI (vs. UA; P<0.001), STEMI (vs. UA; P<0.001), CRUSADE score (≥41 vs. <40; P=0.001), operative timing (emergency operation vs. elective operation; P<0.001) and total stent length (>33.0 vs. ≤33.0 mm; P=0.020) forecasted higher risks of NACEs (Table III).

Table II. Comparison of NACEs, MACCEs, BARC 2-5 bleeding events and BARC 3-5 bleeding events between groups.

Items	Heparin group (n=1433)	Bivalirudin group (n=944)	P-value
NACEs, n (%)	192 (13.4)	88 (9.3)	0.003
MACCEs, n (%)	109 (7.6)	56 (5.9)	0.116
All-cause mortality	65 (4.5)	35 (3.7)	0.325
Cardiac mortality	49 (3.4)	28 (3.0)	0.541
Recurrent myocardial infarction	29 (2.0)	15 (1.6)	0.442
Ischemia-driven revascularization	19 (1.3)	18 (1.9)	0.263
Stroke	21 (1.5)	15 (1.6)	0.809
BARC 2-5 bleeding events, n (%)	125 (8.7)	45 (4.8)	<0.001
BARC 3-5 bleeding events, n (%)	63 (4.4)	18 (1.9)	0.001

NACEs, net adverse clinical events; MACCEs, major adverse cardiac and cerebral events; BARC 2-5 bleeding events, Bleeding Academic Research Consortium grades 2 to 5; BARC 3-5 bleeding events, Bleeding Academic Research Consortium grades 3 to 5.

According to forward stepwise multivariate logistic regression analysis, bivalirudin treatment [vs. heparin treatment; odds ratio (OR), 0.587; P<0.001] independently estimated a lower risk of NACEs. However, age (≥65 years vs. <65 years; OR, 1.455; P=0.008), a history of hypertension (yes vs. no; OR, 1.447; P=0.016), clinical manifestation of SCAD (vs. UA; OR, 2.054; P=0.005), NSTEMI (vs. UA; OR, 2.164; P=0.001), operative timing (emergency operation vs. elective operation; OR, 2.352; P<0.001), lesional vessel (multiple vs. single; OR, 1.561; P=0.010) and total stent length (>33.0 vs. ≤33.0 mm; OR, 1.405; P=0.015) independently predicted higher risks of NACEs (Table III).

Independent factors for MACCEs. Based on univariate logistic regression analysis, bivalirudin treatment (vs. heparin treatment; P=0.117) was not associated with risk of MACCEs. Age (≥65 years vs. <65 years; P=0.028), a history of hypertension (yes vs. no; P=0.034), clinical manifestation of SCAD (vs. UA; P<0.001), NSTEMI (vs. UA; P=0.007), STEMI (vs. UA; P=0.001), CRUSADE score (≥41 vs. <40; P=0.024), operative timing (emergency operation vs. elective operation; P<0.001) and lesional vessel (multiple vs. single; P=0.044) estimated higher risks of MACCEs (Table IV).

According to forward stepwise multivariate logistic regression analysis, bivalirudin treatment (vs. heparin treatment; OR, 0.689; P=0.041) independently predicted a lower risk of MACCEs. Age (≥65 years vs. <65 years; OR, 1.531; P=0.016), a history of hypertension (yes vs. no; OR, 1.460; P=0.047), operative timing (emergency operation vs. elective operation; OR, 1.982; P<0.001) and lesional vessel (multiple vs. single; OR, 1.613; P=0.019) independently forecasted higher risks of MACCEs (Table IV).

Independent factors for BARC 2-5 bleeding events. In accordance with univariate logistic regression analysis, bivalirudin treatment (vs. heparin treatment; P<0.001) estimated a lower risk of BARC 2-5 bleeding events, whereas clinical manifestation of SCAD (vs. UA; P<0.001), NSTEMI (vs. UA; P<0.001), STEMI (vs. UA; P<0.001), CRUSADE score (≥41 vs. <40; P=0.001) and operative timing (emergency operation vs. elective operation; P<0.001) predicted higher risks of BARC 2-5 bleeding events (Table V).

Based on further forward stepwise multivariate logistic regression analysis, bivalirudin treatment (vs. heparin treatment; OR, 0.459; P<0.001) independently forecasted a lower risk of BARC 2-5 bleeding events. However, age (≥65 years vs. <65 years; OR, 1.498; P=0.024), a history of diabetes mellitus (yes vs. no; OR, 1.568; P=0.019), clinical manifestation of SCAD (vs. UA; OR, 2.356; P=0.009), NSTEMI (vs. UA; OR, 2.632; P=0.002), operative timing (emergency operation vs. elective operation; OR, 2.535; P<0.001) and total stent length (>33.0 vs. ≤33.0 mm; OR, 1.431; P=0.040) independently predicted higher risks of BARC 2-5 bleeding events (Table V).

Independent factors for BARC 3-5 bleeding events. According to the univariate logistic regression analysis, bivalirudin treatment (vs. heparin treatment; OR, 0.423; P=0.001) was related to a lower risk of BARC 3-5 bleeding events. Nevertheless, a history of diabetes mellitus (yes vs. no; OR, 1.798; P=0.013), the clinical manifestation of SCAD (vs. UA; OR, 3.470; P=0.001), NSTEMI (vs. UA; OR, 2.275; P=0.036), STEMI (vs. UA; OR, 2.128; P=0.017), CRUSADE score (≥41 vs. <40; OR, 3.100; P<0.001), operative timing (emergency operation vs. elective operation; OR, 1.859; P=0.007) and stent diameter (≥3.5 vs. <3.5 mm; OR, 1.743; P=0.018) were associated with a higher risk of BARC 3-5 bleeding events (Table VI).

Additionally, forward stepwise multivariate logistic regression analysis demonstrated that bivalirudin treatment (vs. heparin treatment; OR, 0.386; P=0.002) was independently associated with a lower risk of BARC 3-5 bleeding events. Nevertheless, a history of diabetes mellitus (yes vs. no; OR, 1.805; P=0.024), the CRUSADE score (≥41 vs. <40; OR, 2.313; P=0.001), operative timing (emergency operation vs. elective operation; OR, 2.379; P=0.001) and stent diameter (≥3.5 vs. <3.5 mm; OR, 1.635; P=0.048) were independently associated with a higher risk of BARC 3-5 bleeding events (Table VI).

Table III. Logistic regression analysis for NACEs.

A, Univariate logistic regression analysis

Items	P-value	OR	95% CI	
			Lower	Upper
Group (bivalirudin group vs. heparin group)	0.003	0.664	0.509	0.868
Age (≥65 years vs. <65 years)	0.017	1.363	1.057	1.756
Sex (male vs. female)	0.119	1.250	0.945	1.654
BMI (>28 kg/m^2 vs. ≤28 kg/m^2)	0.123	0.687	0.426	1.108
History of hypertension (yes vs. no)	0.013	1.420	1.078	1.869
History of diabetes mellitus (yes vs. no)	0.151	1.226	0.928	1.618
History of cardiac surgery (yes vs. no)	0.446	0.836	0.528	1.325
Clinical manifestation				
UA	Reference			
SCAD	<0.001	3.409	2.227	5.219
NSTEMI	<0.001	2.702	1.773	4.119
STEMI	<0.001	2.320	1.645	3.273
CRUSADE score (≥41 vs. <40)	0.001	1.665	1.240	2.236
Operative timing (emergency operation vs. elective operation)	<0.001	2.246	1.736	2.906
Lesional vessel (multiple vs. single)	0.087	1.288	0.964	1.723
PCI type (stent vs. balloon)	0.193	0.702	0.412	1.197
Stent diameter (≥3.5 mm vs. <3.5 mm)	0.179	1.196	0.921	1.551
Total stent length (>33.0 mm vs. ≤33.0 mm)	0.020	1.359	1.050	1.759

B, Forward stepwise multivariate logistic regression analysis

Items	P-value	OR	95% CI	
			Lower	Upper
Group (bivalirudin group vs. heparin group)	<0.001	0.587	0.437	0.788
Age (≥65 years vs. <65 years)	0.008	1.455	1.101	1.923
History of hypertension (yes vs. no)	0.016	1.447	1.072	1.952
Clinical manifestation				
UA	Reference			
SCAD	0.005	2.054	1.243	3.394
NSTEMI	0.001	2.164	1.362	3.438
STEMI	0.110	1.424	0.923	2.198
Operative timing (emergency operation vs. elective operation)	<0.001	2.352	1.664	3.324
Lesional vessel (multiple vs. single)	0.010	1.561	1.114	2.188
Total stent length (>33.0 mm vs. ≤33.0 mm)	0.015	1.405	1.070	1.846

NACEs, net adverse clinical events; OR, odds ratio; CI, confidence interval; BMI, body mass index; UA, unstable angina; SCAD, stable coronary artery disease; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; CRUSADE, Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA guidelines; PCI, percutaneous coronary intervention.

Discussion

Bivalirudin plays an anticoagulant role by inhibiting thrombin directly, repressing circulating and clot-bound thrombin, but not combining antithrombin III, which is considered to have certain clinical advantages over heparin in patients receiving PCI (20-22). For example, a previous study suggests that among patients with STEMI who undergo primary PCI and receive

Table IV. Logistic regression analysis for MACCEs.

A, Univariate logistic regression analysis

Items	P-value	OR	95% CI	
			Lower	Upper
Group (bivalirudin group vs. heparin group)	0.117	0.766	0.549	1.069
Age (≥65 years vs. <65 years)	0.028	1.439	1.041	1.990
Sex (male vs. female)	0.394	1.165	0.820	1.657
BMI (>28 kg/m^2 vs. ≤28 kg/m^2)	0.560	0.845	0.479	1.489
History of hypertension (yes vs. no)	0.034	1.467	1.030	2.089
History of diabetes mellitus (yes vs. no)	0.156	1.286	0.908	1.820
History of cardiac surgery (yes vs. no)	0.999	1.000	0.577	1.734
Clinical manifestation				
UA	Reference			
SCAD	<0.001	2.928	1.729	4.960
NSTEMI	0.007	2.097	1.224	3.592
STEMI	0.001	2.039	1.331	3.124
CRUSADE score (≥41 vs. <40)	0.024	1.540	1.059	2.239
Operative timing (emergency operation vs. elective operation)	<0.001	1.812	1.313	2.500
Lesional vessel (multiple vs. single)	0.044	1.444	1.010	2.065
PCI type (stent vs. balloon)	0.847	1.080	0.494	2.363
Stent diameter (≥3.5 mm vs. <3.5 mm)	0.771	1.050	0.755	1.461
Total stent length (>33.0 mm vs. ≤33.0 mm)	0.131	1.284	0.928	1.775

B, Forward stepwise multivariate logistic regression analysis

Items	P-value	OR	95% CI	
			Lower	Upper
Group (bivalirudin group vs. heparin group)	0.041	0.689	0.482	0.985
Age (≥65 years vs. <65 years)	0.016	1.531	1.084	2.162
History of hypertension (yes vs. no)	0.047	1.460	1.005	2.122
Operative timing (emergency operation vs. elective operation)	<0.001	1.982	1.391	2.824
Lesional vessel (multiple vs. single)	0.019	1.613	1.081	2.407

MACCEs, major adverse cardiac and cerebral events; OR, odds ratio; CI, confidence interval; BMI, body mass index; UA, unstable angina; SCAD, stable coronary artery disease; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; CRUSADE, Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA guidelines; PCI, percutaneous coronary intervention.

aspirin and ticagrelor, bivalirudin reduces the incidence of NACEs compared with heparin (23). Moreover, another study indicated that in patients with STEMI who undergo PCI, bivalirudin decreases all-cause mortality compared with heparin (24). These findings are similar to those of the present study, which revealed that among patients who underwent PCI, bivalirudin decreased the incidence of NACEs compared with heparin, and bivalirudin treatment (vs. heparin treatment) was an independent factor for predicting a low risk of NACEs. This may be due to the following: i) Bivalirudin directly inhibited thrombin, while heparin indirectly inhibited thrombin through antithrombin III activation; thus, bivalirudin decreased the incidence of bleeding events compared with heparin in patients who underwent PCI (22,25). ii) Bivalirudin exerted a regulatory effect on inflammation in patients who underwent PCI, thereby inhibiting atherosclerosis and further decreasing the incidence of MACCEs to a certain extent compared with heparin in those patients (14,26,27). For the aforementioned reasons, bivalirudin decreased the incidence of NACEs compared with heparin.

However, the incidence of MACCEs in patients who undergo PCI continues to be a matter of concern. A previous study demonstrated that, compared with heparin, bivalirudin decreases the risk of 30-day MACCEs in patients with coronary

Table V. Logistic regression analysis for BARC 2-5 bleeding events.

A, Univariate logistic regression analysis

Items	P-value	OR	95% CI	
			Lower	Upper
Group (bivalirudin group vs. heparin group)	<0.001	0.524	0.369	0.744
Age (≥65 years vs. <65 years)	0.056	1.364	0.992	1.874
Sex (male vs. female)	0.148	1.300	0.912	1.853
BMI (>28 kg/m^2 vs. ≤28 kg/m^2)	0.145	0.627	0.334	1.174
History of hypertension (yes vs. no)	0.220	1.235	0.881	1.732
History of diabetes mellitus (yes vs. no)	0.058	1.388	0.989	1.948
History of cardiac surgery (yes vs. no)	0.079	0.540	0.272	1.073
Clinical manifestation				
UA	Reference			
SCAD	<0.001	3.789	2.205	6.511
NSTEMI	<0.001	3.161	1.852	5.397
STEMI	<0.001	2.515	1.600	3.953
CRUSADE score (≥41 vs. <40)	0.001	1.876	1.315	2.677
Operative timing (emergency operation vs. elective operation)	<0.001	2.377	1.715	3.296
Lesional vessel (multiple vs. single)	0.820	1.045	0.716	1.526
PCI type (stent vs. balloon)	0.106	0.599	0.322	1.115
Stent diameter (≥3.5 mm vs. <3.5 mm)	0.070	1.350	0.975	1.869
Total stent length (>33.0 mm vs. ≤33.0 mm)	0.066	1.356	0.980	1.877

B, Forward stepwise multivariate logistic regression analysis

Items	P-value	OR	95% CI	
			Lower	Upper
Group (bivalirudin group vs. heparin group)	<0.001	0.459	0.310	0.678
Age (≥65 years vs. <65 years)	0.024	1.498	1.055	2.126
History of diabetes mellitus (yes vs. no)	0.019	1.568	1.075	2.287
Clinical manifestation				
UA	Reference			
SCAD	0.009	2.356	1.241	4.473
NSTEMI	0.002	2.632	1.445	4.791
STEMI	0.179	1.484	0.835	2.636
Operative timing (emergency operation vs. elective operation)	<0.001	2.535	1.649	3.896
Total stent length (>33.0 mm vs. ≤33.0 mm)	0.040	1.431	1.016	2.017

BARC 2-5 bleeding events, Bleeding Academic Research Consortium grades 2 to 5; OR, odds ratio; CI, confidence interval; BMI, body mass index; UA, unstable angina; SCAD, stable coronary artery disease; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; CRUSADE, Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA guidelines; PCI, percutaneous coronary intervention.

artery disease complicated by diabetes who undergo PCI (14). Another study disclosed that the incidence of MACCEs does not vary between bivalirudin and the unfractionated heparin in patients with STEMI undergoing primary PCI (23). Moreover, in female patients with acute myocardial infarction who undergo emergency PCI, no discrepancy is observed in the incidence of MACCEs between bivalirudin and heparin (28). In the present study, bivalirudin numerically reduced the incidence rate of MACCEs compared with heparin, although there was no significant difference. Moreover, bivalirudin treatment (vs. heparin treatment) was not associated with a risk of MACCEs in univariate logistic regression analysis, while it was independently related to a low risk of MACCEs in forward stepwise multivariate logistic regression analysis. This

Table VI. Logistic regression analysis for BARC 3-5 bleeding events.

A, Univariate logistic regression analysis

Items	P-value	OR	95% CI	
			Lower	Upper
Group (bivalirudin group vs. heparin group)	0.001	0.423	0.249	0.718
Age (≥65 years vs. <65 years)	0.167	1.377	0.875	2.166
Sex (male vs. female)	0.811	1.061	0.653	1.723
BMI (>28 kg/m^2 vs. ≤28 kg/m^2)	0.298	0.614	0.246	1.538
History of hypertension (yes vs. no)	0.086	1.554	0.939	2.574
History of diabetes mellitus (yes vs. no)	0.013	1.798	1.134	2.851
History of cardiac surgery (yes vs. no)	0.593	0.795	0.342	1.847
Clinical manifestation				
UA	Reference			
SCAD	0.001	3.470	1.670	7.209
NSTEMI	0.036	2.275	1.057	4.896
STEMI	0.017	2.128	1.145	3.956
CRUSADE score (≥41 vs. <40)	<0.001	3.100	1.945	4.940
Operative timing (emergency operation vs. elective operation)	0.007	1.859	1.182	2.924
Lesional vessel (multiple vs. single)	0.984	0.994	0.577	1.713
PCI type (stent vs. balloon)	0.213	0.581	0.247	1.366
Stent diameter (≥3.5 mm vs. <3.5 mm)	0.018	1.743	1.099	2.764
Total stent length (>33.0 mm vs. ≤33.0 mm)	0.241	1.319	0.831	2.094

B, Forward stepwise multivariate logistic regression analysis

Items	P-value	OR	95% CI	
			Lower	Upper
Group (bivalirudin group vs. heparin group)	0.002	0.386	0.212	0.701
History of diabetes mellitus (yes vs. no)	0.024	1.805	1.079	3.018
CRUSADE score (≥41 vs. <40)	0.001	2.313	1.388	3.857
Operative timing (emergency operation vs. elective operation)	0.001	2.379	1.431	3.954
Stent diameter (≥3.5 mm vs. <3.5 mm)	0.048	1.635	1.005	2.659

BARC 3-5 bleeding events, Bleeding Academic Research Consortium grades 3 to 5; OR, odds ratio; CI, confidence interval; BMI, body mass index; UA, unstable angina; SCAD, stable coronary artery disease; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; CRUSADE, Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA guidelines; PCI, percutaneous coronary intervention.

result may be due to the fact that the result of the univariate logistic regression analysis was affected by some confounding factors, resulting in the concealment of the true effect of bivalirudin treatment. Following adjustment by forward stepwise multivariate logistic regression analysis, the influence of these confounding factors was eliminated, and it was found that bivalirudin treatment (vs. heparin treatment) was independently related to a lower risk of MACCEs. The result from forward stepwise multivariate logistic regression analysis was explained as follows: Compared with heparin, bivalirudin inhibited inflammation in patients who underwent PCI, and thus reduced the MACCEs to a certain extent (14,26,27).

In addition, a previous study has demonstrated that in patients with STEMI who undergo primary PCI, bivalirudin reduces the 30-day incidence of BARC 3-5 major bleeding events compared with heparin (24). In another study on elderly patients with STEMI who underwent primary PCI, bivalirudin decreases the incidence of BARC 2-5 bleeding events compared with unfractionated heparin (29). These findings are partly in accordance with the findings of the present study, which revealed that bivalirudin reduced the incidence of BARC 2-5 and 3-5 bleeding events compared with heparin. In addition, bivalirudin treatment (vs. heparin treatment) was independently associated with low risks of

BARC 2-5 and 3-5 bleeding events. The possible reasons for this were the following: i) Compared with heparin, bivalirudin had a shorter half-life and it was metabolized more rapidly in the plasma of patients undergoing PCI, which may lead to a lower risk of bleeding in these patients (21); and ii) the reduction in the risk of bleeding with the use of bivalirudin might be related to its direct inhibition of thrombin, its non-union with platelet factor 4 and its linear pharmacokinetics (25).

As aforementioned, the present study showed that bivalirudin reduced the risks of NACEs, MACCEs and bleeding events compared with heparin in patients who underwent PCI. Notably, bivalirudin is 10-50 times more expensive compared with heparin (30), thus for clinical management, the cost-effectiveness of the two drugs is also an issue worth taking into consideration. Currently, the results of the comparison of cost-effectiveness between bivalirudin and heparin are inconsistent in previous studies. For example, one study revealed that bivalirudin is less cost-effective compared with heparin in patients who undergo PCI (31). Another study showed that bivalirudin is more cost-effective for only a minority of patients who undergo PCI with a high bleeding risk compared with heparin (32). Nevertheless, one study illustrated that the use of bivalirudin in patients with STEMI who undergo primary PCI is cost-effective compared with the use of heparin (33). These controversial results may be due to the existence of some confounding factors (34). Taken together, the comparison of cost-effectiveness between bivalirudin and heparin is uncertain and required to be verified in further studies.

There were several limitations to the present study, which should be mentioned: i) The present study was a single-center study, which may have led to bias in the selection process. ii) The present study only evaluated NACEs within 30 days after PCI. Thus, the long-term safety of bivalirudin in patients who undergo PCI remains to be further explored. iii) In the present study, the included patients selected medication based on their actual clinical status rather than randomization, which may have led to potential confounders between groups.

In conclusion, the present study demonstrated that bivalirudin reduced the incidence of NACEs (particularly bleeding events) compared with heparin in Chinese patients who underwent PCI, which may serve as a safer anticoagulant in these patients. However, further validation in larger-scale, multi-center and randomized controlled studies is necessary.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

LC, JL, YW and ZB contributed to the conception and design of the study. LC, MZ, ZW, JL and ZB were involved in data collection. YZ, YW and ZQ contributed to data analysis. LC and JL confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Handan Central Hospital (Handan, China; approval no. 20230816001). The patients or their families provided written informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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