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EXPERT REVIEWS

Bivalirudin in ST-segment-elevation myocardial infarction: for better or worse?

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Bivalirudin and heparin are the major available parenteral anticoagulants for percutaneous coronary intervention (PCI) in ST-segment-elevation myocardial infarction. Even though hard clinical outcomes are comparable with both drugs, bivalirudin appears to be safer (less bleeding events) at the expense of lower short-term efficacy (more acute stent thrombosis events). The selection of anticoagulation during PCI in ST-segment-elevation myocardial infarction should be individualized, taking into account the patient's ischemic and bleeding risk. In patients with increased bleeding risk, bivalirudin might be preferable to heparin, whereas in complex PCI with increased risk for stent thrombosis, heparin is preferable. Further clinical studies are needed to elucidate the role of these drugs in PCI for ST-segment-elevation myocardial infarction in the era of radial approaches, new potent antiplatelet agents and the use of glycoprotein IIb/IIIa inhibitors.

Keywords: bivalirudin • bleeding • heparin • stent thrombosis • ST-segment elevation myocardial infarction

Bivalirudin, a direct thrombin inhibitor, is one of the available parenteral anticoagulants currently used during percutaneous coronary intervention (PCI) in acute coronary syndromes [1]. More evidence is available for ST-segment-elevation myocardial infarction (STEMI) patients with four randomized clinical trials published recently (Table 1).

Initial evidence from the HORIZONS-AMI trial showed that compared with heparin, bivalirudin is associated with a net clinical benefit at 30 days. The study used a composite outcome including death, re-infarction, stroke, revascularization or major bleeding [2]. The EUROMAX trial compared bivalirudin with heparin and demonstrated a lower composite event rate of mortality and major bleeding at 30 days in bivalirudin-treated patients [3]. Interestingly, there were higher stent thrombosis rates at 24 h with bivalirudin in both trials.

In these studies, the differences in outcomes between bivalirudin and heparin groups were mostly driven by a significantly lower bleeding rate in the bivalirudin arm and might be attributed to the higher frequency of glycoprotein IIb/IIIa inhibitors use in the heparin arm of these studies. This hypothesis became more plausible when the HEAT-PPCI study, an open-label single-center trial, showed a clinical benefit with heparin compared with bivalirudin for the composite outcome of all-cause mortality, stroke, re-infarction or unplanned target vessel revascularization at 28 days [4]. In this trial, glycoprotein IIb/IIIa inhibitors use was similar in both arms, and the major bleeding event rate did not differ between the studied groups. The heparin advantage was explained by a higher incidence of acute stent thrombosis in bivalirudin-treated patients.

Thereafter, data from two recent clinical trials questioned again whether bivalirudin offers any significant advantage compared with heparin. The BRIGHT study, which enrolled patients with STEMI and non-STEMI, demonstrated a significant lower event rate (death, stroke, re-infarction, target vessel revascularization, or any bleeding) in the bivalirudin arm compared with heparin [5]. Glycoprotein IIb/IIIa inhibitors use was similar in heparin

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Table 1. Ischemic and bleeding risk of bivalirudin versus heparin in STEMI PCI across clinical trials and meta-analyses.

	Bivalirudin versus heparin in STEMI	
	More acute stent thrombosis	*Less bleeding*
Clinical trials		
HORIZONS-AMI	✓	✓
EUROMAX	✓	✓
HEAT-PPCI	✓	–;
BRIGHT	–	✓
MATRIX	✓	✓
Meta-analyses		
Lancet 2014	✓	✓
BMJ 2014	✓	✓

and bivalirudin group. Acute stent thrombosis rates did not differ between the study groups, but bleeding events were more common with heparin. The results were applicable in the STEMI subgroup.

Preliminary results from the MATRIX trial in patients with any acute coronary syndrome, recently presented at the American College of Cardiology Scientific Sessions 2015 in San Diego, showed a similar major adverse cardiovascular events rate with heparin and bivalirudin. However, stent thrombosis was more frequent with bivalirudin, whereas major bleeding events were more common with heparin [6].

The lower incidence of acute stent thrombosis in the BRIGHT trial, compared with the HORIZONS-AMI, EUROMAX and HEAT-PPCI trials, may be explained by the prolonged post-PCI bivalirudin administration (for 0.5–4 hours) at the dose of 1.75 mg/kg·h. In the first three trials, bivalirudin was stopped at the end of PCI (HORIZONS-AMI and HEAT-PPCI) or continued at a lower dose (0.25 mg/kg·h for 0.5–4 h in EUROMAX). A *post hoc* analysis of the EUROMAX trial [7] also supports this observation that needs to be confirmed in further clinical trials.

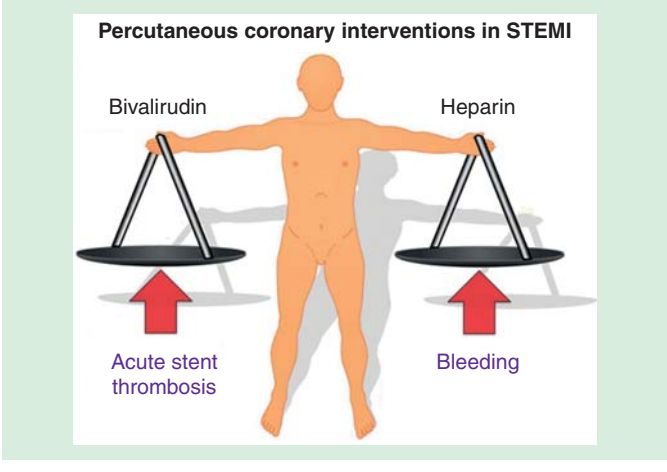

Figure 1. Risk-benefit ratio of bivalirudin versus heparin in percutaneous coronary intervention for STEMI.

Two recent meta-analyses, published before BRIGHT and MATRIX studies, shed further light on the efficacy and safety of bivalirudin versus heparin (Table 1). The first one (including patients undergoing elective or urgent PCI) was in favor of heparin concerning the major adverse cardiovascular events rate at 30 days, mostly driven by an increase in myocardial infarction and ischemia-driven revascularization in the bivalirudin arm [8]. The second meta-analysis included randomized trials in STEMI patients undergoing primary PCI and showed no difference in the in-hospital or 30-day major adverse cardiovascular events rate between heparin and bivalirudin [9]. However, the acute stent thrombosis rate was higher with bivalirudin, and the major bleeding events rate was higher with heparin.

Is there clinical equipoise regarding the use of bivalirudin and heparin in STEMI? Composite hard clinical outcomes appear to be comparable with both drugs. Current evidence suggests that bivalirudin is associated with a safety benefit (less major bleeding events) at the expense of lower short-term efficacy (more acute stent thrombosis events) (Figure 1). Therefore, anticoagulation choice during PCI in STEMI should be individualized taking into account patient's ischemic and bleeding risk. In patients with increased bleeding risk, bivalirudin appears to be preferable to heparin, whereas in complex PCI with increased risk for stent thrombosis, heparin might be preferable. The significantly higher cost of bivalirudin compared with heparin should also be taken into account. Further clinical studies are needed to elucidate the role of these drugs in STEMI PCI in the era of radial approach, new potent antiplatelet agents and provisional glycoprotein IIb/IIIa inhibitors use.

Expert commentary & five-year view

On the basis of current evidence, bivalirudin is associated with a safety benefit (less bleeding) at the expense of lower short-term efficacy (more ischemic events) in STEMI PCI. In the following years, as radial approach becomes even more widespread and new stents and potent antiplatelet agents come on board, a personalized anticoagulation management is anticipated to further reduce major adverse cardiovascular events and bleeding complications post PCI.

Financial & competing interests disclosure

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Key issues

- Composite hard clinical outcomes appear to be comparable with both drugs. Current evidence suggests that bivalirudin is associated with a safety benefit (less major bleeding events) at the expense of lower short-term efficacy (more acute stent thrombosis events).
- Anticoagulation management during PCI in STEMI should be individualized, taking into account patient's ischemic and bleeding risk. In patients with increased bleeding risk, bivalirudin appears to be preferable to heparin, whereas in complex PCI with increased risk for stent thrombosis, heparin might be more preferable. The significantly higher cost of bivalirudin compared with heparin should be also taken into account.
- Further clinical studies are needed to elucidate the role of these drugs in STEMI PCI in the era of radial approach, new potent antiplatelet agents and provisional glycoprotein IIb/IIIa inhibitors use.

References

1. Mavrakanas TA, Chatzizisis YS. Bivalirudin in stable angina and acute coronary syndromes. Pharmacol Ther 2015;152:1-10
2. Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med 2008;358:2218-30
3. Steg PG, van 't Hof A, Hamm CW, et al. Bivalirudin started during emergency transport for primary PCI. N Engl J Med 2013;369:2207-17
4. Shahzad A, Kemp I, Mars C, et al. Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. Lancet 2014;384:1849-58
5. Han Y, Guo J, Zheng 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;313:1336-46
6. Valgimigli M. Bivalirudin infusion compared to unfractionated heparin in patients with acute coronary syndromes undergoing invasive management: results from the Minimizing Adverse Hemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox (MATRIX) antithrombin program. Presented at: American College of Cardiology/i2 Scientific Session; 16 March 2015; San Diego, CA
7. Clemmensen P, Wiberg S, Van't Hof A, et al. Acute stent thrombosis after primary percutaneous coronary intervention: insights from the EUROMAX trial (European Ambulance Acute Coronary Syndrome Angiography). JACC Cardiovasc Interv 2015;8:214-20
8. Cavender MA, Sabatine MS. Bivalirudin versus heparin in patients planned for percutaneous coronary intervention: a meta-analysis of randomised controlled trials. Lancet 2014;384:599-606
9. Bangalore S, Toklu B, Kotwal A, et al. 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