Int J Clin Exp Med 2017;10(11):15359-15367
www.ijcem.com /ISSN:1940-5901/IJCEM0057429

Original Article

Comparison of anticoagulant and antiplatelet therapy in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention (PCI)

Qianhui Li, Yin Xiang, Yong Tang, Yachen Zhang

Department of Cardiology, Xinhua Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China

Received December 8, 2016; Accepted October 5, 2017; Epub November 15, 2017; Published November 30, 2017

Abstract: Objective: The aim of this study was to investigate the safety and efficacy of bivalirudin plus ticagrelor compared with heparin plus clopidogrel in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI). Methods: 630 patients with ST-segment elevation myocardial infarction undergoing PCI were divided into a bivalirudin plus ticagrelor group and a heparin plus clopidogrel group. Patients assigned to ticagrelor were given a loading dose of 180 mg orally before PCI, followed by a maintenance dose of 90 mg twice a day. Clopidogrel was initiated with a loading dose of 600 mg and carried on with a maintenance dose of at least 75 mg every day. Bivalirudin or heparin was given to patients during the PCI. Results: At the end of 12-month follow-up, net adverse clinical events were observed in 32 patients (10.4%) of 308 given bivalirudin plus ticagrelor and 58 patients (18.4%) of 315 given heparin plus clopidogrel [relative risk (RR), 0.564; 95% confidence interval (CI), 0.377-0.843; *P*=0.004]. The composite ischemic endpoint of death, re-infarction, target vessel revascularization, or stroke did not significantly differ between the two groups (RR, 0.670; 95% CI, 0.384-1.169; *P*=0.155). The rate of 12-month bleeding in the bivalirudin plus ticagrelor group was lower than that in the heparin plus clopidogrel group (4.2% versus 9.2%, *P*=0.013; RR=0.458; 95% CI, 0.243-0.865). In addition, bivalirudin combined with ticagrelor did not raise the incidence of 12-month stent thrombosis in the present study (0.6% vs 1.3% respectively, *P*=0.686). Conclusions: Among patients with STEMI undergoing primary PCI, bivalirudin plus ticagrelor reduced net adverse clinical events compared with heparin plus clopidogrel. This observation was mainly attributed to a decrease in bleeding events in the bivalirudin plus ticagrelor group, without statistical differences in major adverse cardiac or cerebral events or stent thrombosis compared with the heparin plus clopidogrel group.

Keywords: Bivalirudin, ticagrelor, heparin, clopidogrel, percutaneous coronary intervention (PCI)

Introduction

Coronary artery heart diseases, especially acute myocardial infarction, are the most common cause of death worldwide. More than 700 million people die from coronary artery disease each year, accounting for 12.8% among all-cause mortality. In Europe, one out of every six men and one out of every seven women die of myocardial infarction [1]. Coronary artery plaque fissures cause platelet aggregation, adhesion, and thrombosis, giving rise to partial or overall obstructive coronary arteries, which is the pathophysiological basis of acute myocardial infarction [2]. Primary percutaneous coronary intervention (PCI) is the main treatment strategy among acute ST-segment elevation myocardial infarction (STEMI) patients admitted to a hospital in time [1, 3]. Adjunctive antithrombotic and antiplatelet agents are required to sustain patency of the infarct-related artery during and after PCI. It is necessary to find a balance between safety and efficacy.

In a previous study, bivalirudin and ticagrelor respectively showed considerable benefits [4, 5]. In the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial, STEMI patients undergoing primary PCI showed reduced net clinical outcomes after pretreatment with clopidogrel and the direct thrombin inhibitor bivalirudin compared with heparin plus glycoprotein (GP) IIb/IIIa inhibitors [6]. This result was attrib-

uted to a lower rate of major bleeding. Nevertheless, there was a high incidence of acute (<24 h) stent thrombosis after PCI with bivalirudin [6]. Ticagrelor is an oral P2Y12 anti-platelet drug that can provide a fast and invertible anti-platelet aggregation effect [7-10]. Ticagrelor was once compared with clopidogrel in the Platelet Inhibition and Patient Outcomes (PLATO) trial [11], which was a large-scale, prospective, randomized trial. Regardless of treatment strategy with or without ST-segment elevation, PLATO showed that ticagrelor had a lower rate of death, myocardial infarction, and stroke than clopidogrel. In patients with STEACS undergoing PCI, ticagrelor did not increase incidence of major bleeding but reduced several secondary end points, including definite stent thrombosis [5]. Prasugrel plus bivalirudin is superior to a strategy based on clopidogrel plus heparin in terms of net clinical outcome in STEMI patients with planned primary PCI [12]. Whether a combination of bivalirudin and ticagrelor may have synergistic effects with respect to ischemic and bleeding complications remains unclear. The study aimed at assessing the safety and efficacy of bivalirudin plus ticagrelor versus clopidogrel plus heparin for ST-segment elevation myocardial infarction patients during and after PCI.

Materials and methods

Ethics statement

The study procedures were reviewed and approved by the medical ethics committee of Xinhua Hospital, Shanghai Jiaotong University School of Medicine. All patients signed informed consent forms before randomization.

Study population

All 630 patients with ST-segment elevation MI (STEMI) were recruited at Xinhua Hospital, Shanghai Jiaotong University School of Medicine between October 2015 and February 2016. Patients were eligible for enrollment if they were aged 18 to 80 years with STEMI within 12 hours from symptom onset, or within 12 to 24 hours presented with lasting chest pain or new left bundle-branch block. The major exclusion criteria were as follows: cardiogenic shock; thrombolytic and anticoagulant administered within 48 hours; history of major bleeding or hemorrhagic tendency in the past three months; surgical operation within 1 month; aortic dissection; infectious endocarditis; blood pressure >180/110 mmHg; known hemoglobin <100 g/L; thrombocytopenia; severe liver or kidney dysfunction; history of bronchial asthma; CABG; allergies or prohibitions to the study drugs; patient unwilling or unable to submit informed consent.

Randomization and treatment

Patients were randomly assigned 1:1 to receive bivalirudin plus ticagrelor or heparin plus clopidogrel after admission. Bivalirudin (Salubris Pharmaceuticals Co) was initiated as an intravenous bolus of 0.75 mg/kg followed by infusion of 1.75 mg/kg/h during the PCI procedure and for at least 30 minutes after PCI until heparin administration. Patients receiving ticagrlor (AstraZeneca Pharmaceuticals) were given a loading dose of 180 mg orally, followed by a maintenance dose of 90 mg twice a day. The heparin was granted a bolus dose of 100 U/kg per current guidelines [1, 13, 14]. Subsequent heparin was accorded with the target activated clotting time of 250-300 s. Clopidogrel (Sanofi Pharmacy) was initiated with a loading dose of 600 mg and carried on with a maintenance dose of at least 75 mg every day. If clopidogrel had already been taken prior to the study, an additional loading dose was given to reach a goal loading dose of 600 mg. On condition that the no-reflow phenomenon or other thrombotic complications occurs, temporary emergency use of tirofiban was allowed.

All patients who had not been taking long-term aspirin received an oral loading dose of 300 mg aspirin prior to the randomization followed by a maintenance dose of 100 mg once daily.

End points and definitions

To gain comprehensive information concerning compliance and any occurrence of adverse events, patients were followed up by special clinic reexamination, telephones, and e-mail for 12 months after randomization or until death occurred before 12 months. Seven patients dropped out during the study period in bivalirudin plus ticagrelor group.

The primary end point was a composite of net adverse clinical events (NACE), including major adverse cardiac or cerebral events (MACCE)

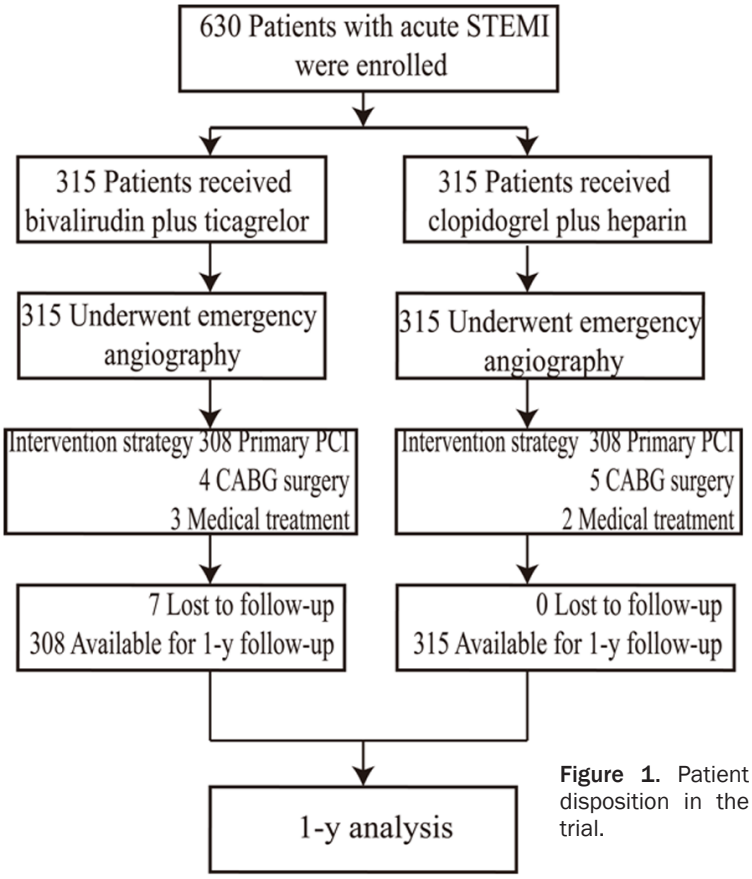

Figure 1. Patient disposition in the trial.

Table 1. Baseline characteristics of the two groups[a]

Characteristics	Bivalirudin + ticagrelor (n=308)	Heparin + clopidogrel (n=315)	*P*
Age, mean ± SD, y	66.39±10.35	67.76±10.21	0.098
Men, No. (%)	219 (71.3)	233 (74.0)	0.461
Body mass index, mean ± SD	24.37±0.58	24.45±0.56	0.089
Medical history, No. (%)			
Diabetes	103 (33.4)	127 (40.3)	0.081
Hypertension	217 (70.5)	217 (68.9)	0.573
Hyperlipidemia	114 (37.0)	122 (38.7)	0.659
Current smoker	133 (43.3)	156 (49.5)	0.121
Old myocardial infarction	15 (4.9)	20 (6.3)	0.423
Previous PCI	19 (6.2)	15 (4.8)	0.440
Previous stroke	12 (3.9)	15 (4.8)	0.596
Chronic kidney disease	12 (3.9)	16 (5.1)	0.476
Killip class ≥II, NO. (%)	46 (14.9)	42 (13.3)	0.566
Anemia, No. (%)[b]	34 (11.0)	40 (12.7)	0.513

[a]There were no significant differences between groups. [b]Anemia was defined as hemoglobin less than 120 g/L for men or less than 110 g/L for women.

(all-cause death, reinfarction, target vessel revascularization, or stroke) or any bleeding defined by the Bleeding Academic Research Consortium (BARC) [15].

Secondary end points were major adverse cardiac or cerebral events and any bleeding at 12 months. In the BARC study, types 2-5 were considered to require clinical intervention. BARC types 3-5 were regarded as major clinical bleeding events. At 12 months, extra safety end points included stent thrombosis per Academic Research Consortium criteria [16].

Statistical analysis

Statistical analyses were two-sided test ($P<0.05$) and performed with SPSS version 19.0. Continuous data were conveyed as the mean ± standard deviation, and categorical variables were summarized using frequencies and percentages. Basic clinical characteristics were compared between two groups using the student's t-test, the chi-square test, or the Fisher exact test. The clinical endpoint events were assessed by means of the chi-square test or Fisher exact test. The main analysis was performed to evaluate difference in the light of primary endpoint at 12 months. RR with 95% CI was assessed by means of the chi-square test. Survival curves according to the Kaplan-Meier method were estimated. All statistical analyses used two-sided *P* values of <0.05, which is considered statistically significant.

Results

Patients and clinical characteristics

The patients' disposition flowchart is shown in **Figure 1**. A total of 623 patients were enrolled

Table 2. Treatment and procedural characteristics

Characteristics	Bivalirudin + ticagrelor (n=308)	Heparin + clopidogrel (n=315)	*P*
Before randomization, No. (%)			
Aspirin	308 (100)	315 (100)	-
Clopidogrel	0 (0)	315 (100)	<0.001
Ticagrelor	308 (100)	0 (0)	<0.001
Intravenous drugs, No. (%)			
Bivalirudin	308 (100)	0 (0)	<0.001
Unfractionated heparin	0 (0)	315 (100)	<0.001
Tirofiban	16 (5.2)	22 (7.0)	0.351
Arterial access, No. (%)			0.468
Transfemoral	74 (24.0)	68 (21.6)	
Transradial	234 (76.0)	247 (78.4)	
Multivessel disease, No. (%)	148 (48.2)	151 (48.1)	0.976
Revascularization strategy, No. (%)			0.921
None (medical therapy only)	3 (1.0)	2 (0.6)	
Coronary artery bypass graft surgery	4 (1.3)	5 (1.6)	
PCI	301 (97.7)	308 (97.8)	
Culprint vessel treated with PCI			0.251
Left main	5 (1.6)	5 (1.6)	
Left anterior descending	160 (51.9)	139 (44.1)	
Left circumflex	63 (20.5)	71 (22.5)	
Right	80 (26.0)	100 (31.7)	
No. of stents per patient, mean ± SD	1.20±0.54	1.14±0.41	0.114
TIMI flow, No. (%)			
Pre-PCI			0.398
0/1	248 (80.6)	269 (85.4)	
2	34 (11.0)	24 (7.6)	
3	26 (8.4)	22 (7.0)	
Post-PCI			0.836
0/1	5 (1.6)	7 (2.2)	
2	6 (1.9)	7 (2.2)	
3	297 (96.4)	301 (95.6)	

Abbreviations: PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

in the study from October 2015 until February 2016. The baseline clinical data of patients undergoing PCI treatment are illustrated in **Table 1**. There was no significant difference between the two groups ($P>0.05$). The compliance of all patients was high.

PCI treatment and procedural characteristics

The two groups in this study were matched in terms of baseline characteristics of treatments and procedures. There was no obvious difference in culprit lesion characteristics or the number of stent implantation between two groups. The TIMI flow grade was generally coordinate prior to PCI and after PCI between the two groups. The results described above were showed in **Table 2**. The oral medicines were almost consistent except study medications (**Table 3**).

End points

Follow-up at 12 months was complete for enrolled patients (**Figure 1**). As demonstrated in **Table 4**, 32 patients (10.4%) given bivalirudin plus ticagrelor versus 58 (18.4%) given heparin plus clopidogrel underwent net adverse clinical events at the primary 12-month end point (relative risk [RR], 0.564; 95% CI, 0.377-0.843; $P=0.004$). The composite ischemic endpoint of death, including myocardial infarction, related artery revascularization, stroke, or all-cause death, occurred in 19 patients (6.1%) in the bivalirudin plus ticagrelor and 29 patients (9.2%) in the heparin plus clopidogrel group (RR, 0.670; 95% CI, 0.384-1.169; $P=0.155$, **Table 4**; **Figure 2B**). The 12-month rates of stent thrombosis (0.6% vs 1.3%, RR, 0.511, $P=0.686$) in patients receiving stents did not significantly differ between two groups (**Table 4**). Bivalirudin plus ticagrelor reduced the incidence of 12-month bleeding compared with heparin plus clopidogrel (4.2% vs 9.2%, RR, 0.458, $P=0.013$) (**Table 4**). Bivalirudin plus ticagrelor also reduced actionable hemorrhagic complications. Bivalirudin plus ticagrelor resulted in significantly different rates of net adverse clinical events and bleeding evaluated by Kaplan-Meier survival curves (**Figure 2A** and **2C**). Relative risk and 95% CI for all adverse events were described in **Table 4** and **Figure 3**.

Table 3. Oral medication treatment after PCI

Treatment	Bivalirudin + ticagrelor (n=308)	Heparin + clopidogrel (n=315)	*P*
Medications at discharge, No. (%)			
Aspirin	303 (98.4)	307 (97.5)	0.424
Clopidogrel	4 (1.3)	315 (100)	<0.001
Ticagrelor	304 (98.7)	0 (0)	<0.001
Statin	287 (93.2)	298 (94.6)	0.505
β-Blocker	251 (81.5)	256 (81.3)	1.000
Calcium channel blocker	37 (12.0)	30 (9.5)	0.366
ACEI/ARB	220 (71.4)	234 (73.4)	0.471
Proton pump inhibitor	83 (27.2)	94 (29.8)	0.478

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor II blocker.

Table 4. Clinical outcomes between the two groups

Events	Bivalirudin + ticagrelor (n=308) No. (%)	Heparin + clopidogrel (n=315) No. (%)	*P*	RR (95% CI)
12-Month Outcomes				
NACE (primary end point)	32 (10.4)	58 (18.4)	0.004	0.564 (0.377-0.843)
MACCE	19 (6.1)	29 (9.2)	0.155	0.670 (0.384-1.169)
All-cause death	8 (2.6)	10 (3.2)	0.667	0.818 (0.327-2.046)
Cardiac death	7 (2.3)	9 (2.9)	0.645	0.795 (0.300-2.109)
Reinfarction	3 (1.0)	4 (1.3)	1.000	0.767 (0.173-3.399)
Stroke	3 (1.0)	6 (1.9)	0.505	0.511 (0.129-2.026)
Ischemic TVR	5 (1.6)	9 (2.9)	0.299	0.568 (0.193-1.676)
All bleeding	13 (4.2)	29 (9.2)	0.013	0.458 (0.243-0.865)
BARC 3-5	4 (1.3)	6 (1.9)	0.752	0.682 (0.194-2.393)
Stent thrombosis (definite)	2 (0.6)	4 (1.3)	0.686	0.511 (0.094-2.772)

Abbreviations: BARC, Bleeding Academic Research Consortium; The BARC bleeding is defined on a scale of 1 to 5, ranging from minor bleeding that is not actionable (type 1) to fatal bleeding (type 5). MACCE, major adverse cardiac or cerebral events; NACE, net adverse clinical events; TVR, target vessel revascularization.

Discussion

In the randomized study of STEMI patients with instant PCI, we compared all adverse events of bivalirudin plus ticagrelor with clopidogrel plus heparin. Bleeding was markedly reduced by bivalirudin plus ticagrelor compared with clopidogrel plus heparin. The reduction in net adverse clinical events was favorably affected by bivalirudin plus ticagrelor compared with clopidogrel plus heparin.

Compared with unfractionated heparin or heparin plus Gp IIb/IIIa inhibitors among STEMI patients with undergoing primary PCI, both HORIZONS-AMI [6, 17] and EUROMAX [4, 18, 19] reported that bivalirudin succeeded in offering a bleeding benefit. However, bivalirudin was observed to have an increased risk of stent thrombosis within 24 hours in STEMI patients after undergoing PCI, not influencing major adverse cardiac or cerebral events. As demonstrated in the trial, bivalirudin statistically decreased the primary end point of death or major bleeding compared with heparin plus provisional Gp IIb/IIIa inhibitor [19]. The results were consistent with a large registry randomized study that verified the effect of low bleeding incidence with bivalirudin compared with heparin alone in AMI patients with and without PCI treatment [20-22].

One purpose of our study was to improve the anti-thrombotic advantage by means of combining bivalirudin with ticagrelor. Therefore, a nonsignificant trend was apparent for stent thrombosis with bivalirudin plus ticagrelor compared with clopidogrel plus heparin (0.6% vs 1.3%, RR, 0.511, 95% CI, *P*=0.686). The increase in stent thrombosis did not occur in the

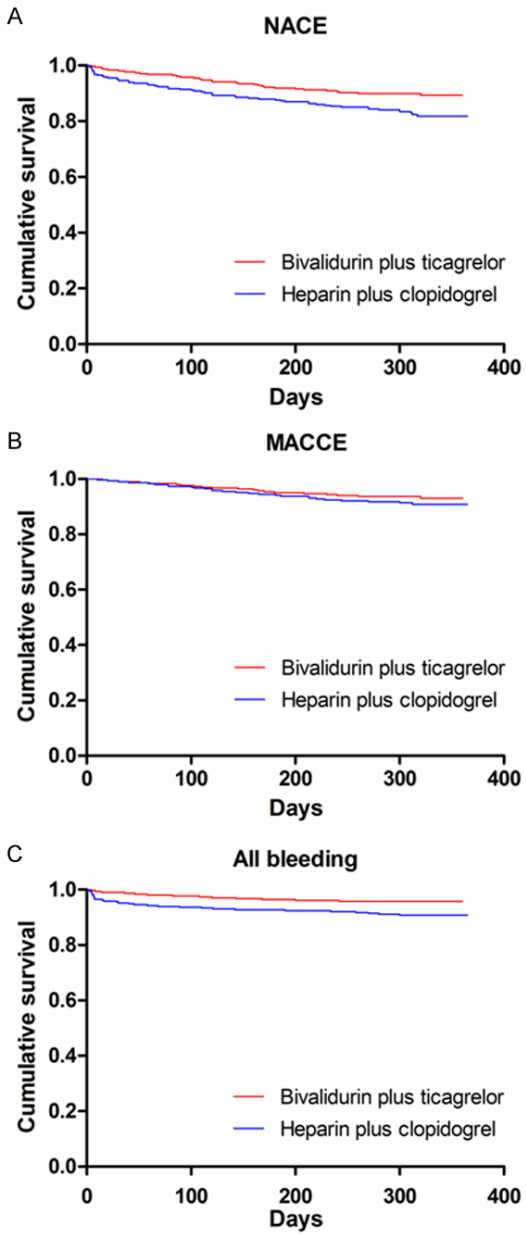

Figure 2. Time-related Kaplan-Meier curves assessment within 12 months after randomization. A. Net adverse clinical events include major adverse cardiac or cerebral events (all-cause death, reinfarction, ischemia-driven target vessel revascularization, or stroke) or any bleeding as defined by the Bleeding Academic Research Consortium (BARC) definition. A. Showed a distinct difference between the two groups (10.4% versus 18.4%, *P*=0.04). B. Demonstrated no obvious difference in MACCE. C. Illustrates the comparison with all bleeding (4.2% versus 9.2%, *P*=0.013).

present study. In the previous trials, the elevation of early stent thrombosis rate with bivalirudin alone may be due to the activity of residual thrombin after suspension bivalirudin or platelet activation, which results from insufficient inhibition of adenosine diphosphate-induced platelet aggregation attributable to the slow action of maximal thienopyridine blockade of clopidogrel.

Ticagrelor is a new cyclopentyl-triazolopyrimidine oral anti-platelet drug that is a potent selective P2Y12 receptor inhibitor. Ticagrelor is quickly absorbed, has a median peak time of 1.5 h, and mainly eliminated through fecal excretion. Ticagrelor provides platelet inhibition activity with rapid onset. The ONSET/OFFSET study [10] reported that ticagrelor took about 2 h to achieve the highest degree of platelet inhibition, exerting a quicker effect compared with a clopidogrel loading dose. The degree of platelet aggregation inhibition was higher than clopidogrel at any time point within 24 h after oral medication or during the maintenance treatment phase. Ticagrelor directly plays a direct role at the P2Y12 receptor without metabolic activation in the liver, and quickly generates the major circulating metabolite AR-C124910XX. The drug itself and its metabolites are active, thus inhibiting ADP-mediated platelet aggregation rapidly and effectively. Consequently, this indicates that ticagrelor escapes from ABCB1 and CYP2C19 genotype influence so that it is equally effective for patients with low response to clopidogrel [23].

Clopidogrel combined with the platelet receptor irreversibly, which led to the platelet function progressive recovery after withdrawal, generating adverse effects for patients taking clopidogrel and then undergoing emergency surgery. Nevertheless, ticagrelor provided the invertible combination with the platelet receptor, resulting in the prompt termination of efficacy after discontinuance of treatment. In our study, ticagrelor could have provided sufficient antithrombotic protection after bivalirudin cessation. Thus, stent thrombosis was not more common compared with heparin plus clopidogrel in the present study.

An additional finding in our study was associated with a low bleeding risk. Bivalirudin plus ticagrelor suppressed net adverse clinical events by reducing bleeding and not increasing major adverse clinical events. Notably, GP IIb/IIIa inhibitors were only regarded as a bail-out

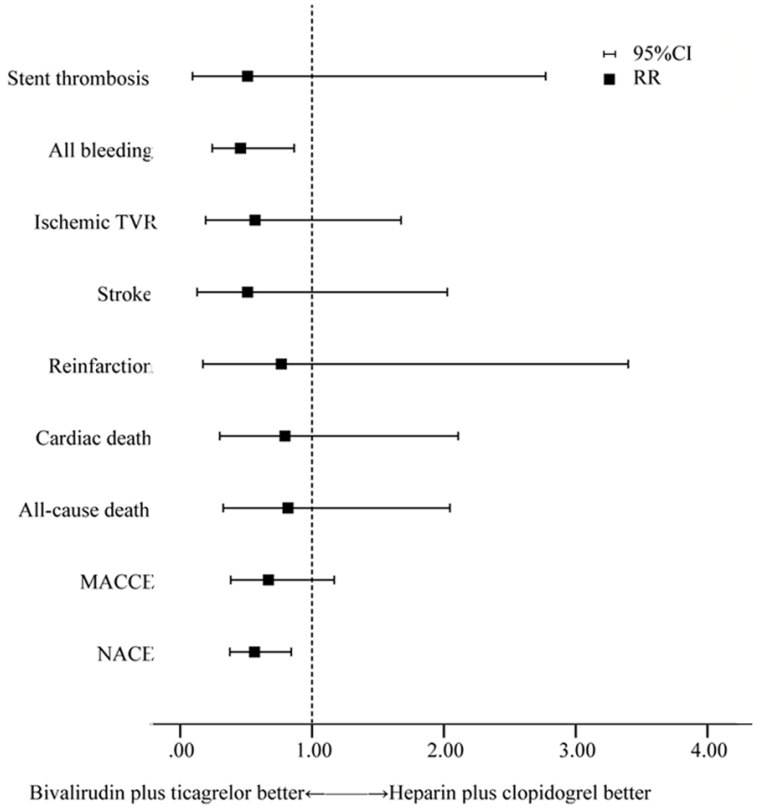

Figure 3. Analyses for all adverse events at 12-month follow-up among patients. The plot exhibits relative risk of the 12-month incidence of all adverse events, comparing outcomes in patients with bivalirudin plus ticagrelor and heparin plus clopidogrel. MACCE, major adverse cardiac or cerebral events; NACE, net adverse clinical events.

in both the bivalirudin plus ticagrelor (5.2%) and heparin plus clopidogrel (7.0%). The Platelet Inhibition and Patient Outcomes (PLATO) trial [11] declared that ticagrelor did not affect major bleeding for patients with AMI. In patients with STEMI undergoing PCI [5], the impact of ticagrelor on bleeding was consistent with that surveyed in the PLATO trial. In this study, bivalirudin plus ticagrelor appeared to lessen bleeding complications, which was compatible with the outcome from the meta-analysis [24].

Limitations

We found that bivalirudin plus ticagrelor appears to diminish bleeding risk and did not result in a high stent thrombosis rate compared with heparin plus clopidogrel. However, there were some limitations to our study. First, this was a single-center study that lacked generality and had limited external validation. Multi-center studies would enhance the research power and provide reliable evidence that can be widely accepted. Second, the sample was small, so the clinical efficacy and safety of the drugs were hard to evaluate precisely. Third, follow-up time was too short to assess long-term efficacy of the drugs. Larger sample sizes are needed to verify our observations. Finally, the study particularly concentrated on STEMI patients.

Conclusions

In summary, in patients undergoing PCI who were diagnosed with ST-segment elevation myocardial infarction, bivalirudin plus ticagrelor was associated with a low bleeding risk and decreased net adverse clinical events compared with heparin plus clopidogrel. Bivalirudin plus ticagrelor did not appear to have a greater effect on stent thrombosis rate and major adverse clinical events than heparin plus clopidogrel at 12-month follow-up duration. Future studies with larger sample sizes should be conducted.

Acknowledgements

This work was supported by the Three-Year Action Plan (2014-2016) of Shanghai Municipality for further acceleration of the development of Chinese medicine (no. ZY3-CCCX-3-3040). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the paper.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yachen Zhang, Division of Cardiology, Xinhua Hospital, School of Medicine, Shanghai Jiaotong University, 1665 Kong Jiang Road, Shanghai 200092, China. E-mail: zhangyachen1965@163.com

References

[1] Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lun-

dqvist C, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, van't Hof A, Widimsky P and Zahger D. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012; 33: 2569-2619.

[2] Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA, Investigators P, Freij A and Thorsen M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009; 361: 1045-1057.

[3] Kushner FG, Hand M, Smith SC Jr, King SB 3rd, Anderson JL, Antman EM, Bailey SR, Bates ER, Blankenship JC, Casey DE Jr, Green LA, Hochman JS, Jacobs AK, Krumholz HM, Morrison DA, Ornato JP, Pearle DL, Peterson ED, Sloan MA, Whitlow PL, Williams DO; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update): a report of the American college of cardiology foundation/American heart association task force on practice guidelines. Circulation 2009; 120: 2271-2306.

[4] Stone GW, Mehran R, Goldstein P, Witzenbichler B, Van't Hof A, Guagliumi G, Hamm CW, Genereux P, Clemmensen P, Pocock SJ, Gersh BJ, Bernstein D, Deliargyris EN and Steg PG. Bivalirudin versus heparin with or without glycoprotein IIb/IIIa inhibitors in patients with STEMI undergoing primary percutaneous coronary intervention: pooled patient-level analysis from the HORIZONS-AMI and EUROMAX trials. J Am Coll Cardiol 2015; 65: 27-38.

[5] Steg PG, James S, Harrington RA, Ardissino D, Becker RC, Cannon CP, Emanuelsson H, Finkelstein A, Husted S, Katus H, Kilhamn J, Olofsson S, Storey RF, Weaver WD, Wallentin L and Group PS. Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: A Platelet Inhibition and Patient Outcomes (PLATO) trial subgroup analysis. Circulation 2010; 122: 2131-2141.

[6] Stone GW, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, Kornowski R, Hartmann F, Gersh BJ, Pocock SJ, Dangas G, Wong SC, Kirtane AJ, Parise H, Mehran R; HORIZONS-AMI Trial Investigators. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med 2008; 358: 2218-2230.

[7] Cannon CP, Husted S, Harrington RA, Scirica BM, Emanuelsson H, Peters G, Storey RF; DISPERSE-2 Investigators. Safety, tolerability, and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-ST-segment elevation acute coronary syndrome: primary results of the DISPERSE-2 trial. J Am Coll Cardiol 2007; 50: 1844-1851.

[8] Husted S, Emanuelsson H, Heptinstall S, Sandset PM, Wickens M and Peters G. Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y12 antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin. Eur Heart J 2006; 27: 1038-1047.

[9] Storey RF, Husted S, Harrington RA, Heptinstall S, Wilcox RG, Peters G, Wickens M, Emanuelsson H, Gurbel P, Grande P and Cannon CP. Inhibition of platelet aggregation by AZD6140, a reversible oral P2Y12 receptor antagonist, compared with clopidogrel in patients with acute coronary syndromes. J Am Coll Cardiol 2007; 50: 1852-1856.

[10] Gurbel PA, Bliden KP, Butler K, Tantry US, Gesheff T, Wei C, Teng R, Antonino MJ, Patil SB, Karunakaran A, Kereiakes DJ, Parris C, Purdy D, Wilson V, Ledley GS and Storey RF. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. Circulation 2009; 120: 2577-2585.

[11] James S, Akerblom A, Cannon CP, Emanuelsson H, Husted S, Katus H, Skene A, Steg PG, Storey RF, Harrington R, Becker R and Wallentin L. Comparison of ticagrelor, the first reversible oral P2Y(12) receptor antagonist, with clopidogrel in patients with acute coronary syndromes: rationale, design, and baseline characteristics of the PLATelet inhibition and patient outcomes (PLATO) trial. Am Heart J 2009; 157: 599-605.

[12] Schulz S, Richardt G, Laugwitz KL, Mehran R, Gershlick AH, Morath T, Mayer K, Neudecker J, Tolg R, Ibrahim T, Hauschke D, Braun D, Schunkert H, Kastrati A, Mehilli J and Bavarian Reperfusion Alternatives Evaluation I. Comparison of prasugrel and bivalirudin vs clopidogrel and heparin in patients with ST-segment elevation myocardial infarction: design and rationale of the bavarian reperfusion alternatives evaluation (BRAVE) 4 trial. Clin Cardiol 2014; 37: 270-276.

[13] American College of Emergency Physicians; Society for Cardiovascular Angiography and Interventions, O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, Et-

tinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX, Anderson JL, Jacobs AK, Halperin JL, Albert NM, Brindis RG, Creager MA, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Kushner FG, Ohman EM, Stevenson WG and Yancy CW. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American college of cardiology foundation/American heart association task force on practice guidelines. J Am Coll Cardiol 2013; 61: 485-510.

[14] Collet JP, Cuisset T, Range G, Cayla G, Elhadad S, Pouillot C, Henry P, Motreff P, Carrie D, Boueri Z, Belle L, Van Belle E, Rousseau H, Aubry P, Monsegu J, Sabouret P, O'Connor SA, Abtan J, Kerneis M, Saint-Etienne C, Barthelemy O, Beygui F, Silvain J, Vicaut E, Montalescot G and Investigators A. Bedside monitoring to adjust antiplatelet therapy for coronary stenting. N Engl J Med 2012; 367: 2100-2109.

[15] Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, Serebruany V, Valgimigli M, Vranckx P, Taggart D, Sabik JF, Cutlip DE, Krucoff MW, Ohman EM, Steg PG and White H. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the bleeding academic research consortium. Circulation 2011; 123: 2736-2747.

[16] Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW and Academic Research C. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007; 115: 2344-2351.

[17] Stone GW, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, Kornowski R, Hartmann F, Gersh BJ, Pocock SJ, Dangas G, Wong SC, Fahy M, Parise H, Mehran R; HORIZONS-AMI Trial Investigators. Heparin plus a glycoprotein IIb/IIIa inhibitor versus bivalirudin monotherapy and paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction (HORIZONS-AMI): final 3-year results from a multicentre, randomised controlled trial. Lancet 2011; 377: 2193-2204.

[18] Steg PG, van't Hof A, Hamm CW, Clemmensen P, Lapostolle F, Coste P, Ten Berg J, Van Grunsven P, Eggink GJ, Nibbe L, Zeymer U, Campo dell'Orto M, Nef H, Steinmetz J, Soulat L, Huber K, Deliargyris EN, Bernstein D, Schuette D, Prats J, Clayton T, Pocock S, Hamon M, Goldstein P and Investigators E. Bivalirudin started during emergency transport for primary PCI. N Engl J Med 2013; 369: 2207-2217.

[19] Zeymer U, van't Hof A, Adgey J, Nibbe L, Clemmensen P, Cavallini C, ten Berg J, Coste P, Huber K, Deliargyris EN, Day J, Bernstein D, Goldstein P, Hamm C and Steg PG. Bivalirudin is superior to heparins alone with bailout GP IIb/IIIa inhibitors in patients with ST-segment elevation myocardial infarction transported emergently for primary percutaneous coronary intervention: a pre-specified analysis from the EUROMAX trial. Eur Heart J 2014; 35: 2460-2467.

[20] Marso SP, Amin AP, House JA, Kennedy KF, Spertus JA, Rao SV, Cohen DJ, Messenger JC, Rumsfeld JS; National Cardiovascular Data Registry. Association between use of bleeding avoidance strategies and risk of periprocedural bleeding among patients undergoing percutaneous coronary intervention. JAMA 2010; 303: 2156-2164.

[21] Bangalore S, Pencina MJ, Kleiman NS and Cohen DJ. Heparin monotherapy or bivalirudin during percutaneous coronary intervention in patients with non-ST-segment-elevation acute coronary syndromes or stable ischemic heart disease: results from the evaluation of drug-eluting stents and ischemic events registry. Circ Cardiovasc Interv 2014; 7: 365-373.

[22] Wise GR, Schwartz BP, Dittoe N, Safar A, Sherman S, Bowdy B and Hahn HS. Comparative effectiveness analysis of anticoagulant strategies in a large observational database of percutaneous coronary interventions. J Interv Cardiol 2012; 25: 278-288.

[23] Tantry US, Bliden KP, Wei C, Storey RF, Armstrong M, Butler K and Gurbel PA. First analysis of the relation between CYP2C19 genotype and pharmacodynamics in patients treated with ticagrelor versus clopidogrel: the ONSET/OFFSET and RESPOND genotype studies. Circ Cardiovasc Genet 2010; 3: 556-566.

[24] Bangalore S, Toklu B, Kotwal A, Volodarskiy A, Sharma S, Kirtane AJ and Feit F. Anticoagulant therapy during primary percutaneous coronary intervention for acute myocardial infarction: a meta-analysis of randomized trials in the era of stents and P2Y12 inhibitors. BMJ 2014; 349: g6419.