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Original Article

Comparisons of effectiveness and safety between bivalirudin and heparin with tirofiban in ST-segment elevation myocardial infarction treated with percutaneous coronary intervention

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Abstract: Objective: To compare the effectiveness and safety between bivalirudin and heparin with tirofiban in patients with acute myocardial infarction by percutaneous coronary intervention. Methods: A randomized controlled, open-label experiment was performed. 260 cases of hospitalized patients with acute ST-segment elevation myocardial infarction (STEMI) who accepted emergency PCI were enrolled in the study. They were randomly divided into bivalirudin group (129 cases), heparin plus tirofiban group (131 cases). In Bivalirudin group, they were given intravenous injection 0.75 mg/kg for the first dose. Then they were given 1.75 mg/(kg·h) continuous intravenous infusion until PCI surgery was completed. 1.75 mg/(kg·h) intravenous infusion was followed after the surgery and sustained with an average time of 190 min. Patients were followed-up for 30 days. Results: A total of 259 patients completed 30 days of follow-up (99.6%). 14 cases (10.9%) in the bivalirudin group and 32 cases (24.4%) in heparin plus tirofiban group showed 30 days of net adverse clinical events (RR, 0.45; 95% CI, 0.19~0.75; P=0.004). Two major adverse cardiac and cerebrovascular events (a given group bivalirudin 5.4%, heparin plus tirofiban 9.2%; P=0.25), stent thrombosis (1.6% vs 3.1%; P=0.42), acquired platelet less disease (0.8% vs 0; P=0.32) and the incidence of acute stent thrombosis (0 vs 0.8%; P=0.25) showed statistical significance. Conclusion: In emergency PCI treated STEMI patients, compared with heparin combined tirofibantreatment, bivalirudin (1.75 mg/kg/h) postoperative continuous with the average of 190 min) can decrease the incidence of net adverse clinical events in 30 days.

Keywords: Acute ST-segment elevation myocardial infarction, bivalirudin, acute percutaneous coronary intervention, tirofiban, unfractionated heparin

Introduction

Percutaneous coronary intervention (PCI) is the most effective treatment for acute ST-segment elevation myocardial infarction (STEMI) patients with coronary reperfusion. Antithrombotic therapy was performed during Emergency PCI surgery and postoperative to prevent from stent thrombosis and reinfarction [1-3]. Generally, during the emergency PCI surgery, heparin (with or without the addition of glycoprotein (GP) IIb/IIIa blocker) or direct thrombin inhibitor bivalirudin was used for anticoagulation. HORIZONS-AMI experiment [4] showed that compared with heparin combining GP IIb/IIIa blockers, bivalirudin can reduce 30 days of major bleeding events, the incidence of net adverse clinical events and lower 30-day mortality. This sustained benefit lasted for 3-year followed up [5], but the incidence of acute stent thrombosis (<24 h) increased.

EUROMAX test [6, 7] results still showed that bivalirudin reduced the incidence of 30-day major bleeding and the composite end point events; some patients still used bivalirudin for 4 hours after PCI, but the incidence of acute stent thrombosis still significantly increased [8]. Single center HEAT-PPCI experiments [9] showed that, compared with heparin alone, in bivalirudin group (no postoperative prolonged injection) incidence of 30-day stent thrombosis

and myocardial reinfarction increased, but there were no significant differences in bleeding events. BRIGHT experiment [10] showed that, compared with heparin or heparin plus tirofiban, bivalirudin (an average of 3 hours of prolonged injection after PCI) can reduce the incidence of 30-day bleeding events and net clinical events, without increasing the stent thrombosis and major adverse cardiovascular events. In order to further clarify safety and effectiveness of bivalirudin in the emergency PCI, STEMI patients receiving emergency PCI were randomly divided into bivalirudin group and heparin plus tirofiban group.

Experimental method

This study was a randomized, controlled, open-label clinical study.

Inclusion criteria: The study included the patients with acute ST-segment elevation myocardial infarction >18 years old, including the patients accompanied by chest pain, persistent ST-segment elevation or new left bundle branch blocking in 12 hours and 12-24 hours of onset. Acute ST segment elevation myocardial infarction was diagnosed according to the standard of American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC): chest pain or discomfort for at least 30 min, 12-lead ECG-adjacent two or more than two leads had ST-segment elevation of more than 0.1 mV, or the new left bundle branch blocking.

The main exclusion criteria: Before random grouping, receive thrombolytic therapy or receive any anticoagulant therapy within 48 hours; active bleeding or a recent history of bleeding or known bleeding tendencies; there is a history of surgery within the past month: aortic dissection is not excluded; at admission high blood pressure is serious (>180/110 mmHg) and not controlled; transaminases three times higher than the upper limit of normal or creatinine clearance <30 ml/min; there is a history of acquired thrombocytopenia caused by heparin; allergic to any study drugs and devices; pregnant or lactating persons; the patient does not or cannot agree to sign a written informed consent. The experiments were reviewed and approved by the Ethics Committee of the Research Centre, and informed consent was signed before random grouping.

Grouping method and method of administration

In this study, patients were randomly assigned to bivalirudin group and heparin plus tirofiban group at a 1:1 ratio using envelope method; drugs were administered before coronary angiography. Bivalirudin (Salubris Pharmaceutical Co, Ltd.): the first dose-intravenous bolus 0.75 mg/kg, then 1.75 mg/(kg·h) continuous intravenous infusion until PCI surgery was completed; this dose was maintained at least 30 min after surgery, but no more than 4 hours. After the prescribed medication, the doctor may propose intravenous infusion of bivalirudin [0.2 mg/(kg·h)] according to the disease condition, no more than 20 h. Heparin plus tirofiban: first dose-intravenous bolus of unfractionated heparin 100 U/kg and tirofiban 10 ug/kg; then intravenous tirofiban 0.15 ug/(kg·min) for 18-36 hours. In the bivalirudin group, if no-reflow or other thrombotic complications occurred during surgery, tirofiban can be applied in temporary.

All patients received dual antiplatelet therapy; if no long-term use of aspirin or clopidogrel, before surgery aspirin (300 mg) and clopidogrel (300 mg) of loading dose were given. Surgical puncture site, stent type and thrombectomy devices were decided by surgeons.

Endpoint definition

The primary endpoint was 30-day net adverse clinical events (NACE); the composite endpoints included major adverse cardiac or cerebral events (MACCE) (including all-cause death, myocardial re-infarction, ischemia-driven target vessel revascularization and stroke) as well as all bleeding events in line with Bleeding Academic Research Consortium Consensus Report (BRAC) [11].

Secondary endpoint was 30-day MACCE and any bleeding events. BRAC2-5 type bleeding in bleeding events required clinical intervention; BRAC3-5 bleeding event belonged to clinical massive hemorrhage.

Security Evaluation indicators: 30-day stent thrombosis in line with the definitions of Academic Research Consortium (ARC) [12]. 30-day acquired thrombocytopenia: compared with baseline, platelet declined more than 50

Table 1. Baseline characteristics according to the randomized treatment[a]

Characterstic	Heparin + Tirofiban (N=131)	Bivalirudin (N=129)	P
Age, mean (SD), y	54.4 ± 11.8	56.8 ± 10.1	0.07
Men, No. (%)	110 (84.0)	117 (90.7)	0.10
Weight, mean (SD), kg	77.9 ± 11.4	76.2 ± 8.6	0.20
Medical history, No. (%)			
Diabetes	29 (22.1)	19 (14.7)	0.12
Hypertension	64 (48.9)	66 (51.2)	0.32
Hyperlipidemia	58 (44.3)	45 (34.9)	0.12
Previous myocardial infarction	12 (9.3)	15 (11.9)	0.50
Previous percutaneous coronary intervention	16 (12.2)	18 (14.0)	0.68
Previous stroke	1 (0.8)	0	0.32
Current smoker	84 (64.1)	92 (71.3)	0.22
Symptom onset to hospital arrival, median (IQR), h	5.61 [3.0, 7.0]	5.61 [3.0, 7.5]	0.40
NT-proBNP, mean (SD), pg/mL	535.1 ± 1392.2	731.1 ± 1624.5	0.30
The end-diastolic inner diameter of the left ventricular, mean (SD), mm	49.9 ± 4.5	50.4 ± 5.6	0.51
Left ventricular injection fraction, median (IQR), (%)	60 [57.0, 63.0]	59 [55.0, 63.0]	0.14
Anemia, No./total (%)[b]	6 (4.6)	9 (7.0)	0.40
Creatinine clearance ≤60 ml/min, No./total (%)	11 (8.4)	15 (11.7)	0.37
Killipclass ≥II, No. (%)	10 (7.6)	17 (13.2)	0.14
GRACE score, mean (SD)[c]	128.1 ± 32.9	136.6 ± 32.1	0.28
GRSADE bleeding score, mean (SD)[d]	23.1 ± 12.3	24.2 ± 12.2	0.95
>30 (moderate or high bleeding risk), No./total (%)	32/131 (24.4)	38/129 (29.5)	0.36

Abbreviations: GRUSADE, CanRaqid Risk Stratification of Unstable Angina Patients SuppressAdverse Outcomes With Early Implementation of the ACC/AHA. Guidelines; IQR, interquartilerange; GRACE, the Global Registry of Acute Coronary Events; [a]There were no significant differences-between groups. [b]Anemia was defines as hemoglobin less than 13 g/dl for men or less than 12 g/dl for women. [c]The GRACE score ranged from 1 to 372; The higher the Score, the higher the riskof cardiovascular events; in the population in this study, GRACE score ranged from 65 to 244. [d]The GRUSADE bleeding scale can range from 1 to 96, with higher numbers representing a greater riskof bleeding. in the population in this study, GRUSADE score ranged from 2 to 66.

percent, or 150×10^9/L. Tertiary endpoints included 30-day all-cause death, cardiac death, myocardial re-infarction, ischemia-driven target vessel revascularization, and stroke.

Baseline data and follow-up data of all patients were reviewed and recorded by certain person. All NACE and stent thrombosis events were blindly reviewed by independent clinical event review committee.

Sample size calculation and statistical analysis

Sample size calculation was based on assessing whether bivalirudin is superior to heparin plus tirofiban in NACE within 30 days; two tests were performed in order to retain α values. According to previous report, the NACE incidence is 17.0% (heparin plus tirofiban group) and 8.8% (bivalirudin group), respectively. Considering 5% dropout rate during the experiment, when the two-tailed significance level was 0.05 and degree of certainty was 0.80, after calculated by PEMS 3.1 software, 125 cases of subjects were needed in each group. Count data were analyzed using X^2 test or Fisher's exact test; continuous variables or data were analyzed using t-test or one-way ANOVA; in secondary analysis, Kaplan-Meier method was used to assess the incidence of events. Analysis of all statistics were performed by SPSS 17.0 software package, using two-sided test.

Results

Sources of patients and treatment programs

Between October 8 2013 and May 26 2015 in the First Affiliated Hospital of Xinjiang Medical University, 260 cases of hospitalized patients with STEMI who would accept emergency PCI were enrolled in the study. They were randomly divided into bivalirudin group (129 cases, 49.6%), heparin plus tirofiban group (131 cases, 50.4%). Baseline information, treatment and surgical characteristics were matched between the two groups (**Tables 1**, **2**). A

Table 2. Basic information of treatment and surgical intervention in each group

Items	Heparin + tirofiban group (N=131)	Bivalirudin group (N=129)	P
Preoperative aspirin (%)	131 (100)	129 (100)	
Preoperative clopidogrel (%)	131 (100)	131 (100)	
Study medication (%)			
Bivalirudin	0	129 (100)	0.00
Heparin	131 (100)	0	0.00
Tirofiban	131 (100)	8 (6.2)	0.00
Door-to-Device time, mean (SD), min	109.5 ± 63.2	98.1 ± 60.9	0.09
Surgical approach (%)			
Through Radial Artery	107 (81.7)	111 (86.0)	0.34
Through the femoral artery	24 (18.3)	18 (14.0)	0.77
Multivessel disease (%)	85 (64.9)	80 (62.0)	0.63
Revascularization strategy (%)			
Non-immersed interventions (conservative treatment)	3 (2.3)	3 (2.3)	0.99
Coronary artery bypass grafting	0	1 (0.8)	0.31
Coronary intervention	3 (2.3)	3 (2.3)	0.69
Balloon angioplasty alone	5 (3.8)	1 (0.8)	0.10
Stenting	123 (93.9)	124 (96.1)	0.41
Criminal vessel (%)			
LM	1/128 (0.7)	0	0.32
LAD	72/128 (52.2)	66/125 (52.8)	0.58
Left circumflex artery	18/128 (14.1)	16/125 (12.8)	0.77
Right coronary artery	37/128 (29.7)	43/125 (34.4)	0.35
Thrombectomy (%)	31/128 (24.2)	37/125 (29.6)	0.33
TIMI flow			
Before PCI (%)			
0/1	108/123 (87.8)	101/124 (81.5)	0.35
2	6/123 (4.9)	11/124 (8.9)	0.35
3	9/123 (7.3)	14/124 (9.7)	0.35
After PCI (%)			
0/1	4/123 (3.3)	3/124 (2.4)	0.57
2	1/123 (0.8)	3/124 (2.4)	0.57
3	118/123 (95.9)	118/124 (95.2)	0.57
Medications at discharge (%)			
Aspirin	128 (97.7)	125 (96.9)	0.69
Clopidogrel	128 (97.7)	127 (98.4)	0.99
Statins	128 (97.7)	127 (98.4)	0.66
β-blockers	118 (90.1)	120 (93.0)	0.49
ACEI/ARB	113 (86.9)	106 (82.2)	0.29

total of 247 cases underwent PCI (95%), and 218 cases were through transradial route (83.8%). During follow-up compliance of patients was good. For patients who received bivalirudin, postoperative 1.75 mg/kg/h continuous intravenous infusion was sustained an average of 190 min (interquartile range, 177-212 min). In bivalirudin group the proportion of urgent tirofiban replacement was 6.2%.

Clinical results

A total of 259 cases completed 30-day follow-up (99.6%) (**Figure 1**). As shown in the **Table 3**,

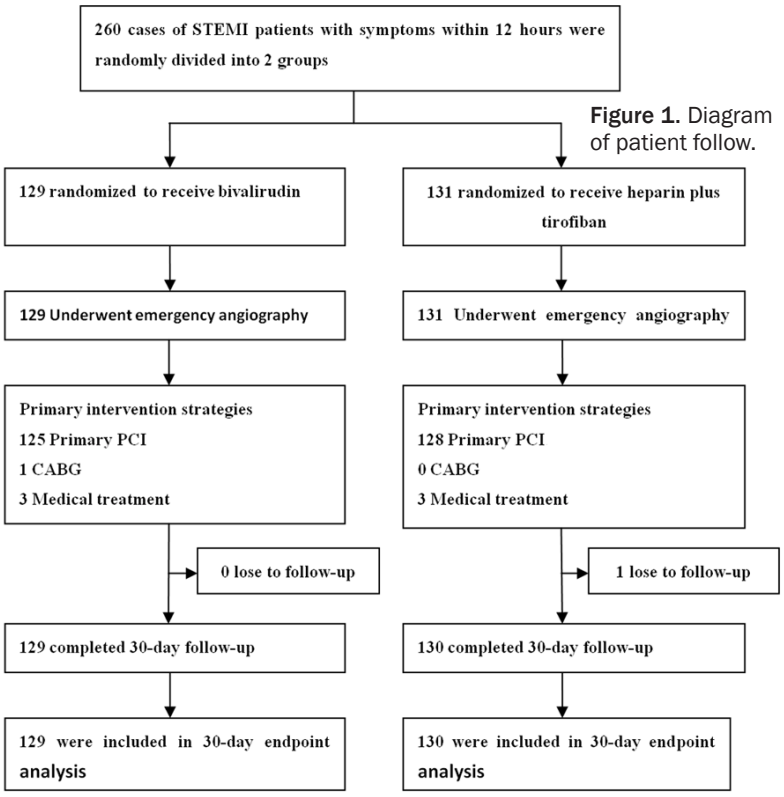

Figure 1. Diagram of patient follow.

during the 30-day follow-up a total of 14 cases in bivalirudin group (10.9%) and 32 cases in heparin plus tirofiban group (24.4%) had NACE (relative risk [RR], 0.45; 95% CI, 0.19~0.75; P=0.004) (**Table 3**); in MACCE (5.4% vs 9.2; P=0.25) there was no significant difference. Between two groups, there was no statistically significant difference in all-cause death, cardiac death, myocardial re-infarction, target vessel revascularization, and stroke. In 247 stent patients, no significant difference had been found in incidence of 30-day stent thrombosis (3.1% vs 1.6%; P=0.42), as well as the incidence of acute (<24 h) stent thrombosis (**Table 3**).

Compared with heparin plus Tirofiban, bivalirudin significantly reduced the incidence of bleeding events during 30-day follow-up (5.4% vs 15.3%; P=0.009). Bivalirudin also reduced bleeding events requiring medical intervention (BRAC2-5 type bleeding). There was no statistically significant difference in primary bleeding events (BRAC3-5 hemorrhagic). The bleeding events in composite end point were defined as BARC2-5 type bleeding; analysis showed that compared with heparin plus tirofiban, bivalirudin can significantly reduce the incidence of 30-day NACE (6.2% vs 14.5%; P=0.03). There was no significant difference in acquired thrombocytopenia between the two groups.

K-M curves of NACE, MACCE and bleeding events were shown in **Figure 2**.

Discussion

This study showed that, compared with tirofiban + heparin, bivalirudin can significantly reduce the incidence of postoperative bleeding events, without increasing the incidence of MACCE and stent thrombosis, thus significantly reducing the 30-day occurrence of NACE.

In this study, 260 cases of STEMI patients were from the First Affiliated Hospital of Xinjiang Medical University Heart Center; the study has a strong internal validity; the green channel of acute myocardial infarction (ambulance and emergency medical PCI teams) is reassuring; all the NACE and stent thrombosis events are blindly reviewed by independent clinical event review committee. But there are some drawbacks of single-center experiment.

In the two randomized controlled trials of HORIZONS-AMI [4, 5] and EUROMAX [6, 7], compared with heparin plus GP IIb/IIIa receptor antagonist, bivalirudin alone can reduce the incidence of bleeding events, and reduce the incidence of cardiac death; However, the incidence of acute stent thrombosis was increased. Further follow-up of 3 years by HORIZONS-AMI found that bivalirudin can reduce cardiac death and all-cause mortality [13]. In BRIGHT [10] trials, compared with tirofiban plus heparin or heparin, bivalirudin alone significantly reduced the incidence of bleeding events, but did not increase the incidence of stent thrombosis, thus reducing

Table 3. Clinical events of 30 days in each group

Events, n (%)	Heparin plus tirofiban group (N=131)	Bivalirudin group (N=129)	Relative risk (95% CI)	*P* value
NACE (primary endpoint)	32 (24.4)	14 (10.9)	0.45 (0.19, 0.75)	0.004
MACCE	12 (9.2)	7 (5.4)	0.59 (0.22, 1.50)	0.25
All-cause death	4 (3.1)	2 (1.6)	0.52 (0.09, 0.05)	0.42
Cardiac death	3 (2.3)	2 (1.6)	0.70 (0.11, 4.09)	0.55
Reinfarction	4 (3.1)	2 (1.6)	0.52 (0.20, 5.13)	0.42
Stroke	1 (0.8)	0	...	0.32
Ischemic target vessel revascularization	3 (2.3)	3 (2.3)	1.00 (0.45, 0.57)	0.99
All bleeding	20 (15.3)	7 (5.4)	0.35 (0.13, 0.78)	0.009
BRAC2-5 level	7 (5.3)	1 (0.8)	0.15 (0.002, 1.14)	0.03
BRAC3-5 level	1 (0.8)	0	...	0.32
Acquired thrombocytopenia	1 (0.8)	0	...	0.32
Stent thrombosis	4 (3.1)	2 (1.6)	0.52 (0.09, 2.78)	0.42
Definite	3 (2.3)	2 (1.6)	0.70 (0.11, 4.09)	0.55
Possible	1 (0.8)	0	...	0.55
Acute (<24 hours)	0	1 (0.8)	...	0.25
Subacute (1-30 days)	4 (3.1)	1 (0.8)	0.26 (0.08, 2.25)	0.25

Abbreviation: NACE, net adverse clinical events. MACCE, major adverse cardial events; BRAC, Bleeding Academic Research Consortium Consensus Report.

the 30-day and 1-year NACE incidence. These studies have confirmed that, in patients with acute myocardial infarction undergoing emergency PCI, compared with heparin, bivalirudin can reduce the incidence of bleeding events; some of the studies confirmed that bivalirudin can further reduce mortality [14]. The experimental results of HEAT-PPCI [9] showed that compared with heparin alone, bivalirudin can increase the incidence of MACCE, reinfarction, and acute stent thrombosis, but there was no significant difference in the incidence of bleeding events. HEAT-PPCI experiments widely used radial artery and other contemporary clinical practice measures. In the study, bivalirudin application time is short: stop the application of bivalirudin at the end of surgery.

In the present study, with respect to heparin plus tirofiban, bivalirudin can effectively control ischemic events, and all bleeding events were significantly reduced, thus improving the 30-day prognosis of patients. But between two groups, there was no significant difference in clinical bleeding events (BRAC3-5 hemorrhagic), may related with the small sample size of this study. In our study, the bivalirudin group reduced the application of GP IIb/IIIa receptor antagonists [15, 16] but extensively used radial artery route (83.8%), similar with the BRIGHT study (79%); so our conclusions were consistent with a recent Meta-analysis [17], indicating that compared with heparin plus GP IIb/IIIa receptor antagonists, bivalirudin can reduce bleeding events in STEMI patients undergoing emergent PCI.

Different from some past studies [4, 6, 9], this study did not find that bivalirudin was more susceptible to acute stent thrombosis compared with heparin plus tirofiban. In this study, all of patients in bivalirudin group received continuous infusion of high dose (1.75 mg/kg/h) of bivalirudin (average 190 min) after PCI. The efficacy of oral clopidogrel was delayed in STEMI patients [18], while bivalirudin itself has anti-platelet activity [19], so the high-dose prolonged bivalirudin after PCI can play an adequate antithrombotic role in the dangerous period before clopidogrel works, effectively controlling the risk of acute stent thrombosis. In this study, the low incidence of acute stent thrombosis in bivalirudin group was consistent with BRIGHT study results; in BRIGHT study bivalirudin continuous infusion was performed for an average of three hours after PCI [10]. Compared other STEMI studies in which application of bivalirudin was stopped imme-

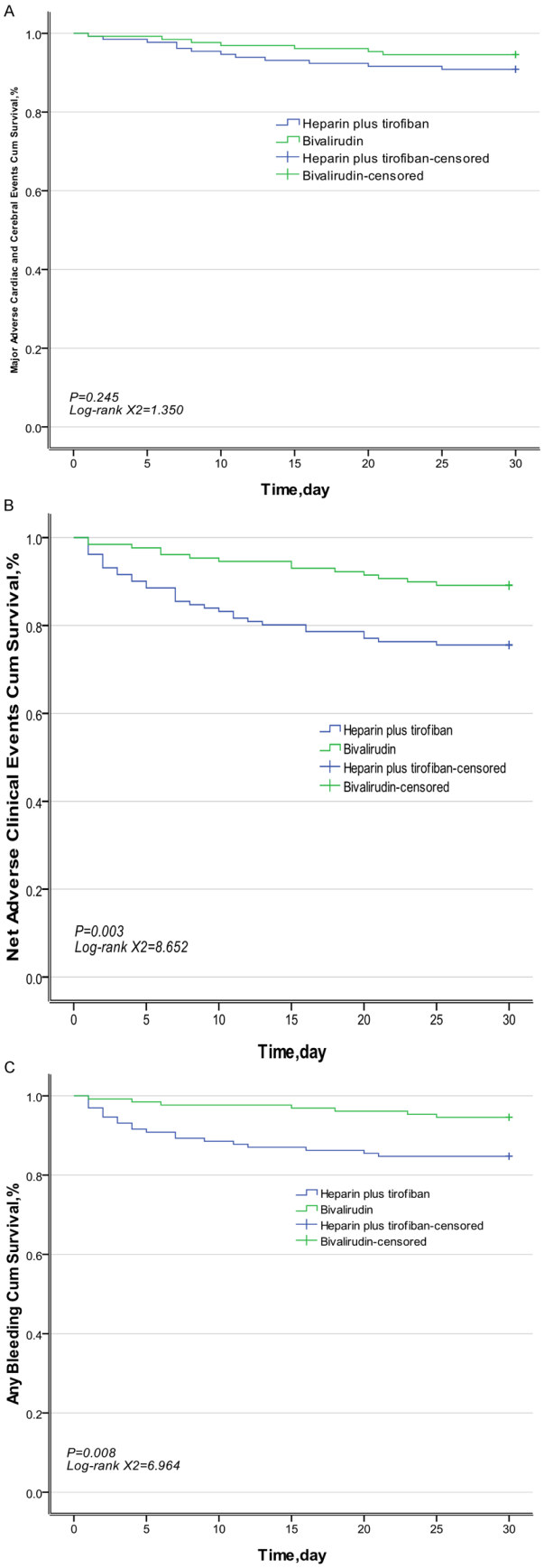

Figure 2. Time-to-Event Curves for the Primary and Major Secondary End Points Through 1-month Follow-up, comparing Outcomes in Patients Randomized to Bivalirudin or Heparin Plus Tirofiban. A. Net adverse clinical events. B. Major adverse cardiac and cerebral events. C. Any BRAC bleeding.

diately after PCI, in this study the incidence of acute stent thrombosis was significantly lower inbivalirudin group, but because it did not divide bivalirudin group into bivalirudin continuous infusion or non-bivalirudin continuous infusion, so it is uncertain that the low incidence of acute stent thrombosis was benefit from 190 min continuous infusion of bivalirudin after PCI.

Both EUROMAX study and HORIZONS-AMI study [4, 6, 13] show that, compared with GP IIb/IIIa receptor antagonist plus heparin, bivalirudin can reduce cardiac mortality; In bivalirudin group reduced bleeding events and acquired thrombocytopenia may be the reasons for the decrease in cardiac death. In this study, although the cardiac mortality was low in bivalirudin group, there was no statistically significant difference compared with heparin + tirofiban, similar to the BRIGHT study (79%).

Limitations

Compared to previous studies on bivalirudin application in acute myocardial infarction after emergency PCI, the present study was an open label study, so there may be a potential bias. In order to reduce bias caused by an open label study, all endpoint events were blindly reviewed by independent clinical review committee, as well as, the compliance to programs and drugs was high. Second, we did not utilize the screening table for the subjects enrollment. Third, any bleeding events are likely to affect the patient's compliance and the use of antithrombotic drugs, so all of BRAC bleeding types are included in the primary endpoint events. When we defined bleeding events as >BRAC2 grade, it can also be found that bivalirudin significantly reduced the incidence of NACE, with prognostic significance [20, 21]. Fourth, in our research,

the testing effectiveness of stent thrombosis and other safety events with low incidence may be insufficient. Fifth, we did not select prasugrel and ticagrelor when the patients were clopidogrel resistance [22].

Conclusion

For STEMI patients intending to accept emergency PCI treatment, compared with heparin plus tirofiban treatment, 190 min continuous infusion of bivalirudin after PCI based on intraoperative dose can decrease the 30-day incidence of NACE, which may be due to that bivalirudin effectively reduce the 30-day incidence of bleeding events, but not increasing the incidence of MACCE and stent thrombosis.

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Disclosure of conflict of interest

None.

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