Efficacy and safety of bivalirudin without post-procedure infusion in patients with coronary heart disease during elective percutaneous coronary intervention: a real-world study

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To the Editor: Antithrombotic therapy is essential to prevent adverse ischemic events during and after percutaneous coronary intervention (PCI). Anticoagulation during PCI is most commonly achieved with heparin or bivalirudin. Bivalirudin does not activate platelets, does not bind to plasma proteins and has linear pharmacokinetics with a short half-life of 25 min.[1-3] These characteristics indicate that bivalirudin may be an ideal anticoagulation drug for PCI. Prior trials which were about patients with acute myocardial infarction (AMI) undergoing primary PCI showed that a bivalirudin-based anticoagulation strategy decreased the risk of major bleeding, but it was associated with an increased risk of acute stent thrombosis (ST) compared with a heparin-based strategy.[4] It was considered that short half-life of bivalirudin and delayed onset of platelet $P2Y_{12}$ receptor inhibitor in AMI patients led to a blank period of antithrombotic therapy after primary PCI.[5] Bivalirudin vs heparin with or without tirofiban during primary percutaneous coronary interventionin acute myocardial infarction: the BRIGHT randomized clinical trial,[5] using a high-dose infusion of bivalirudin for 3 to 4 h after PCI, the results showed that compared with the heparin or heparin combined with platelet glycoprotein IIb/IIIa receptor antagonist (GPI), bivalirudin did not increase acute ST and reduced the occurrence of net adverse clinical events (NACE). However, for patients with coronary heart disease (CHD) who choose elective PCI, there is still no clear evidence of the benefit of post-procedure infusion of bivalirudin for 3 to 4 h. Therefore, our study validates the efficacy and safety of bivalirudin without post-procedure infusion contrasting to heparin during elective PCI.

The present study was a single center and observational study. We selected 2465 consecutive patients with CHD who were referred for elective PCI between January 2015 and June 2017 at the fifth ward of Cardiology in the General Hospital of Northern Theater Command. The study was approved by the Ethics Committee of the General Hospital of Shenyang Military (No. [2017] 16). Exclusion criteria include: long-term use of oral anticoagulants; continued use bivalirudin after PCI; severe renal insufficiency (creatinine clearance rate < 30 mL/min); transaminase which was three times higher than the upper limit of normal value; new stroke in the last 3 months; new ulcerative gastrointestinal bleeding occurred within 2 weeks; severe abnormal blood routine (hemoglobin < 80 g/L, platelet count $< 80 \times 10^9$/L); lack of important clinical research data.

Bivalirudin (Salubris Pharmaceuticals Co, Shenzhen, China) was administered as a bolus of 0.75 mg/kg followed by infusion of 1.75 $mg \cdot kg^{-1} \cdot h^{-1}$ until the end of the PCI. In the heparin group, a bolus dose of 70 to 100 U/kg was administered, 2000 U of heparin was added every 1 h until the end of the PCI. If the patient had slow reflow, no reflow, or other thrombotic complications during surgery, the two groups were administered a provisional intra-coronary injection of tirofiban 5 to 10 mL/time, for a total amount of $\leq$50 mL. If necessary, a 0.15 $\mu g \cdot kg^{-1} \cdot min^{-1}$ tirofiban infusion was used 18 to 36 h after PCI.

The primary end point was the rate of NACE at 30 days, a composite of major adverse cardiac or cerebral events (MACCE; all-cause death, reinfarction, ischemic driven target vessel revascularization, or stroke) or any bleeding events defined by the Bleeding Academic Research Consortium definition (types 1–5). The major secondary

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end points were MACCE and any bleeding events at 30 days and 6 months and NACE at 6 months. Additional safety end points included ST at 30 days and acquired thrombocytopenia before discharge, defined as a platelet count decrease of more than 50% or more than 150×10^9/L from baseline.

Categorical variables were compared using the χ^2 or Fisher exact test and continuous data using the *t* test. A propensity score matching (PSM) strategy was utilized to reduce the influence of observed imbalances in two groups. As a secondary analysis, time-to-event data with estimated event rates determined according to the Kaplan-Meier method were compared with a log-rank test. The subgroup analysis used a multivariate logistic regression analysis. All of the statistical analyses were conducted using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA).

We enrolled 2313 patients, 613 were treated with bivalirudin and 1700 with heparin. After PSM, we obtained a cohort of 1198 matched patients [Supplementary Table 1, http://links.lww.com/CM9/A755 and Supplementary Table 2, http://links.lww.com/CM9/A755]. The NACE occurred in 27 (4.4%) patients treated with bivalirudin and 113 (6.6%) patients with heparin ($P = 0.046$) at 30 days after PCI. There was no statistically significant difference in the incidence of MACCE, any bleeding events or ST between the two groups at 30 days after PCI. After PSM, there was no statistically significant difference in the incidence of NACE (4.3% *vs.* 6.5%, $P = 0.097$), MACCE, any bleeding events or ST between the two groups at 30 days after PCI [Table 1].

Before PSM or after, compared with heparin, there was no statistical difference in NACE, MACCE, or bleeding events between the two groups at 6 months after PCI [Supplementary Table 3, http://links.lww.com/CM9/A755].

The subgroup analysis showed that the reduction in 30-day NACE and any bleeding events with bivalirudin was more pronounced in the patients with diabetes or a high risk of bleeding (The Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the American College of Cardiology/American Heart Association guidelines [CRUSADE] score >30) [Supplementary Table 4, http://links.lww.com/CM9/A755 and Supplementary Table 6, http://links.lww.com/CM9/A755].

The results showed that compared with heparin or heparin combined with GPI, bivalirudin without post-procedure infusion after PCI did not increase acute ST. In our study, all patients underwent elective PCI, and had taken aspirin and $P2Y_{12}$ receptor antagonists with a continuous week or a loading dose before PCI. And there was no empty window period for anti-thromboembolism. Naples[6] published was a study about bivalirudin compared with heparin during elective PCI, mainly transfemoral artery access. The study population comprised of stable angina or unstable angina patients with high risk of bleeding, among which stable angina patients in bavalirudin group was 58.4%. The results showed that the incidence of ST was not statistically different between the two groups at 30 days after PCI (0.5% *vs.* 0.5%, $P = 0.990$). In our study, patients with acute coronary syndrome were 97.2% and patients with AMI were 22.3%. Compared with the Naples research,[6] patients in our study had a higher risk of ischemia. So GPI utilization rate in bivalirudin group was 10.9% in our study, significantly higher than that of the Naples research[6] by 0.5% ($P < 0.001$). In contrast, the incidence of ST in the Naples study[6] was 0.5% compared with 0.2% in our study ($P > 0.050$). Studies showed that without post-procedure infusion of bivalirudin for 3 to 4 h is safe and reliable.

This study also found that, compared with the heparin group, bivalirudin reduced the incidence of NACE 30 days after PCI before PSM. This was mainly due to the tendency to reduce bleeding events while not increasing MACCE. The results did not show these advantages in bivalirudin group after PSM. There were two possible reasons for this. Firstly, the utilization rate of GPI in the heparin group was significantly higher than that in the bivalirudin group (10.6% *vs.* 25.8%, $P < 0.001$) before PSM and GPI utilization rate was similar between the two groups (10.9% *vs.* 13.0%, $P = 0.247$) after PSM. The higher incidence of bleeding events in the heparin group before PSM might be related to the higher utilization rate of GPI.

Table 1: 30-day outcomes of patients with coronary heart disease during elective percutaneous coronary intervention.

	Before PSM				After PSM			
Events	Bivalirudin ($n = 613$)	Heparin ($n = 1700$)	95% CI	*P*	Bivalirudin ($n = 599$)	Heparin ($n = 599$)	95% CI	*P*
NACE	27 (4.4)	113 (6.6)	0.421–0.995	0.046	26 (4.3)	39 (6.5)	0.391–1.085	0.097
MACCE	6 (1.0)	17 (1.0)	0.384–2.493	0.687	6 (1.0)	10 (1.7)	0.215–1.650	0.314
All-cause death	1 (0.2)	9 (0.5)	0.039–2.428	0.409	1 (0.2)	5 (0.8)	0.023–1.706	0.220
Ischemic TVR	3 (0.5)	7 (0.4)	0.307–4.614	1.000	3 (0.5)	5 (0.8)	0.142–2.513	0.723
Stroke	2 (0.3)	1 (0.1)	0.503–61.441	0.173	2 (0.3)	0	–	0.479
Reinfarction	1 (0.2)	0	–	0.265	1 (0.2)	0	–	1.000
All bleeding	23 (3.8)	97 (5.7)	0.405–1.025	0.061	22 (3.7)	29 (4.8)	0.425–1.320	0.316
BARC 2–5	12 (2.0)	44 (2.6)	0.394–1.432	0.384	11 (1.8)	14 (2.3)	0.352–1.736	0.544
BARC 3–5	3 (0.5)	1 (0.1)	0.869–80.480	0.103	3 (0.5)	0	–	0.248

Data was presented as *n* (%); BARC: Bleeding Academic Research Consortium; CI: Confidence interval; MACCE: Major adverse cardiac or cerebral events; NACE: Net adverse clinical events; PSM: Propensity score matching; TVR: Target vessel revascularization.

Secondly, the CRUSADE score for patients in the bivalirudin group was significantly higher than that in the heparin group before PSM ($P < 0.001$), indicating that the bleeding risk was higher in the bivalirudin group than in the heparin group. Subgroup analysis after PSM showed that the application of bivalirudin in patients with a high bleeding risk (CRUSADE >30) reduced the rate of bleeding events. Therefore, reduced the rate of NACE. This further confirmed that patients with high risk of bleeding might be more suitable to use bivalirudin.

BRIGHT adopted a high dose delayed infusion of bivalirudin for 3 to 4 h after PCI and the incidence of any bleeding events at 30 days after PCI was 4.1%. In our study, it was 3.7% under the strategy of non-delayed infusion of bivalirudin. Concerning the CRUSADE scores, it was found that the CRUSADE score in bivalirudin group was 19.6 ± 11.9 points in BRIGHT, while the CRUSADE score was 23.6 ± 12.8 points in our study, and the bleeding risk of the patients in our study was relatively high. This indicated that without post-procedure infusion of bivalirudin was significant in controlling bleeding complications. At the same time, shortening the duration of bivalirudin also decreased the economic burden of patients, which had important social and economic benefits.

Further validation and head-to-head study of bivalirudin with or without post-procedure infusions are needed in large clinical randomized controlled studies.

In the real world, compared with heparin, bivalirudin without post-procedure infusion did not increase the incidence of ST, MACCE, and NACE after PCI in patients with CHD undergoing elective PCI. In addition, bivalirudin may have a favorable outcome in patients with diabetes or those with a high risk of bleeding.

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Conflicts of interest

None.

References

1. Reed MD, Bell D. Clinical pharmacology of bivalirudin. Pharmacotherapy 2002;22:105S–111S. doi: 10.1592/phco.22.10.105s.33616.
2. Zeymer U, Rao SV, Montalescot G. Anticoagulation in coronary intervention. Eur Heart J 2016;37:3376–3385. doi: 10.1093/eurheartj/ehw061.
3. Steg PG, van 't Hof A, Hamm CW, Clemmensen P, Lapostolle F, Coste P, *et al*. Bivalirudin started during emergency transport for primary PCI. N Eng J Med 2013;369:2207–2217. doi: 10.1056/NEJMoa1311096.
4. Lincoff AM, Bittl JA, Harrington RA, Feit F, Kleiman NS, Jackman JD, *et al*. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. JAMA 2003;289:853–863. doi: 10.1001/jama.289.7.853.
5. Han Y, Guo J, Zheng Y, Zang H, Su X, Wang Y, *et al*. Bivalirudin vs heparin with or without tirofiban during primary percutaneous coronary intervention in acute myocardial infarction: the BRIGHT randomized clinical trial. JAMA 2015;313:1336–1346. doi: 10.1001/jama.2015.2323.
6. Briguori C, Visconti G, Focaccio A, Donahue M, Golia B, Selvetella L, *et al*. Novel approaches for preventing or limiting events (Naples) III trial: randomized comparison of bivalirudin versus unfractionated heparin in patients at increased risk of bleeding undergoing transfemoral elective coronary stenting. JACC Cardiovasc Interv 2015;8:414–423. doi: 10.1016/j.jcin.2014.10.015.

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