State of the Art

Cardiology Discovery 心血管病探索（英文）

OPEN

Bivalirudin in Primary PCI: Can Its Glory Being Restored?

Yang Li[1], Yi Li[1], Gregg W. Stone[2], Yaling Han[1,*]

Abstract

Intravenous anticoagulant therapy is critical to prevent ischemic recurrences and complications without increasing the risk of bleeding in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PPCI). It includes the indirect thrombin inhibitor heparins and the direct thrombin inhibitor bivalirudin. However, the ideal anticoagulant for patients undergoing PPCI remains controversial. In this review, we provide an overview of currently available anticoagulant therapies used in STEMI patients undergoing PPCI, including describing the rationale for their use, pivotal clinical trial data, and treatment recommendations of guidelines, providing much-needed clarity to guide the selection of the safest and most effective anticoagulant regimens for PPCI.

Keywords: Bivalirudin; Heparin; ST-segment elevation myocardial infarction; Primary percutaneous coronary intervention

Worldwide, acute ST-segment elevation myocardial infarction (STEMI) remains the leading cause of morbidity, mortality, and disability.[1,2] The gold standard treatment in STEMI patients is early, sustained and effective reperfusion of culprit coronary artery by primary percutaneous coronary intervention (PPCI).[3] Over the past 30 years, both in-hospital and 1-year mortality from STEMI (5%–6% and 7%–18%, respectively) have decreased significantly with advances in reperfusion therapy, but cardiovascular outcomes may still be improved.[4,5] Once the decision is made to perform PPCI, selection of arterial access site and stent type, whether to use thrombectomy and circulatory support devices, and optimization of adjunctive medical therapy (including perioperative antithrombotic therapy) need to be optimized by the interventional cardiologist during the PPCI procedure to improve immediate and long-term results.

Intravenous anticoagulant therapy is mandatory in PPCI. Currently, bivalirudin and unfractionated heparin (UFH) are used for procedural anticoagulation in nearly all PPCI patients.[6,7] Bivalirudin is touted for its predictable pharmacokinetics, effects on thrombin-mediated platelet inhibition, and reduced bleeding outcomes in most prior studies, whereas UFH, the most commonly used anticoagulant during PPCI, remains a viable treatment strategy.[8] Both are recommended in the setting of STEMI in guidelines stems from the broad comparative evidence.[5,9,10] Yet optimal adjunctive therapy in STEMI patients treated with PPCI remains a matter of debate. In this review, we provide an overview of currently available anticoagulant therapies used in STEMI patients undergoing PPCI, including describing the rationale for their use, pivotal clinical trial data, and treatment recommendations of guidelines, providing much-needed clarity to guide the selection of the safest and most effective anticoagulant regimens for PPCI.

Necessity of anticoagulation therapy in STEMI patients

STEMI is an acute thrombus-driven event. Atherosclerotic plaque rupture or erosion followed by arterial thrombosis and formation of an occlusive thrombus is the major determinant leading to STEMI.[11,12] Platelets and coagulation factors are the main elements involved in this process. In plaque rupture, the cap collagen and the highly thrombogenic lipid core, enriched in tissue factor-expressing apoptotic microparticles left behind after apoptotic cell death, are exposed to the thrombogenic factors of the blood, which activates the coagulation cascade leading to clot formation and further thrombin generation.[13,14] Thrombin converts fibrinogen to fibrin, an essential component of arterial thrombus, and the fibrin-rich thrombi lead to activation, amplification, and propagation of the coagulation cascade.[15] Plaque erosion is a weaker thrombogenic stimulus, and thus, other factors may be particularly important in this setting.[13] In coronary thrombosis, the initial flow obstruction is usually caused by platelet aggregation, but fibrin is important for the subsequent stabilization of the early and fragile platelet thrombus.[12]

Anticoagulation therapy is a mainstay of modern medical therapy for acute and chronic thrombotic diseases. Anticoagulants in STEMI are given to prevent expansion and enhancement of thrombi. Furthermore, contemporary management with PPCI requires a suitable antithrombotic environment to prevent catheter thrombosis. The quest for the ideal parenteral anticoagulant agent remains an ongoing topic of investigation.

Editor: Xiaoxia Fu and Tianyu Xu.

[1] Cardiovascular Research Institute and Department of Cardiology, General Hospital of Northern Theater Command, Shenyang, Liaoning 110016, China; [2] Icahn School of Medicine at Mount Sinai, Mount Sinai Heart and the Cardiovascular Research Foundation, New York, New York 10029-5674, USA.

[*] Corresponding author: Yaling Han, E-mail: hanyaling@263.net.

Received: 24 October 2020; Accepted: 18 January 2021

http://dx.doi.org/10.1097/CD9.0000000000000016

Limitations of the pharmacological property of UFH in PPCI

The ideal anticoagulation drug in PCI acute coronary syndromes should have a rapid onset of action, a predictable dose-dependent anticoagulation effect, a short half-life or quick reversibility, a broad therapeutic window, and be effective in reducing ischemic complications.[16]

UFH, an indirect thrombin inhibitor, is a mix of sulfated polysaccharides with molecular weight ranging from 3000 to 30,000 kDa (mean 15,000 kDa).[17] UFH is derived from mucosal tissues of porcine intestines or bovine lungs and had been the mainstay for PPCI procedural anticoagulation prior to the introduction of bivalirudin in the 1990s.[18] It exerts its effects by blocking the activation of thrombin (factor IIa) and factor X through an antithrombin-dependent mechanism.[8] The heparin-antithrombin complex inactivates not only thrombin but also factors Xa, IXa, XIa, and XIIa. The complex kinetics of heparin clearance renders the anticoagulant response to UFH non-linear at therapeutic doses, with both the peak activity and the duration of effect increasing disproportionately with increasing doses.[16] Major limitations of UFH include its unpredictable pharmacokinetic profile with high inter- and intra-individual variability, low bioavailability, the lack of ability to bind to and inhibit clot-bound thrombin, platelet activation, influence by the inflammatory state of the patient and the increased risk of heparin-induced thrombocytopenia, which is a serious, potentially lethal, immunologically mediated adverse reaction to UFH.[4,19,20] In addition, there are no randomized trials to determine the optimal dose and duration of UFH in PPCI. The current dose recommendations for UFH were based on retrospective analyses and expert opinions.

Bivalirudin is a polypeptide of 20 amino acids that directly binds to thrombin at both the active site and the fibrinogen-binding site (exo-site 1) without the need for a cofactor (in contrast to UFH), inhibiting thrombin in both circulating and bound clots.[21] Uniquely, bivalirudin also has antiplatelet effects through inhibition of thrombin-mediated platelet aggregation.[22] Bivalirudin is given by intravenous infusion and produces an immediate and predictable anticoagulant effect, as demonstrated by dose-dependent prolongation of the activated clotting time (ACT), activated partial thromboplastin time, and thrombin clotting time. Once bound to thrombin, proteolytic cleavage of the Arg3-Pro4 bond of bivalirudin results in functional recovery of the active site of thrombin.[23] Bivalirudin is degraded by endogenous peptidases and its clearance is only partially dependent on renal function. The half-life of bivalirudin is 25 minutes with linear pharmacokinetics in patients with normal renal function, 1 hour in patients with severe renal impairment, and 3.5 hours in patients undergoing hemodialysis.[24] For these reasons, bivalirudin may be pharmacologically favored for anticoagulation in STEMI patients for PPCI [Table 1].

Table 1

Properties of bivalirudin and unfractionated heparin (UFH)

Property	Bivalirudin	UFH
Factor Xa: IIa inhibition	Only IIa	1: 1
Onset of action	Immediate	Immediate
Time to peak plasma concentration (min)	2–15	20–60
Action independent of antithrombin	Yes	No
Half-life	25 min (1 h in patients with renal impairment)	30–120 min (dose-dependent)
Non-specific binding	No	Yes
Variable PK/PD measures	Yes	No
Inhibition of fibrin-bound thrombin	Yes	No
Effect on platelets	Inhibition	Activation
Risk of HIT	No	Yes

HIT: Heparin-induced thrombocytopenia; PD: Pharmacodynamic; PK: Pharmacokinetic.

Bivalirudin became favored in PPCI

The HORIZONS-AMI trial,[25] the first multicenter RCT in which bivalirudin was compared to UFH plus glycoprotein IIb/IIIa receptor inhibitor (GPI) for PPCI, served as the basis for the European Society of Cardiology (ESC) 2012 STEMI guidelines[26] and the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) 2013 STEMI guidelines[10] in which bivalirudin received a class I (level of evidence B) recommendation in preference to UFH plus GPI for patients with STEMI undergoing PPCI, particularly those at high risk of bleeding.

In HORIZONS-AMI trial, 3602 patients with STEMI were randomly assigned within 12 hours of symptom onset to receive bivalirudin (0.75 mg/kg intravenous bolus followed by 1.75 mg/(kg·h) infusion) with provisional (bailout) use of GPI, or heparin (60 U/kg bolus plus additional boluses to achieve an ACT of 200–250 s) plus a routine GPI (52% abciximab, 48% eptifibatide or tirofiban).[27] All patients undergoing PPCI were pretreated with 300 or 600 mg of clopidogrel, at the discretion of the investigator. The majority of patients underwent PPCI ($n=3348$) and the remainder underwent coronary artery bypass graft (CABG) surgery ($n=63$) or were managed medically ($n=191$). In the bivalirudin group, only 7.2% of patients received a GPI. The main results showed that compared with UFH plus a GPI, bivalirudin significantly reduced the 30-day net clinical composite outcome of death, reinfarction, target vessel revascularization, stroke, or major bleeding not related to CABG surgery (9.2% *vs.* 12.1%; RR = 0.76, 95% CI: 0.63–0.92, $P=0.005$), mainly driven by a 40% reduction in major bleeding (4.9% *vs.* 8.3%; RR = 0.60, 95% CI: 0.46–0.77, $P<0.001$) and a 34% reduction in all-cause mortality (2.1% *vs.* 3.1%; RR = 0.66, 95% CI: 0.44–1.00, $P=0.047$). Consistent results were observed at 1 year and 3 years.[28,29] Composite major adverse cardiovascular events (MACE) were similar between the 2 treatments.

In the decade after the publication of HORIZONS-AMI trial, clinical practice evolved, including reduced GPI use, routine use of the potent $P2Y_{12}$ receptor inhibitors prasugrel and ticagrelor, and use of radial access instead of femoral access, all of which may influence bleeding outcomes.[8] The EUROMAX trial was designed to investigate whether the benefit of bivalirudin over heparin in PPCI persisted in the setting of a more contemporary approach. The study population included 2218 patients at least 18 years of age with presumed STEMI randomized to receive bivalirudin (bolus and infusion for at least 4 hours after PPCI at 0.25 mg/(kg·h), however, the continuation of the high dose of 1.75 mg/(kg·h) used during PCI was also permitted) or UFH with optional GPI use, initiated in the ambulance or a hospital without PPCI capacity. The composite of death from any cause or non-CABG major bleeding at 30 days was significantly reduced in patients who received bivalirudin compared with UFH (5.1% *vs.* 8.5%; RR = 0.60, 95% CI: 0.43–0.82, $P=0.001$).[30] Compared

with UFH, bivalirudin also significantly reduced the composite of death, re-infarction, or non-CABG major bleeding (6.6% *vs.* 9.2%; $P=0.02$).[30] These results were primarily driven by a 57% reduction in major bleeding with bivalirudin compared with UFH (2.6% *vs.* 6.0%; RR = 0.43; 95% CI: 0.28–0.66; $P<0.001$).[30]

Nevertheless, the clinical benefits of bivalirudin use and whether bivalirudin is the optimal regimen have still been the subject of debate in STEMI patients, who need more careful evaluation and attention to anticoagulant management.

Challenges to bivalirudin in PPCI

The results of HORIZONS-AMI and EUROMAX demonstrated that bivalirudin was associated with a reduced risk of bleeding and an overall favorable outcomes profile, including reduced cardiovascular mortality. However, these promising findings were hindered by an increased risk of thrombotic events, particularly acute stent thrombosis with bivalirudin. In the HORIZONS-AMI trial, an increased risk of stent thrombosis within 24 hours was observed in the bivalirudin group (1.3% *vs.* 0.3%; $P<0.001$), with no differences in the rate of subacute (between 24 hours to 30 days) stent thrombosis. The risk of acute stent thrombosis in the bivalirudin group was also significantly higher in EUROMAX trial (1.1% *vs.* 0.2%; RR = 6.11; 95% CI: 1.24–27.24; $P=0.007$).[30,31] This increase occurred despite prolonged bivalirudin infusion after PCI in 93% of patients (although only 22.5% received a high infusion dose) and the use of prasugrel or ticagrelor in half of the patients.[32] Accordingly, prescribing information for bivalirudin was changed in the United States in March, 2016 to note that "Acute stent thrombosis (<4 hours) has been observed at a greater frequency in bivalirudin treated patients compared to UFH treated patients with STEMI undergoing PPCI.[33] These patients should remain for at least 24 hours in a facility capable of managing ischemic complications and should be carefully monitored following PPCI for signs and symptoms consistent with myocardial ischemia."

The single-center trial HEAT-PPCI compared bivalirudin to UFH alone (without GPI) in 1829 patients with suspected STEMI undergoing planned PPCI. Only provisional use of GPIs (abciximab) was allowed in both groups. Bivalirudin compared with UFH increased early stent thrombosis again (3.4% *vs.* 0.9%; RR = 3.91; 95% CI: 1.61–9.52; $P=0.001$), but contrary to prior trials did not reduce bleeding complications (3.5% *vs.* 3.1%; RR = 1.15; 95% CI: 0.7–1.9; $P=0.59$).[34] Based on this data, bivalirudin use was downgraded in the 2014 ESC myocardial revascularization guidelines[35] and 2017 ESC STEMI guidelines (recommendation IIa-A).[5] Of note, the rate of acute stent thrombosis with bivalirudin was two to three-folds higher than in any previous study, and as HEAT-PPCI was a single-centered study, the external validity of these findings required replication in additional multicenter studies.

The subsequent MATRIX trial is the largest study to date comparing anticoagulant agents in STEMI patients undergoing PPCI. In this trial, 7213 patients with an acute coronary syndrome (56% with STEMI) in whom PCI was anticipated were randomly assigned to receive either bivalirudin or UFH (with GPI only in bail-out circumstances).[36] Additionally, patients could receive either a short-term infusion of bivalirudin at a high-dose 1.75 mg/(kg·h) for up to 4 hours post-PCI or a long-term infusion of bivalirudin at a reduced dose of 0.25 mg/(kg·h) for at least 6 hours, at the discretion of the physician. The rates of MACE and net adverse clinical events were not significantly lower with bivalirudin than with UFH, despite a significant reduction in major bleeding, all-cause death, and cardiac death.[37,38] Additionally, there was no significant difference in urgent target vessel revascularization, definite stent thrombosis, or net adverse clinical events in patients receiving a prolonged bivalirudin infusion when compared with those who only received a bivalirudin infusion for the duration of PCI (11.0% *vs.* 11.9%; RR = 0.91; 95% CI: 0.74–1.11; $P=0.34$).[37,39] The results for the STEMI group ($n=4010$) were not different from the overall study results. Bivalirudin use was associated with a reduction in major bleeding (1.7% *vs.* 2.8%; RR = 0.60; 95% CI: 0.39–0.92; $P=0.019$), with no significant difference in acute stent thrombosis (0.9% *vs.* 0.5%; RR = 1.88; 95% CI: 0.87–4.06; $P=0.10$).[40] However, these results were interpreted with caution as they derived from a *post hoc* analysis and were thus considered as hypothesis-generating.

In the newly published registry-based, open-label VALIDATE-SWEDEHEART trial, 3005 patients with STEMI and 3001 patients with non-STEMI were randomly assigned to bivalirudin or heparin during PCI (using predominantly radial access).[41] Patients also received potent $P2Y_{12}$ receptor inhibitors with neither group intended to receive a GPI. The clinical impact of bivalirudin was similar to UFH in monotherapy in the overall cohort (12.3% *vs.* 12.8%; RR = 0.96; 95% CI: 0.83–1.10; $P=0.54$) as well as in the STEMI subgroup (12.5% *vs.* 13.0%; RR = 0.95; 95% CI: 0.78–1.17) in terms of the composite primary endpoint of all-cause mortality, myocardial infarction (MI) or major bleeding during 180 days of follow-up.[42]

Overall, results of these large-scale clinical trials [Tables 2 and 3],[25,30,34,37,42–58] as well as data from several meta-analyses [Table 4],[6,59–68] show that bivalirudin compared with UFH yields similar rates of MACE and net adverse clinical events at 30 days, with an increased risk of acute stent thrombosis. These findings led to a downgrade in the recommendation (from class IIa to IIb) for bivalirudin in the most recent 2018 ESC guideline for myocardial revascularization.[69]

Should bivalirudin use be reconsidered in PPCI?

The goal of anticoagulant management is to balance the risk of thrombotic complications, such as reinfarction and stent thrombosis, with the risk of bleeding complications. During this long-lasting journey, contrasting evidence has been accumulated on the efficacy and safety profile of bivalirudin compared with UFH. Numerous trials have shown that the risk of bleeding associated with bivalirudin is lower than that associated with UFH. However, whether bivalirudin increases the rate of acute stent thrombosis has become a focus of controversy.

The pooled analysis from the HORIZONS-AMI and EUROMAX trials demonstrated that bivalirudin compared with UFH plus GPI resulted in an increased rate of acute stent thrombosis by an absolute increment of ~1% occurring within the first 4 hours after abrupt discontinuation of bivalirudin infusion, with non-significantly different rates of subacute stent thrombosis (between 24 hours to 30 days).[31] Because bivalirudin has a short half-life, plasma levels decrease rapidly after infusion discontinuation. This increased acute stent thrombosis rate may be due to insufficient residual thrombin activity after bivalirudin cessation with inadequate time to have achieved the inhibition of $P2Y_{12}$ receptor-induced platelet aggregation. Numerous previous studies have demonstrated that the onset time for maximal inhibition of platelet aggregation after treatment with clopidogrel before PCI is dependent on the loading dose of clopidogrel. The

Table 2

Major clinical trials of bivalirudin compared with heparin in STEMI

Items	HORIZONS-AMI[25]	EUROMAX[30]	HEAT-PPCI[34]	BRAVE 4[44]	BRIGHT[43]	MATRIX[37]	VALIDATE-SWEDEHEART[42]
Study characteristics							
Design	Multicenter, open-label, RCT	Multicenter, open-label, RCT	Single-center, open-label, RCT	Multicenter, open-label, RCT	Multicenter, open-label, RCT	Multicenter, open-label, RCT	Multicenter, open-label, registry-based RCT
Year published	2008	2013	2014	2014	2015	2015	2017
Number of centers	123	65	1	3	82	78	25
Population	STEMI	STEMI	STEMI	STEMI	AMI (87.7% STEMI)	ACS (55.6% STEMI)	AMI (50.0% STEMI)
Total number of patients (percentage bivalirudin/UFH)	3602 (50.0%/50.0%)	2218 (49.7%/50.3%)	1812 (49.9%/50.1)	548 (49.5%/50.5%)	2194 (33.5% bivalirudin, 33.2% UFH, 33.3% UFH + GPI)	7213 (50.0%/50.0%)	6006 (50.0%/50.0%)
Mean age (years)	60	62	63	61	58	66	68
Percentage male (%)	76.6	76.2	72.3	77.4	82.1	76.2	73.4
Femoral access (%)	93.7	52.9	18.3	All but 1 patient	21.5	52.1	9.5
$P2Y_{12}$-receptor inhibitor	Clopidogrel 300–600 mg	Clopidogrel (50%), prasugrel (30%), or ticagrelor (20%)	Clopidogrel (11%), prasugrel (27%), or ticagrelor (62%)	Clopidogrel (90.2%) in heparin group; prasugrel (94.6%) in bivalirudin group	Clopidogrel 300–600 mg	Clopidogrel (45.9%), prasugrel (12.8%), or ticagrelor (62%)	Ticagrelor (94.9%), prasugrel (2.1%), cangrelor (0.3%)
Group	Bivalirudin *vs.* Heparin + GPI	Bivalirudin *vs.* Heparin + optional GPI	Bivalirudin *vs.* Heparin	Bivalirudin+prasugrel *vs.* Heparin + clopidogrel	Bivalirudin *vs.* Heparin *vs.* Heparin + GPI	Bivalirudin *vs.* Heparin	Bivalirudin *vs.* Heparin
Timing of randomization	In the emergency room at the PCI hospital	In the ambulance or the non-PCI hospital	In the cath laboratory, prior to completion of angiography	At the admitting unit	In the cath laboratory, prior to angiography	For patients with STEMI, before angiography, for patients with NSTEMI, after diagnostic catheterization but prior to PCI	After angiography but prior to PCI
Heparin dose	60 U/kg	UFH: 100 U/kg without GPI or 60 U/kg with GPI; Enoxaparin: 0.5 mg/kg	70 U/kg	70–100 U/kg	100 U/kg in heparin only group; 60 U/kg in heparin + GPI group	70–100 U/kg without GPI or 50–70 U/kg with GPI	70–100 U/kg
GPI use in heparin group	Routine (97.7%)	Routine or bailout (69.1%)	Bailout (15.5%)	Bailout (6.1%)	Bailout (5.6%) in heparin-only group; routine (100%) in heparin + GPI group	Routine or bailout (25.9%)	Bailout (2.8%)
Bivalirudin dose	0.75 mg/kg IV, then 1.75 mg/(kg·h)	0.75 mg/kg IV, then 1.75 mg/(kg·h)	0.75 mg/kg IV, then 1.75 mg/(kg·h)	0.75 mg/kg IV, then 1.75 mg/(kg·h)	0.75 mg/kg IV, then 1.75 mg/(kg·h)	0.75 mg/kg IV, then 1.75 mg/(kg·h)	0.75 mg/kg IV, then 1.75 mg/(kg·h) (91% patients received heparin, mean 3469 U)
GPI use in bivalirudin group	Bailout (7.5%)	Bailout (11.5%)	Bailout (13.5%)	Bailout (3.0%)	Bailout (4.4%)	Bailout (4.6%)	Bailout (2.4%)
Post-PCI bivalirudin infusion	None (but could be continued at low doses if clinically indicated)	4 h after PCI at 0.25 mg/(kg·h); continuation of PCI dose was also permitted (22.5%)	None	None	30 min–4 h after PCI (mean 180 min) at PCI dose	Patients randomized 1:1 to receive or not receive post-PCI infusion (full dose for up to 4 h or reduced dose of 0.25 mg/(kg·h) for ≥6 h.	Continuation of PCI dose was strongly recommended (done in 65% of patients, mean 57 min)

(*continued*)

Table 2
(continued).

Items	HORIZONS-AMI[25]	EUROMAX[30]	HEAT-PPCI[34]	BRAVE 4[44]	BRIGHT[43]	MATRIX[37]	VALIDATE-SWEDEHEART[42]
						Bivalirudin dose was determined by physician)	
Primary endpoint	Non-CABG-related major bleeding at 30 days; NACE (major bleeding or MACE (death, reinfarction, TVR for ischemia, and stroke)) at 30 days	Death from any cause or non-CABG-related major bleeding at 30 days	Efficacy: MACE (all-cause death, CVA, reinfarction, or additional unplanned TLR) at 28 days. Safety: major bleeding at 28 days	NACE (MACE (all-cause death, reinfarction, unplanned revascularization of IRA, definite stent thrombosis or stroke) or major bleeding (non-CABG related)) at 30 days	NACE (MACE (all-cause death, reinfarction, ischaemia-driven TVR, or stroke) or any bleeding) at 30 days	MACE (death, MI or stroke) at 30 days; NACE (MACE or non-CABG-related major bleeding) at 30 days	Death from any cause, MI, or major bleeding at 180 days
Bleeding definition	Protocol-defined	Protocol-defined	BARC type 3–5	HORIZONS-AMI definition	BARC	BARC type 3–5	BARC type 2, 3 or 5
Study results							
Primary endpoint	NACE: bivalirudin 9.3% *vs.* heparin + GPI 12.2% ($P=0.005$); non-CABG-related major bleeding: bivalirudin 5.0% *vs.* heparin + GPI 8.4% ($P<0.001$)	Bivalirudin 5.1% *vs.* Heparin + optional GPI 8.5% ($P=0.001$)	MACE: Bivalirudin 8.7% *vs.* Heparin 5.7% ($P=0.02$); major bleeding: Bivalirudin 3.5% *vs.* Heparin 3.1% ($P=0.59$)	Bivalirudin 15.6% *vs.* Heparin 14.5% ($P=0.68$)	Bivalirudin 8.8% *vs.* Heparin 13.2% *vs.* Heparin + GPI 17.0% ($P<0.001$)	MACE: bivalirudin 10.3% *vs.* heparin 10.9% ($P=0.44$); NACE: bivalirudin 11.2% *vs.* heparin 12.4% ($P=0.12$)	Bivalirudin 12.3% *vs.* Heparin 12.8% ($P=0.54$)
MACE	Bivalirudin 5.5% *vs.* heparin + GPI 5.5% ($P=0.95$)	Bivalirudin 6.0% *vs.* Heparin + optional GPI 5.5% ($P=0.64$)	Bivalirudin 8.7% *vs.* Heparin 5.7% ($P=0.02$)	Bivalirudin 4.8% *vs.* Heparin 5.5% ($P=0.89$)	Bivalirudin 5.0% *vs.* Heparin 5.8% *vs.* Heparin + GPI 4.9% ($P=0.83$)	Bivalirudin 10.3% *vs.* Heparin 10.9% ($P=0.44$)	Not reported
Major bleeding	Bivalirudin 5.0% *vs.* heparin + GPI 8.4% ($P<0.001$)	Bivalirudin 2.6% *vs.* Heparin + optional GPI 6.0% ($P<0.001$)	Bivalirudin 3.5% *vs.* Heparin 3.1% ($P=0.59$)	Bivalirudin 14.1% *vs.* Heparin 12.0% ($P=0.54$)	Bivalirudin 0.5% *vs.* Heparin 1.5% *vs.* Heparin + GPI 2.1% ($P=$NS)	Bivalirudin 1.4% *vs.* Heparin 2.5% ($P<0.001$)	Bivalirudin 8.6% *vs.* Heparin 8.6% ($P=0.98$)
Cardiac death	Bivalirudin 1.8% *vs.* heparin + GPI 2.9% ($P=0.03$)	Bivalirudin 2.5% *vs.* Heparin + optional GPI 3.0% ($P=0.48$)	Not reported	Bivalirudin 2.2% *vs.* Heparin 1.8% ($P=0.97$)	Bivalirudin 1.6% *vs.* Heparin 1.8% *vs.* Heparin + GPI 2.1% ($P=$NS)	Bivalirudin 1.5% *vs.* Heparin 2.2% ($P=0.03$)	Bivalirudin 2.4% *vs.* Heparin 2.3% ($P=0.80$)
Acute stent thrombosis ($\leq$24 h)	Bivalirudin 1.3% *vs.* heparin 0.3% ($P<0.001$)	Bivalirudin 1.1% *vs.* Heparin + optional GPI 0.2% ($P=0.007$)	Bivalirudin 2.9% *vs.* Heparin 0.9% ($P=0.007$)	Not reported	Bivalirudin 0.3% *vs.* Heparin 0.3% *vs.* Heparin + GPI 0.3% ($P=$NS)	Bivalirudin 0.6% *vs.* Heparin 0.4% ($P=0.34$)	Not reported

ACS: Acute coronary syndrome; AMI: Acute myocardial infarction; BARC: Bleeding Academic Research Consortium; CABG: Coronary artery bypass graft; CVA: Cerebrovascular accident; GPI: Glycoprotein IIb/IIIa inhibitor; IRA: Infarct related artery; IV: Intravenous; MACE: Major adverse cardiac events; MI: Myocardial infarction; NACE: Net adverse clinical events; NS: Non-significant; NSTEMI: Non-ST segment elevation myocardial infarction; PCI: Percutaneous coronary intervention; PPCI: Primary percutaneous coronary intervention; RCT: Randomized controlled trial; STEMI: ST-segment elevation myocardial infarction; TLR: Target lesion revascularization; TVR: Target vessel revascularization; UFH: Unfractionated heparin.

Table 3

Major registry studies of bivalirudin compared with heparin in STEMI

Studies	Data	Population	Group	Antithrombotic therapy	Results
Venetsanos et al (2018)[45]	SWEDEHEART Registry	23,800 STEMI (2008–2014)	Bivalirudin ± GPI (15,017) *vs.* Heparin ± GPI (8783)	• Prehospital treatment with heparin in bivalirudin group (79.5%) • 68.5% concomitant GPI in heparin group; 3.5% concomitant GPI in bivalirudin group • Widespread use of a prolonged bivalirudin infusion (unspecified)	• Primary efficacy outcome: 30-day all-cause mortality: Bivalirudin ± GPI 5.5% *vs.* Heparin ± GPI 5.3% ($P=0.56$) • In-hospital major bleeding (fatal or cerebral bleeding, bleeding requiring surgical intervention, blood transfusion or leading to a decrease in haemoglobin >5.0 g/dL): Bivalirudin ± GPI 1.1% *vs.* Heparin ± GPI 1.8% ($P<0.01$) • 30-day definite stent thrombosis: Bivalirudin ± GPI 0.5% *vs.* Heparin ± GPI 0.6% ($P=0.09$) • 30-day MI: Bivalirudin ± GPI 2.1% *vs.* Heparin ± GPI 2.9% ($P<0.01$)
Grimfjärd et al (2017)[46]	SCAAR/SWEDEHEART registry	20,612 STEMI (2007–2014)	Bivalirudin (16,891) *vs.* Heparin (3721)	• 78% concomitant heparin in bivalirudin group	• Primary outcome: 30-day definite stent thrombosis: Bivalirudin 0.8% *vs.* Heparin 0.9% ($P=0.365$) • Acute stent thrombosis: Bivalirudin 0.29% *vs.* Heparin 0.32% • 30-day all-cause death: Bivalirudin 5.4% *vs.* Heparin 6.9% ($P<0.001$) • 30-day major bleeding (intracerebral, subarachnoidal or subdural haematoma; gastrointestinal tract bleeds including oesophageal, gastric, duodenal, lower gastrointestinal tract and rectal bleeds; haematemesis or melena): Bivalirudin 0.6% *vs.* Heparin 0.8% ($P=0.212$)
Hasun et al (2017)[47]	Austrian Acute PCI Registry	7023 STEMI (2010–2014)	Bivalirudin ± GPI (593) *vs.* Heparin ± GPI (6430)	• Prehospital treatment with heparin in bivalirudin group (76%) • 40% concomitant GPI in heparin group; 15% concomitant GPI in bivalirudin group	• Primary outcome: in-hospital all-cause mortality: Bivalirudin ± GPI 3.7% *vs.* Heparin ± GPI 4.9% ($P=0.19$) • In-hospital MACE (death, reinfarction, or stroke): Bivalirudin ± GPI 4.7% *vs.* Heparin ± GPI 5.8% ($P=0.35$) • In-hospital NACE (composite of MACE and TIMI non-CABG related major bleeding): Bivalirudin ± GPI 5.1% *vs.* Heparin ± GPI 6.4% ($P=0.25$) • In-hospital TIMI non-CABG related major bleeding (any intracranial hemorrhage, a decrease in hemoglobin of ≥5g/dL, the need for blood transfusion, or surgical intervention): Bivalirudin ± GPI 0.3% *vs.* Heparin ± GPI 0.9% ($P=0.17$)
Jovin et al (2017)[48]	NCDR CathPCI Registry	67,368 STEMI (2009–2015)			

(*continued*)

Table 3
(continued).

Studies	Data	Population	Group	Antithrombotic therapy	Results
			Bivalirudin (29,660) *vs.* Heparin (37,708)	• 66.8% concomitant heparin in bivalirudin group • 59.4% concomitant GPI in heparin group; 22.9% concomitant GPI in bivalirudin group	• Primary outcome: in hospital death, MI, or stroke: Bivalirudin *vs.* Heparin: 0.95 (95% CI: 0.87–1.05; $P=0.152$) • Acute stent thrombosis: Bivalirudin *vs.* Heparin: 2.11 (95% CI: 1.73–2.57) • In hospital major bleeding: Bivalirudin *vs.* Heparin: 0.98 (95% CI: 0.91–1.05)
Wang et al (2017)[49]	65 Chinese Centers Registry	2047 STEMI	Post-procedural bivalirudin high dose *vs.* low dose or none	• High dose (1.75 mg/(kg·h), mean 120 min) • Low dose (0.25 mg/(kg·h), mean 240 min) • 46.7% concomitant GPI in high dose group; 42.0% concomitant GPI in low dose or none group	• Acute stent thrombosis: High dose 0.0% *vs.* Low dose or none 0.3% ($P=0.092$) • 30-day MACCE (all-cause death, reinfarction, ischemia-driven TVR, or stroke): High dose 2.1% *vs.* Low dose or none 2.7% ($P=0.402$) • 30-day any bleeding: High dose 2.1% *vs.* Low dose or none 1.4% ($P=0.217$)
Sirker et al (2016)[50]	United Kingdom national PCI registry	61,136 STEMI (2008–2012)	Bivalirudin (4158) *vs.* Heparin (21,849) *vs.* Heparin ± GPI (35,129)	• 14.5% concomitant GPI in bivalirudin group • 85.5% concomitant heparin in bivalirudin group	• Primary outcome: 30-day mortality: Bivalirudin *vs.* Heparin+GPI (OR = 1.00, 95% CI: 0.84–1.18, $P=0.98$); Heparin *vs.* Heparin + GPI (OR = 1.17, 95% CI: 1.08–1.27, $P<0.0001$); Heparin *vs.* Bivalirudin (OR = 1.18, 95% CI: 1.00–1.38, $P=0.05$)
Secemsky et al (2016)[51]	NCDR CathPCI Registry	513,775 STEMI (2009–2014)	Bivalirudin ± GPI (242,087) *vs.* Heparin ± GPI (271,688)	• 26.5% concomitant GPI in bivalirudin group; 74.7% concomitant GPI in heparin group • 49.9% concomitant heparin in bivalirudin group	• Primary outcome: in-hospital bleeding (NCDR Version 4 definition): Bivalirudin ± GPI *vs.* Heparin ± GPI (RD = -3.75%; $P<0.001$) • Primary outcome: in-hospital mortality: Bivalirudin ± GPI *vs.* Heparin ± GPI (RD = -0.10%; $P=0.280$)
Kinnaird et al (2016)[52]	British Cardiovascular Intervention Society Database (BCIS) Central Cardiac Audit (CCAD) database	1389 STEMI (2012–2014)	Bivalirudin ± GPI (1218) *vs.* Heparin ± GPI (171)	• Bivalirudin: 0.75 mg/kg IV, then 1.75 mg/(kg·h) during procedure • Post-procedure: 1.75 mg/(kg·h); median duration: 49 min • 52% concomitant heparin in bivalirudin group • 36.3% concomitant GPI in heparin group; 6.1% concomitant GPI in bivalirudin group	• Acute stent thrombosis: Bivalirudin ± GPI without heparin 0.0% *vs.* Heparin ± GPI 0.0%; Bivalirudin ± GPI with heparin 0.7% *vs.* Heparin ± GPI 0.0% ($P=0.58$); Bivalirudin ± GPI without heparin 0.0% *vs.* Bivalirudin ± GPI with heparin 0.7% ($P=0.07$) • Repeat revascularization: Bivalirudin ± GPI without heparin 13.3% *vs.* Heparin ± GPI 14.3% ($P=0.77$); Bivalirudin ± GPI with heparin 10.1% *vs.* Heparin ± GPI 14.3% ($P=0.20$); Bivalirudin ± GPI without heparin 13.3% *vs.* Bivalirudin ± GPI with heparin 10.1% ($P=0.14$)

(*continued*)

Table 3
(continued).

Studies	Data	Population	Group	Antithrombotic therapy	Results
					• All-cause mortality: Bivalirudin ± GPI without heparin 1.4% *vs.* Heparin ± GPI 2.5% ($P=0.49$); Bivalirudin ± GPI with heparin 2.0% *vs.* Heparin ± GPI 2.5% ($P=0.76$); Bivalirudin ± GPI without heparin 1.4% *vs.* Bivalirudin ± GPI with heparin 2.0% ($P=0.51$)
Bheemarasetti et al (2015)[53]	University of Texas Medical Branch local registry	139 STEMI (2010–2013)	Radial access bivalirudin (9) *vs.* Radial access heparin (19) *vs.* Femoral access bivalirudin (83) *vs.* Femoral access heparin (28)	• Bivalirudin: 0.75 mg/kg IV, then 1.75 mg/(kg·h) during procedure • Heparin: 60 U/kg • 91.3% concomitant GPI in bivalirudin group; 100% concomitant GPI in heparin group	• Primary outcome: 30-day composite of death from any cause or stent thrombosis or non-CABG related major bleeding (CathPCI Registry definition): radial/bivalirudin 22% *vs.* radial/heparin 5% *vs.* femoral/bivalirudin 17% *vs.* femoral/heparin 28%, $P=0.2$)
Limbruno et al (2014)[54]	EUROVISION registry	678 STEMI (2009–2010)	Bivalirudin	• 0.70 ± 0.25 mg/kg IV, then 1.58 ± 0.47 mg/(kg·h) • 60.9% Post-procedural bivalirudin infusion; median time: 122 min; total dose of bivalirudin: post-PCI infusion group 274 mg *vs.* no post-PCI infusion group 127 mg • 84% concomitant heparin • 7.2% concomitant GPI	• 30-day all cause death: 2.1%; non-fatal myocardial reinfarction: 0.3%; unplanned revascularization: 0.6% and non-fatal stroke: 0.4% • Acute stent thrombosis: 0.0% • 30-day major bleeding (ACUITY criteria): 1.5%
Shelton et al (2013)[55]	Leeds General Infirmary database	968 STEMI (2009–2010)	Bivalirudin (882) *vs.* Heparin + GPI (85)	• Bivalirudin: 0.75 mg/kg IV, then 1.75 mg/(kg·h) during procedure, 0.25 mg/(kg·h) for 4 h post-procedure • 12.9% concomitant GPI in bivalirudin group • 13.9% concomitant heparin or fondaparinux in bivalirudin group	• 30-day all cause death: Bivalirudin 5.2% *vs.* Heparin + GPI 7.1% ($P=0.450$) • 30-day cardiac death: Bivalirudin 4.4% *vs.* Heparin + GPI 7.1% ($P=0.277$) • 30-day MACE (death, reinfarction, stroke, or unplanned TVR): Bivalirudin 7.5% *vs.* Heparin + GPI 9.4% ($P=0.520$) • 30-day major bleeding (HORIZONS-AMI definition): Bivalirudin 3.8% *vs.* Heparin + GPI 4.7% ($P=0.560$) • Acute stent thrombosis: Bivalirudin 1.0% *vs.* Heparin + GPI 1.2% ($P=0.604$)
Hibbert et al (2012)[56]	Ottawa STEMI Registry	2,313 STEMI (2004–2010)	Bivalirudin (748) *vs.* Heparin + GPI (699) *vs.* Heparin (676)	• All patients received 60 U/kg heparin (maximum of 4000 U) at FMC • 7.5% concomitant GPI in bivalirudin group; no concomitant GPI in heparin group	• Primary outcome: in hospital non-CABG related TIMI major bleeding (fall in hemoglobin of >5g/dL once adjusted for transfusion or intracranial bleeding): Bivalirudin 2.7% *vs.* Heparin + GPI 7.3% ($P<0.001$); Bivalirudin 2.7% *vs.* Heparin 3.3% ($P=0.59$) • Composite end point of in hospital death, stroke, reinfarction and major bleed:

(*continued*)

Table 3
(continued).

Studies	Data	Population	Group	Antithrombotic therapy	Results
Pinto et al (2012)[57]	Premier hospital database	59,917 STEMI (2004–2008)	Bivalirudin (6735) *vs.* Heparin + GPI (53,182)	• Treatment with heparin in bivalirudin group before PPCI (28%)	Bivalirudin 7.6% *vs.* Heparin + GPI 11.4% ($P=0.01$); Bivalirudin 7.6% *vs.* Heparin 9.5% ($P=0.83$) • Acute stent thrombosis: Bivalirudin 1.6% *vs.* Heparin + GPI 0.6% *vs.* Heparin 0.3% • Primary outcome: in-hospital death: Bivalirudin 3.2% *vs.* Heparin + GPI 4.0% ($P=0.011$) • In-hospital clinically apparent bleeding (ICD-9 diagnosis code for bleeding): Bivalirudin 6.9% *vs.* Heparin + GPI 10.5% ($P<0.0001$) • In-hospital clinically apparent bleeding with transfusion: Bivalirudin 1.6% *vs.* Heparin + GPI 3.0% ($P<0.0001$) • Length of stay: Bivalirudin 4.3 days *vs.* Heparin + GPI 4.5 days ($P<0.0001$) • In-hospital cost: Bivalirudin $14,462 *vs.* Heparin + GPI $16,003 ($P<0.0001$)
Bonello et al (2009)[58]	Washington Hospital Local Registry	899 STEMI (2003–2007)	Bivalirudin (566) *vs.* Heparin (333)	• Heparin: 50 U/kg (ACT 200–250 s) • Bivalirudin: 0.75 mg/kg IV, then 1.75 mg/(kg·h) during procedure • No concomitant GPI in both group	• Primary outcome: in-hospital major bleeding (major hematoma, gastrointestinal bleeding and hematocrit drop $>15\%$ during hospitalization): Bivalirudin 4.1% *vs.* Heparin 4.2% ($P=0.92$) • In-hospital MACE (death, ischemic stroke and urgent repeated revascularization): Bivalirudin 2.7% *vs.* Heparin 1.2% ($P=0.15$)

ACT: Activated clotting time; CABG: Coronary artery bypass graft; CI: Confidence interval; FMC: First medical contact; GPI: Glycoprotein IIb/IIIa inhibitor; ICD: International classification of diseases; IV: Intravenous; MACE: Major adverse cardiac events; MI: Myocardial infarction; NACE: Net adverse clinical events; NCDR: National cardiovascular data registry; OR: Odds ratio; PCI: Percutaneous coronary intervention; PPCI: Primary percutaneous coronary intervention; RD: Risk difference; STEMI: ST-segment elevation myocardial infarction; TIMI: Thrombolysis in Myocardial Infarction; TVR: Target vessel revascularization.

Table 4

Major published meta-analysis of bivalirudin compared with heparin in STEMI

Authors (year)	Included trials	Patients	Results
Shah et al (2019)[61]	EUROMAX, BRIGHT, MATRIX, VALIDATESWEDEHEART	ACS	• Early stent thrombosis: Bivalirudin (with a post-procedure infusion) *vs.* Heparin (RR = 0.45, 95% CI: 0.23–0.85, *P* = 0.015) Bivalirudin (with a post-procedure infusion) *vs.* Heparin + GPI (RR = 0.52, 95% CI: 0.18–1.50, *P* = 0.227) • 30-day major bleeding: Bivalirudin (with a post-procedure infusion) *vs.* Heparin (RR = 0.44, 95% CI: 0.20–0.97, *P* = 0.043) Bivalirudin (with a post-procedure infusion) *vs.* Heparin + GPI (RR = 0.25, 95% CI: 0.10–0.63, *P* = 0.003)
Shah et al (2019)[62]	HORIZONS-AMI, EUROMAX, HEAT-PPCI, BRIGHT, MATRIX	STEMI	• 30-day all-cause mortality: Switch (switching to bivalirudin during PPCI from preprocedure heparin) *vs.* Heparin (OR = 0.47, 95% CI: 0.30–0.71) Switch *vs.* Bivalirudin (OR = 0.50, 95% CI: 0.31–0.78) Bivalirudin *vs.* Heparin (OR = 0.93, 95% CI: 0.70–1.22) • 30-day MACE: Switch *vs.* Heparin (OR = 0.63, 95% CI: 0.45–0.86) Switch *vs.* Bivalirudin (OR = 0.52, 95% CI: 0.37–0.73) Heparin *vs.* Bivalirudin (OR = 0.83, 95% CI: 0.67–1.02) • 30-day major bleeding: Switch *vs.* Heparin (OR = 0.57, 95% CI: 0.37–0.86) Switch *vs.* Bivalirudin (OR = 0.98, 95% CI: 0.63–1.50) Bivalirudin *vs.* Heparin (OR = 0.59, 95% CI: 0.43–0.78) • 30-day NACE: Switch *vs.* Heparin (OR = 0.53, 95% CI: 0.36–0.78) Switch *vs.* Bivalirudin (OR = 0.69, 95% CI: 0.47–1.02) Bivalirudin *vs.* Heparin (OR = 0.77, 95% CI: 0.58–1.02)
Shah et al (2017)[63]	HORIZONS-AMI, EUROMAX, HEAT-PPCI, BRIGHT, BRAVE 4, MATRIX	ACS	• 30-day NACE: Post-procedural bivalirudin high dose *vs.* Heparin (OR = 0.51, 95% CI: 0.35–0.75) Post-procedural bivalirudin high dose *vs.* No post-procedural bivalirudin (OR = 0.51, 95% CI: 0.32–0.82) Post-procedural bivalirudin high dose *vs.* Post-procedural bivalirudin low dose (OR = 0.57, 95% CI: 0.36–0.98) Post-procedural bivalirudin low dose *vs.* Heparin (OR = 0.90, 95% CI: 0.56–1.41) Post-procedural bivalirudin low dose *vs.* No post-procedural bivalirudin (OR = 0.91, 95% CI: 0.52–1.49) No post-procedural bivalirudin *vs.* Heparin (OR = 1.00, 95% CI: 0.71–1.42) • 30-day all-cause mortality: Post-procedural bivalirudin high dose *vs.* Heparin (OR = 0.51, 95% CI: 0.29–0.89) Post-procedural bivalirudin high dose *vs.* No post-procedural bivalirudin (OR = 0.53, 95% CI: 0.29–0.96) Post-procedural bivalirudin high dose *vs.* Post-procedural bivalirudin low dose (OR = 0.62, 95% CI: 0.28–1.49) Post-procedural bivalirudin low dose *vs.* Heparin (OR = 0.81, 95% CI: 0.40–1.65) Post-procedural bivalirudin low dose *vs.* No post-procedural bivalirudin (OR = 0.84, 95% CI: 0.41–1.72) No post-procedural bivalirudin *vs.* Heparin (OR = 0.97, 95% CI: 0.68–1.40) • 30-day cardiac mortality: Post-procedural bivalirudin high dose *vs.* Heparin (OR = 0.50, 95% CI: 0.28–0.78) Post-procedural bivalirudin high dose *vs.* No post-procedural bivalirudin (OR = 0.67, 95% CI: 0.37–1.91) Post-procedural bivalirudin high dose *vs.* Post-procedural bivalirudin low dose (OR = 0.69, 95% CI: 0.36–1.21) Post-procedural bivalirudin low dose *vs.* Heparin (OR = 0.73, 95% CI: 0.51–1.03) Post-procedural bivalirudin low dose *vs.* No post-procedural bivalirudin (OR = 0.74, 95% CI: 0.33–1.49) No post-procedural bivalirudin *vs.* Heparin (OR = 0.95, 95% CI: 0.49–1.68)
Capodanno et al (2016)[64]	HORIZONS-AMI, EUROMAX, HEAT-PPCI, BRIGHT, BRAVE 4	AMI	• 30-day all cause death: Bivalirudin *vs.* Heparin (OR = 0.97, 95% CI: 0.74–1.28, *P* = 0.84) • 30-day major bleeding: Bivalirudin *vs.* Heparin (OR = 0.58, 95% CI: 0.40–0.85, *P* = 0.005)

(*continued*)

Table 4
(continued).

Authors (year)	Included trials	Patients	Results
			• 30-day definite stent thrombosis: Bivalirudin *vs.* Heparin (OR = 1.71, 95% CI: 0.84–3.49, $P = 0.14$) • Acute stent thrombosis: Bivalirudin *vs.* Heparin (OR = 3.55, 95% CI: 1.67–7.56, $P = 0.001$) • 30-day reinfarction: Bivalirudin *vs.* Heparin (OR = 1.47, 95% CI: 0.94–2.30, $P = 0.10$) • 30-day cardiovascular death: Bivalirudin *vs.* Heparin (OR = 0.76, 95% CI: 0.56–1.02, $P = 0.07$)
Fahrni et al (2016)[65]	HORIZONS-AMI, EUROMAX, HEAT-PPCI, BRIGHT, BRAVE 4	AMI	• Acute stent thrombosis: Post-procedural bivalirudin high dose *vs.* Heparin ± GPI (0.26% *vs.* 0.33%, OR = 0.81, 95% CI: 0.27–2.46, $P = 0.71$) • 30-day major bleeding Post-procedural bivalirudin high dose *vs.* Heparin ± GPI (0.79% *vs.* 2.92%, OR = 0.28, 95% CI: 0.13–0.60, $P = 0.001$)
Shah et al (2016)[66]	HORIZONS-AMI, EUROMAX, HEAT-PPCI, BRIGHT, MATRIX	AMI	• Acute stent thrombosis: Post-procedural bivalirudin high dose *vs.* Heparin (OR = 0.97, 95% CI: 0.36–2.21) Heparin *vs.* Post-procedural bivalirudin low dose (OR = 0.25, 95% CI: 0.12–0.57) Heparin *vs.* No post-procedural bivalirudin (OR = 0.33, 95% CI: 0.17–0.56) • 30-day major bleeding Post-procedural bivalirudin high dose *vs.* Heparin (OR = 0.26, 95% CI: 0.14–0.46)
Ferrante et al (2015)[67]	HORIZONS-AMI, EUROMAX, HEAT-PPCI	STEMI	• 30-day all cause death: Bivalirudin *vs.* Heparin (3.03% *vs.* 3.38%, OR = 0.90, 95% CI: 0.63–1.29, $P = 0.57$) • 30-day definite stent thrombosis: Bivalirudin *vs.* Heparin (2.39% *vs.* 1.06%, OR = 2.49, 95% CI: 1.30–4.76, $P = 0.006$) • Acute stent thrombosis: Bivalirudin *vs.* Heparin (1.69% *vs.* 0.39%, OR = 4.34, 95% CI: 2.30–8.16, $P < 0.001$) • 30-day MACE: Bivalirudin *vs.* Heparin (6.38% *vs.* 5.55%, OR = 1.18, 95% CI: 0.89–1.54, $P = 0.24$) • 30-day major bleeding: Bivalirudin *vs.* Heparin (3.93% *vs.* 6.39%, OR = 0.63, 95% CI: 0.39–1.04, $P = 0.07$, NNT = 45)
Shah et al (2015)[59]	HORIZONS-AMI, EUROMAX, HEAT-PPCI, BRAVE 4, BRIGHT, MATRIX	STEMI	• 30-day MACE: Bivalirudin *vs.* Heparin ± GPI (RR = 1.02, 95% CI: 0.87–1.19, $P = 0.800$) • 30-day MI: Bivalirudin *vs.* Heparin ± GPI (RR = 1.41, 95% CI: 0.94–2.11, $P = 0.089$) • 30-day target vessel revascularization: Bivalirudin *vs.* Heparin ± GPI (RR = 1.37, 95% CI: 0.91–2.04, $P = 0.122$) • 30-day NACE: Bivalirudin *vs.* Heparin ± GPI (RR = 0.81, 95% CI: 0.64–1.01, $P = 0.069$) • 30-day all cause death: Bivalirudin *vs.* Heparin ± GPI (RR = 0.81, 95% CI: 0.67–0.99, $P = 0.041$) • 30-day cardiac death: Bivalirudin *vs.* Heparin ± GPI (RR = 0.68, 95% CI: 0.51–0.91, $P = 0.009$) • 30-day major bleeding: Bivalirudin *vs.* Heparin ± GPI (RR = 0.63, 95% CI: 0.44–0.90, $P = 0.012$) • Acute stent thrombosis: Bivalirudin *vs.* Heparin ± GPI (RR = 3.31, 95% CI: 1.79–6.10, $P < 0.001$)
Bangalore et al (2014)[6]	HORIZONS-AMI, EUROMAX, HEAT-PPCI, BRIGHT, BRAVE 4	AMI	• 30-day MACE: Heparin *vs.* Heparin + GPI (RR = 1.49, 95% CI: 1.21–1.84); Bivalirudin *vs.* Heparin + GPI (RR = 1.34, 95% CI: 1.01–1.78); Bivalirudin *vs.* Heparin (RR = 0.90, 95% CI: 0.68–1.18) • 30-day major bleeding: Heparin *vs.* Heparin + GPI (RR = 0.82, 95% CI: 0.59–1.14); Bivalirudin *vs.* Heparin + GPI (RR = 0.47, 95% CI: 0.30–0.74); Bivalirudin *vs.* Heparin (RR = 0.58, 95% CI: 0.37–0.90) • 30-day stent thrombosis: Heparin *vs.* Heparin + GPI (RR = 2.01, 95% CI: 0.94–4.29);

(*continued*)

Table 4
(continued).

Authors (year)	Included trials	Patients	Results
Nairooz et al (2014)[60]	HORIZONS-AMI, EUROMAX	STEMI	Bivalirudin *vs.* Heparin + GPI (RR = 2.34, 95% CI: 1.03–5.32); Bivalirudin *vs.* Heparin (RR = 1.16, 95% CI: 0.52–2.61) • 30-day cardiac death: Bivalirudin *vs.* Heparin + GPI (RR = 0.70, 95% CI: 0.50–0.97, *P* = 0.03) • 30-day definite stent thrombosis: Bivalirudin *vs.* Heparin + GPI (RR = 1.88, 95% CI: 2.30–13.07, *P* = 0.02) • Acute stent thrombosis: Bivalirudin *vs.* Heparin + GPI (RR = 5.48, 95% CI: 1.03–5.32, *P* = 0.0001) • 30-day TIMI major bleeding: Bivalirudin *vs.* Heparin + GPI (RR = 0.61, 95% CI: 0.45–0.82, *P* = 0.0009) • 30-day TIMI minor bleeding: Bivalirudin *vs.* Heparin + GPI (RR = 0.60, 95% CI: 0.48–0.75, *P* < 0.000,01)
Kinnaird et al (2013)[68]	HORIZONS-AMI, ASSIST, ON-TIME2, BRAVE-3, CADILLAC, Fu et al, ACE, Montalescot et al	STEMI	• 30-day mortality: Bivalirudin *vs.* Heparin (OR = 0.55, 95% CI: 0.32–0.95) • 30-day stroke: Bivalirudin *vs.* Heparin (OR = 0.88; 95% CI: 0.37–2.13) • 30-day MI: Bivalirudin *vs.* Heparin (OR = 0.79; 95% CI: 0.40–1.55) • 30-day TIMI major and minor bleeding: Bivalirudin *vs.* Heparin (OR = 0. 66; 95% CI: 0.45–0/98)

ACS: Acute coronary syndrome; AMI: Acute myocardial infarction; CI: Confidence interval; GPI: Glycoprotein IIb/IIIa inhibitor; MACE: Major adverse cardiac events; MI: Myocardial infarction; NACE: Net adverse clinical events; NNT: Number needed to treat; OR: Odds ratio; PPCI: Primary percutaneous coronary intervention; RR: Risk ratio; STEMI: ST-segment elevation myocardial infarction; TIMI: Thrombolysis in Myocardial Infarction.

onset to peak action of a 300 mg loading dose of clopidogrel is 6 to 24 hours. Even pretreatment with a 600 mg loading dose of clopidogrel requires 2 to 6 hours to achieve peak effect.[70] Moreover, there is a delay in the action of clopidogrel and even the novel potent $P2Y_{12}$ receptor inhibitors ticagrelor and prasugrel during the first 6 hours post-loading doses in patients with STEMI due to delayed absorption.[71] The half-life of bivalirudin is only 25 minutes; its plasma levels are thus decreased to ~70% and ~11% after bivalirudin discontinuation for 15 minutes and 120 minutes, respectively. At these time points, $P2Y_{12}$ inhibitors have not reached their peak effect in STEMI. Since the PPCI procedure is usually completed within 1 hour, if the bivalirudin infusion is immediately stopped at the end of the PPCI procedure, there is a window of absent anti-thrombotic and anti-platelet efficacy, explaining the increased risk of acute stent thrombosis.

The BRIGHT trial, which was performed in 82 centers in China and randomized 2194 patients with acute MI undergoing emergency PCI (87.7% with STEMI) to receive either bivalirudin, UFH alone, or UFH plus GPI in 1:1:1 ratio, has provided important insights into preventing the increased stent thrombosis risk after bivalirudin in STEMI.[43,72,73] As an important part of the study protocol, bivalirudin infusion was continued post-PCI in all patients for a minimum of 30 minutes and a maximum of 4 hours at a rate of 1.75 mg/(kg·h), with a discretionary extension at a low dose (0.2 mg/(kg·h)) for up to 20 hours. The median post-PCI duration of the infusion with the 1.75 mg/(kg·h) dose was 3 hours. There was no numerical or statistical increase in the acute stent thrombosis rates in BRIGHT (0.3% for bivalirudin *vs.* 0.3% for UFH *vs.* 0.3% for UFH plus GPI, respectively), but a notable reduction in BARC 2 to 5 bleeding with bivalirudin compared to either UFH alone or UFH plus GPI (6.3% *vs.* 9.3% *vs.* 9.0%, respectively, $P = 0.03$) was observed.[43] Although the total dose of bivalirudin per patient was higher in this trial than in earlier studies, bivalirudin maintained its advantages in reducing bleeding and acquired thrombocytopenia. In the subgroup of 1925 patients with STEMI undergoing PPCI, the results were consistent with the overall trial population for the primary endpoint, MACE, acute stent thrombosis, and bleeding. The results were also consistent at the 1-year follow-up.[43] Even though BRIGHT did not specifically test the hypothesis that prolonged high-dose bivalirudin infusion reduces ischemic events and stent thrombosis compared either with no infusion or a low-dose infusion, the study does provide evidence that a prolonged high-dose infusion is safe and may be an effective strategy to reduce the risk of acute stent thrombosis seen with bivalirudin in other trials.[74]

Confirming these findings, subgroup analysis from the EUROMAX trial revealed that the risk of stent thrombosis seemed to be mitigated by prolonging the bivalirudin infusion at the high dose while still reducing bleeding rates compared with UFH alone; in this study, there was no improvement in stent thrombosis rates with prolonged infusion of low-dose bivalirudin.[75] Consistent with this, data from the MATRIX trial showed that the primary endpoint did not differ with or without post-PCI bivalirudin infusion, although a post-PCI high-dose bivalirudin infusion (1.75 mg/(kg·h) for ≤4 hours) was associated with improved outcomes when compared with no or a low-dose (0.25 mg/(kg·h) for ≤6 hours) post-PCI bivalirudin infusion, including lower risks of stent thrombosis.[76] In VALIDATE-SWEDEHEART, 65% of patients in the bivalirudin group received a post-PCI bivalirudin infusion at 1.75 mg/(kg·h), but with an average duration of only 57 minutes. As the half-life of bivalirudin is only 25 minutes, it is not clear whether further prolongation of bivalirudin infusion can improve the outcomes noted in this trial.[77] In addition, most patients treated with bivalirudin in VALIDATE-SWEDEHEART received UFH (mean dose 3470 U) as well, potentially masking the advantage of bivalirudin.[78] Therefore, the generalizability of these findings may be limited.

A new meta-analysis, led by Shah et al,[66] includes HORIZONS-AMI and EUROMAX trials, as well as BRIGHT, HEAT-PPCI, and MATRIX trials for a total of 16,294 patients who were treated with either UFH or one of three bivalirudin regimens: only during PCI or for up to 4 hours after PCI at either a high-dose (1.75 mg/(kg·h)) or a low-dose (0.25 mg/(kg·h)), comparing the efficacy and safety of the above 4 anticoagulant regimens in reducing acute stent thrombosis. This is the first meta-analysis to address the effect of prolonging post-PCI bivalirudin infusion on acute stent thrombosis and major bleeding by using traditional and network meta-analysis. The researchers confirmed a two-fold increased risk of acute stent thrombosis with bivalirudin versus UFH (RR = 2.36, 95% CI: 1.46–3.02, $P < 0.001$), but this phenomenon was ameliorated by continuing high-dose bivalirudin infusion post-PPCI (RR = 0.90, 95% CI: 0.32–2.54, $P = 0.85$). This effect was not seen with low-dose bivalirudin infusion post-PPCI. In summary, a high-dose bivalirudin infusion post-procedure for 2 to 4 hours can effectively cover the period after PPCI when $P2Y_{12}$ receptor inhibitors have not yet become fully active [Tables 2–4].

The meta-analysis also demonstrated that bivalirudin decreased the risk of major bleeding at 30 days by 47% compared with UFH; this benefit persisted even with continued high-dose infusion post-PPCI (RR = 0.29, 95% CI: 0.16–0.53, $P < 0.001$). Peri-procedural bleeding events, up to 50% arise from the access site, remain the most common non-cardiac complication following PCI and have been associated with significant morbidity, mortality, and financial burden to the healthcare system. These events are multifactorial and are associated with: (1) patient-related factors (female sex, age >70 years); (2) comorbidities such as diabetes mellitus, obesity, hypertension, and diseases inhibiting clot formation, such as uremia and thrombocytopenia; (3) and procedural factors (eg, port of access, mode of arterial puncture and anticoagulation regimen).[79] Numerous randomized trials have demonstrated that major bleeding (both access site and non-access site) is less frequent in patients treated with bivalirudin.[37,43,80,81] Thus, bivalirudin is recommended to reduce bleeding events in STEMI patients with a high risk of bleeding, especially those with multiple high-risk factors.

As vascular approaches have shifted to more frequent radial access with associated lower bleeding risk, selecting the optimal antithrombotic to balance efficacy and bleeding risk has also received much attention. Whether the clinical benefits of bivalirudin are maintained in patients with transradial access undergoing PPCI is uncertain. An early access-based meta-analysis involving 8 trials with a total of 27,491 patients (13,757 STEMI and 13,734 non-ST-elevation acute coronary syndrome (NSTE-ACS)) and a larger observational study (132,113 patients) showed that compared with heparin, bivalirudin lowered major bleeding in patients with femoral access but not in those with radial access.[82,83] However, subgroup analyses from randomized trials, including the BRIGHT and EUROMAX trials, have shown a reduced risk of bleeding associated with the combination of radial artery access and bivalirudin.[73,84] Therefore, these conflicting data led us to perform further research to evaluate the comparative efficacy and safety of bivalirudin versus UFH (with or without planned GPIs) in patients undergoing transradial artery coronary interventions.

It may be speculated that compared to clopidogrel, adding the potent $P2Y_{12}$ inhibitors prasugrel or ticagrelor to bivalirudin might further reduce ischemic complications, although perhaps at the cost of increased bleeding. The BRAVE-4 randomized STEMI patients to prasugrel plus bivalirudin and clopidogrel plus heparin, finding no major differences in ischemic or bleeding complications between the 2 arms.[65] However, this trial compared both different antithrombin and antiplatelet regimens in the 2 arms, thus not permitting isolation of the effect of each alone. To date, no head-to-head clinical trial has been performed to compare clopidogrel with the potent $P2Y_{12}$ receptor inhibitors (prasugrel or ticagrelor) in STEMI patients treated with bivalirudin.

Subgroup analyses may help physicians tailor anticoagulant therapy to specific patient characteristics, thus individualizing treatment decisions and improving outcomes. Prespecified subgroup analysis of BRIGHT and VALIDATE-SWEDEHEART trial demonstrated that the reduction in 30-day net adverse clinical events (NACE) with bivalirudin was more pronounced in women,[43,72,85] in patients with creatinine clearance ≤60 mL/min,[43] and in those with high risk of bleeding.[43] Additionally, in a large group pooled analysis of elderly patients enrolled in the EUROMAX and HORIZONS-AMI trials, bivalirudin was associated with lower 30-day rates of non-CABG major bleeding, subacute stent thrombosis and NACE, with similar rates of acute stent thrombosis and 30-day mortality compared with the non-elderly patients.[86] Further studies are required to provide insight into the optimal anticoagulant strategy for patients with STEMI and non-STEMI undergoing PCI.

Conclusions and perspectives

Early mechanical reperfusion by PPCI is the standard treatment strategy for patients with STEMI. Optimal adjunctive antithrombotic therapy with antiplatelet and anticoagulant agents is a prerequisite for the safe and effective performance of PPCI. Antithrombin agent selection in the individual STEMI patient in the perioperative period of PPCI should be conditioned according to the ischemic and bleeding risk. In this regard, bivalirudin may be an optimal agent if used correctly, particularly in the patient at increased bleeding risk. Clinical trials have demonstrated that prolonging the bivalirudin infusion at high-dose (1.75 mg/(kg·h)) for 3 to 4 hours post-PPCI eliminates the excess risk of acute stent thrombosis while maintaining the benefits of bivalirudin in reducing major bleeding and thrombocytopenia. Preloading with a potent $P2Y_{12}$ inhibitor prior to the procedure may also beneficial (although further studies are required in this regard). Therefore, it is not enough to simply choose bivalirudin (or heparin); each agent must be optimally utilized by administering it in the correct dose and duration and with the best procedural technique (eg, radial artery access) and proper additional medications (eg, antiplatelet agents).

The debate on UFH compared with bivalirudin use reminds us once again that rarely does "one size fit all". A panoply of diverse options must be considered when selecting the optimal antithrombotic agent and regimen to minimize both ischemic events and hemorrhagic complications in STEMI patients undergoing PPCI. To gain further insights into the true merits of bivalirudin compared to UFH, an individual patient data (IPD) pooled analysis from the 8 largest randomized controlled trials of bivalirudin versus UFH in 38,565 patients with STEMI and non-STEMI undergoing PCI has been completed.[87] The preliminary results (reported at Transcatheter Cardiovascular Therapeutics 2020 but not yet published) demonstrated that bivalirudin use was associated with reductions in the 30-day rates of mortality,

serious bleeding and NACE despite increased rates of MI and stent thrombosis compared with heparin in patients with STEMI undergoing PPCI. The mortality benefit of bivalirudin in STEMI was pronounced in patients treated with a post-PCI bivalirudin infusion (low-dose or high-dose), and a high-dose infusion mitigated the MI and stent thrombosis risk. As commented by Capodanno and Angiolillo,[88] the pooling of IPD enables more sophisticated efforts, including identification of independent predictors and examining the temporal relationship between treatments and outcomes, and conceptually is at the pinnacle in the hierarchy of evidence. Important details to further examine will be the relationship between access site and outcomes, and in particular subgroups of interest at particularly high-risk for either ischemia or bleeding. In addition, the BRIGHT-4 trial is underway (ClinicalTrials.gov Identifier: NCT03822975). In this large-scale trial, 6000 patients with STEMI undergoing PPCI are randomized to UFH alone versus bivalirudin including a 2 to 4 hour post-PCI full-dose infusion. The results of these studies will provide greater clarity and guidance for the selection of the optimal anticoagulant in patients with STEMI undergoing PPCI.

Funding

This work was supported by the Key Research and Development Program of Liaoning Province (2020JH 2/10300167), Project of Science and Technology Plan of Shenyang (19-112-4-051) and Cardiacare Sponsored Optimizing Antithrombotic Research Fund (BJUHFCSOARF201901-06).

Conflicts of interest

None.

Editor note: Yaling Han is the Editor-in-Chief of *Cardiology Discovery*. Gregg W. Stone is an Associate Editor of *Cardiology Discovery*. Yi Li is an Editorial Board Member of *Cardiology Discovery*. The article was subject to the journal's standard procedures, with peer review handled independently of these editors and their research groups.

References

[1] Pasterkamp G, den Ruijter HM, Libby P. Temporal shifts in clinical presentation and underlying mechanisms of atherosclerotic disease. Nat Rev Cardiol 2017;14(1):21–29. doi: 10.1038/nrcardio.2016.166.

[2] Dai X, Kaul P, Smith SC Jr, et al. Predictors, treatment, and outcomes of STEMI occurring in hospitalized patients. Nat Rev Cardiol 2016;13(3):148–154. doi: 10.1038/nrcardio.2015.165.

[3] Bates ER, Jacobs AK. Time to treatment in patients with STEMI. N Engl J Med 2013;369(10):889–892. doi: 10.1056/NEJMp1308772.

[4] Franchi F, Rollini F, Angiolillo DJ. Antithrombotic therapy for patients with STEMI undergoing primary PCI. Nat Rev Cardiol 2017;14(6):361–379. doi: 10.1038/nrcardio.2017.18.

[5] Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;39(2):119–177. doi: 10.1093/eurheartj/ehx393.

[6] 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. doi: 10.1136/bmj.g6419.

[7] Arsenault KA, Hirsh J, Whitlock RP, et al. Direct thrombin inhibitors in cardiovascular disease. Nat Rev Cardiol 2012;9(7):402–414. doi: 10.1038/nrcardio.2012.61.

[8] Faulkenberg KD, Beavers JC, Finks SW. Heparin versus bivalirudin monotherapy in the setting of primary percutaneous coronary intervention for patients with ST-segment elevation myocardial infarction. Ann Pharmacother 2016;50(2):141–151. doi: 10.1177/1060028015618206.

[9] Chinese Society of Cardiology of Chinese Medical Association, Editorial Board of Chinese Journal of Cardiology. 2019 Chinese Society of Cardiology (CSC) guidelines for the diagnosis and management of patients with ST-segment elevation myocardial infarction. Zhonghua Xin Xue Guan Bing Za Zhi 2019;47(10):766–783. doi: 10.3760/cma.j.issn.0253-3758.2019.10.003.

[10] O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61(4):e78–e140. doi: 10.1016/j.jacc.2012.11.019.

[11] Libby P. Mechanisms of acute coronary syndromes and their implications for therapy. N Engl J Med 2013;368(21):2004–2013. doi: 10.1056/NEJMra1216063.

[12] Falk E, Nakano M, Bentzon JF, et al. Update on acute coronary syndromes: the pathologists' view. Eur Heart J 2013;34(10):719–728. doi: 10.1093/eurheartj/ehs411.

[13] Bentzon JF, Otsuka F, Virmani R, et al. Mechanisms of plaque formation and rupture. Circ Res 2014;114(12):1852–1866. doi: 10.1161/CIRCRESAHA.114.302721.

[14] Rautou PE, Vion AC, Amabile N, et al. Microparticles, vascular function, and atherothrombosis. Circ Res 2011;109(5):593–606. doi: 10.1161/CIRCRESAHA.110.233163.

[15] van Gameren M, Lemmert ME, Wilschut JM, et al. An update on the use of anticoagulant therapy in ST-segment elevation myocardial infarction. Expert Opin Pharmacother 2018;19(13):1441–1450. doi: 10.1080/14656566.2018.1512583.

[16] Zeymer U, Rao SV, Montalescot G. Anticoagulation in coronary intervention. Eur Heart J 2016;37(45):3376–3385. doi: 10.1093/eurheartj/ehw061.

[17] Garcia DA, Baglin TP, Weitz JI, et al. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(2 Suppl):e24S–e43S. doi: 10.1378/chest.11-2291.

[18] Ong C, Bangalore S. Does VALIDATE-SWEDEHEART invalidate the use of bivalirudin in myocardial infarction. J Thorac Dis 2018;10(1):70–74. doi: 10.21037/jtd.2017.12.100.

[19] Condon AJ, Hood AJ, Willenborg KL, et al. Pharmacist involvement in clinical assessment and laboratory testing for heparin-induced thrombocytopenia. J Thromb Thrombolysis 2020;50(1):195–200. doi: 10.1007/s11239-019-02011-8.

[20] De Caterina R, Husted S, Wallentin L, et al. Anticoagulants in heart disease: current status and perspectives. Eur Heart J 2007;28(7):880–913. doi: 10.1093/eurheartj/ehl492.

[21] Warkentin TE, Greinacher A, Koster A. Bivalirudin. Thromb Haemost 2008;99(5):830–839. doi: 10.1160/TH07-10-0644.

[22] Caldeira D, Pereira H. Adjuvant antithrombotic therapy in ST-elevation myocardial infarction: a narrative review. Rev Port Cardiol 2019;38(4):289–297. doi: 10.1016/j.repc.2018.05.020.

[23] Witting JI, Bourdon P, Brezniak DV, et al. Thrombin-specific inhibition by and slow cleavage of hirulog-1. Biochem J 1992;283(Pt 3):737–743. doi: 10.1042/bj2830737.

[24] White HD. Pharmacological and clinical profile of bivalirudin in the treatment of patients with acute coronary syndrome. Expert Opin Drug Metab Toxicol 2009;5(5):529–538. doi: 10.1517/17425250902845646.

[25] Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med 2008;358(21):2218–2230. doi: 10.1056/NEJMoa0708191.

[26] Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012;33(20):2569–2619. doi: 10.1093/eurheartj/ehs215.

[27] Mehran R, Brodie B, Cox DA, et al. The Harmonizing Outcomes with RevasculariZatiON and Stents in Acute Myocardial Infarction (HORIZONS-AMI) Trial: study design and rationale. Am Heart J 2008;156(1):44–56. doi: 10.1016/j.ahj.2008.02.008.

[28] Stone GW, Witzenbichler B, Guagliumi G, et al. 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(9784):2193–2204. doi: 10.1016/S0140-6736(11)60764-2.
[29] Mehran R, Lansky AJ, Witzenbichler B, et al. Bivalirudin in patients undergoing primary angioplasty for acute myocardial infarction (HORIZONS-AMI): 1-year results of a randomised controlled trial. Lancet 2009;374(9696):1149–1159. doi: 10.1016/S0140-6736(09)61484-7.
[30] Steg PG, Van't Hof A, Hamm CW, et al. Bivalirudin started during emergency transport for primary PCI. N Engl J Med 2013;369 (23):2207–2217. doi: 10.1056/NEJMoa1311096.
[31] Stone GW, Mehran R, Goldstein P, et al. 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(1):27–38. doi: 10.1016/j.jacc.2014.10.029.
[32] Dangas GD, Schoos MM, Steg PG, et al. Early stent thrombosis and mortality after primary percutaneous coronary intervention in ST-segment-elevation myocardial infarction: a patient-level analysis of 2 randomized trials. Circ Cardiovasc Interv 2016;9(5):e003272. doi: 10.1161/CIRCINTERVENTIONS.115.003272.
[33] Food and Drug Administration, Maryland U.S.A. ANGIOMAX RTU (bivalirudin) injection, for intravenous use. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211215s000lbl.pdf. Accessed Dec 13, 2020.
[34] 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(9957):1849–1858. doi: 10.1016/S0140-6736(14)60924-7.
[35] Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2014;35(37):2541–2619. doi: 10.1093/eurheartj/ehu278.
[36] Valgimigli M. Design and rationale for the Minimizing Adverse haemorrhagic events by TRansradial access site and systemic Implementation of angioX program. Am Heart J 2014;168(6):838–845. e6. doi: 10.1016/j.ahj.2014.08.013.
[37] Valgimigli M, Frigoli E, Leonardi S, et al. Bivalirudin or unfractionated heparin in acute coronary syndromes. N Engl J Med 2015;373(11):997–1009. doi: 10.1056/NEJMoa1507854.
[38] Valgimigli M, Frigoli E, Leonardi S, et al. Radial versus femoral access and bivalirudin versus unfractionated heparin in invasively managed patients with acute coronary syndrome (MATRIX): final 1-year results of a multicentre, randomised controlled trial. Lancet 2018;392 (10150):835–848. doi: 10.1016/S0140-6736(18)31714-8.
[39] Garcia-Garcia HM, Picchi A, Sardella G, et al. Comparison of intra-procedural vs. post-stenting prolonged bivalirudin infusion for residual thrombus burden in patients with ST-segment elevation myocardial infarction undergoing: the MATRIX (Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and angioX) OCT study. Eur Heart J Cardiovasc Imaging 2019;20(12):1418–1428. doi: 10.1093/ehjci/jez040.
[40] Leonardi S, Frigoli E, Rothenbühler M, et al. Bivalirudin or unfractionated heparin in patients with acute coronary syndromes managed invasively with and without ST elevation (MATRIX): randomised controlled trial. BMJ 2016;354:i4935. doi: 10.1136/bmj.i4935.
[41] Erlinge D, Koul S, Eriksson P, et al. Bivalirudin versus heparin in non-ST and ST-segment elevation myocardial infarction-a registry-based randomized clinical trial in the SWEDEHEART registry (the VALIDATE-SWEDEHEART trial). Am Heart J 2016;175:36–46. doi: 10.1016/j.ahj.2016.02.007.
[42] Erlinge D, Omerovic E, Fröbert O, et al. Bivalirudin versus heparin monotherapy in myocardial infarction. N Engl J Med 2017;377 (12):1132–1142. doi: 10.1056/NEJMoa1706443.
[43] 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(13):1336–1346. doi: 10.1001/jama.2015.2323.
[44] Schulz S, Richardt G, Laugwitz KL, et al. Prasugrel plus bivalirudin vs. clopidogrel plus heparin in patients with ST-segment elevation myocardial infarction. Eur Heart J 2014;35(34):2285–2294. doi: 10.1093/eurheartj/ehu182.
[45] Venetsanos D, Lawesson SS, James S, et al. Bivalirudin versus heparin with primary percutaneous coronary intervention. Am Heart J 2018;201:9–16. doi: 10.1016/j.ahj.2018.03.014.
[46] Grimfjärd P, Erlinge D, Koul S, et al. Unfractionated heparin versus bivalirudin in patients undergoing primary percutaneous coronary intervention: a SWEDEHEART study. EuroIntervention 2017;12 (16):2009–2017. doi: 10.4244/EIJ-D-16-00884.
[47] Hasun M, Dörler J, Edlinger M, et al. In-hospital outcome comparing bivalirudin to heparin in real-world primary percutaneous coronary intervention. Am J Cardiol 2017;120(12):2135–2140. doi: 10.1016/j.amjcard.2017.08.037.
[48] Jovin IS, Shah RM, Patel DB, et al. Outcomes in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction via radial access anticoagulated with bivalirudin versus heparin: a report from the National Cardiovascular Data Registry. JACC Cardiovasc Interv 2017;10(11):1102–1111. doi: 10.1016/j.jcin.2017.03.021.
[49] Wang H, Liang Z, Li Y, et al. Effect of postprocedural full-dose infusion of bivalirudin on acute stent thrombosis in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention: outcomes in a large real-world population. Cardiovasc Ther 2017;35(3):e12251. doi: 10.1111/1755-5922.12251.
[50] Sirker A, Mamas M, Robinson D, et al. Bivalirudin, glycoprotein inhibitor, and heparin use and association with outcomes of primary percutaneous coronary intervention in the United Kingdom. Eur Heart J 2016;37(16):1312–1320. doi: 10.1093/eurheartj/ehv631.
[51] Secemsky EA, Kirtane A, Bangalore S, et al. Use and effectiveness of bivalirudin versus unfractionated heparin for percutaneous coronary intervention among patients with ST-segment elevation myocardial infarction in the United States. JACC Cardiovasc Interv 2016;9 (23):2376–2386. doi: 10.1016/j.jcin.2016.09.020.
[52] Kinnaird T, Yazji K, Thornhill L, et al. Post-procedural bivalirudin infusion following primary PCI to reduce stent thrombosis. J Interv Cardiol 2016;29(2):129–136. doi: 10.1111/joic.12280.
[53] Bheemarasetti MK, Shawar S, Chithri S, et al. Influence of access, anticoagulant, and bleeding definition on outcomes of primary percutaneous coronary intervention: early experience of an US Academic Center. Int J Angiol 2015;24(1):11–18. doi: 10.1055/s-0034-1394158.
[54] Limbruno U, Picchi A, Galli S, et al. Bivalirudin use in patients undergoing percutaneous coronary intervention for acute myocardial infarction. Insights from the prospective, multi-centre EUROVISION registry. Acute Card Care 2014;16(4):127–131. doi: 10.3109/17482941.2014.944542.
[55] Shelton R, Eftychiou C, Somers K, et al. Bivalirudin in patients undergoing primary percutaneous coronary intervention for acute ST-elevation myocardial infarction: outcomes in a large real-world population. EuroIntervention 2013;9(1):118–124. doi: 10.4244/EIJ-V9I1A17.
[56] Hibbert B, MacDougall A, Labinaz M, et al. Bivalirudin for primary percutaneous coronary interventions: outcome assessment in the Ottawa STEMI registry. Circ Cardiovasc Interv 2012;5(6):805–812. doi: 10.1161/CIRCINTERVENTIONS.112.968966.
[57] Pinto DS, Ogbonnaya A, Sherman SA, et al. Bivalirudin therapy is associated with improved clinical and economic outcomes in ST-elevation myocardial infarction patients undergoing percutaneous coronary intervention: results from an observational database. Circ Cardiovasc Qual Outcomes 2012;5(1):52–61. doi: 10.1161/CIRCOUTCOMES.111.961938.
[58] Bonello L, de Labriolle A, Roy P, et al. Head-to-head comparison of bivalirudin versus heparin without glycoprotein IIb/IIIa inhibitors in patients with acute myocardial infarction undergoing primary angioplasty. Cardiovasc Revasc Med 2009;10(3):156–161. doi: 10.1016/j.carrev.2008.12.005.
[59] Shah R, Rogers KC, Matin K, et al. An updated comprehensive meta-analysis of bivalirudin vs heparin use in primary percutaneous coronary intervention. Am Heart J 2016;171(1):14–24. doi: 10.1016/j.ahj.2015.10.006.
[60] Nairooz R, Sardar P, Amin H, et al. Meta-analysis of randomized clinical trials comparing bivalirudin versus heparin plus glycoprotein IIb/IIIa inhibitors in patients undergoing percutaneous coronary intervention and in patients with ST-segment elevation myocardial infarction. Am J Cardiol 2014;114(2):250–259. doi: 10.1016/j.amjcard.2014.04.033.
[61] Shah R, Latham SB, Porta JM, et al. Bivalirudin with a post-procedure infusion versus heparin monotherapy for the prevention of stent

thrombosis. Catheter Cardiovasc Interv 2019;94(2):210–215. doi: 10.1002/ccd.28065.
[62] Shah R, Jovin IS, Chaudhry A, et al. Safety and efficacy of switching from unfractionated heparin to bivalirudin during primary percutaneous coronary intervention. Catheter Cardiovasc Interv 2019;93(2):241–247. doi: 10.1002/ccd.27828.
[63] Shah R, Matin K, Rogers KC, et al. Effect of post-primary percutaneous coronary intervention bivalirudin infusion on net adverse clinical events and mortality: a comprehensive pairwise and network meta-analysis of randomized controlled trials. Catheter Cardiovasc Interv 2017;90 (2):196–204. doi: 10.1002/ccd.26859.
[64] Capodanno D, Gargiulo G, Capranzano P, et al. Bivalirudin versus heparin with or without glycoprotein IIb/IIIa inhibitors in patients with STEMI undergoing primary PCI: an updated meta-analysis of 10,350 patients from five randomized clinical trials. Eur Heart J Acute Cardiovasc Care 2016;5(3):253–262. doi: 10.1177/2048872615572599.
[65] Fahrni G, Wolfrum M, De Maria GL, et al. Prolonged high-dose bivalirudin infusion reduces major bleeding without increasing stent thrombosis in patients undergoing primary percutaneous coronary intervention: novel insights from an updated meta-analysis. J Am Heart Assoc 2016;5(7):e003515. doi: 10.1161/JAHA.116.003515.
[66] Shah R, Rogers KC, Ahmed AJ, et al. Effect of post-primary percutaneous coronary intervention bivalirudin infusion on acute stent thrombosis: meta-analysis of randomized controlled trials. JACC Cardiovasc Interv 2016;9(13):1313–1320. doi: 10.1016/j.jcin.2016.03.031.
[67] Ferrante G, Valgimigli M, Pagnotta P, et al. Bivalirudin versus heparin in patients with acute myocardial infarction: a meta-analysis of randomized trials. Catheter Cardiovasc Interv 2015;86(3):378–389. doi: 10.1002/ccd.25955.
[68] Kinnaird T, Medic G, Casella G, et al. Relative efficacy of bivalirudin versus heparin monotherapy in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention: a network meta-analysis. J Blood Med 2013;4:129–140. doi: 10.2147/JBM.S50595.
[69] Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2019;40 (2):87–165. doi: 10.1093/eurheartj/ehy394.
[70] Heestermans AA, van Werkum JW, Taubert D, et al. Impaired bioavailability of clopidogrel in patients with a ST-segment elevation myocardial infarction. Thromb Res 2008;122(6):776–781. doi: 10.1016/j.thromres.2008.01.021.
[71] Alexopoulos D, Xanthopoulou I, Gkizas V, et al. Randomized assessment of ticagrelor versus prasugrel antiplatelet effects in patients with ST-segment-elevation myocardial infarction. Circ Cardiovasc Interv 2012;5 (6):797–804. doi: 10.1161/CIRCINTERVENTIONS.112.972323.
[72] Liang Z, Li Y, Wang J, et al. The safety and effectiveness of bivalirudin in female patients with acute myocardial infarction undergoing primary angioplasty: A subgroup analysis of the BRIGHT trial. Catheter Cardiovasc Interv 2016;87(Suppl 1):608–615. doi: 10.1002/ccd.26407.
[73] Wang H, Li Y, Cong H, et al. Efficiency and safety of bivalirudin in patients undergoing emergency percutaneous coronary intervention via radial access: a subgroup analysis from the bivalirudin in acute myocardial infarction versus heparin and GPI plus heparin trial. Catheter Cardiovasc Interv 2017;89(7):1157–1165. doi: 10.1002/ccd.26804.
[74] Cavender MA, Faxon DP. Can BRIGHT restore the glow of bivalirudin. JAMA 2015;313(13):1323–1324. doi: 10.1001/jama.2015.2345.
[75] 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(1 Pt B):214–220. doi: 10.1016/j.jcin.2014.11.002.
[76] Gargiulo G, Carrara G, Frigoli E, et al. Post-procedural bivalirudin infusion at full or low regimen in patients with acute coronary syndrome. J Am Coll Cardiol 2019;73(7):758–774. doi: 10.1016/j.jacc.2018.12.023.
[77] Chen W, Lu D, Huang Z, et al. Is a prolongation of bivalirudin infusion needed in patients with STEMI undergoing percutaneous coronary intervention. Catheter Cardiovasc Interv 2019;94(6):898–899. doi: 10.1002/ccd.28368.
[78] Zeymer U. Why did VALIDATE-SWEDEHEART not validate the results of HORIZONS. J Thorac Dis 2018;10(1):35–37. doi: 10.21037/jtd.2017.11.126.
[79] Feldman A, Suleiman K, Bushari L, et al. Bivalirudin versus unfractionated heparin during percutaneous coronary intervention in patients at high risk for bleeding. Int J Angiol 2014;23(4):227–232. doi: 10.1055/s-0034-1372244.
[80] Kilic S, Van't Hof AW, Ten Berg J, et al. Frequency and prognostic significance of access site and non-access site bleeding and impact of choice of antithrombin therapy in patients undergoing primary percutaneous coronary intervention. The EUROMAX trial. Int J Cardiol 2016;211:119–123. doi: 10.1016/j.ijcard.2016.02.131.
[81] Verheugt FW, Steinhubl SR, Hamon M, et al. Incidence, prognostic impact, and influence of antithrombotic therapy on access and nonaccess site bleeding in percutaneous coronary intervention. JACC Cardiovasc Interv 2011;4(2):191–197. doi: 10.1016/j.jcin.2010.10.011.
[82] Mina GS, Gobrial GF, Modi K, et al. Combined use of bivalirudin and radial access in acute coronary syndromes is not superior to the use of either one separately: meta-analysis of randomized controlled trials. JACC Cardiovasc Interv 2016;9(15):1523–1531. doi: 10.1016/j.jcin.2016.05.023.
[83] Perdoncin E, Seth M, Dixon S, et al. The comparative efficacy of bivalirudin is markedly attenuated by use of radial access: insights from Blue Cross Blue Shield of Michigan Cardiovascular Consortium. Eur Heart J 2016;37(24):1902–1909. doi: 10.1093/eurheartj/ehv434.
[84] Hamon M, Coste P, Van't Hof A, et al. Impact of arterial access site on outcomes after primary percutaneous coronary intervention: prespecified subgroup analysis from the EUROMAX trial. Circ Cardiovasc Interv 2015;8(6):e002049. doi: 10.1161/CIRCINTERVENTIONS.114.002049.
[85] Venetsanos D, Sederholm Lawesson S, Fröbert O, et al. Sex-related response to bivalirudin and unfractionated heparin in patients with acute myocardial infarction undergoing percutaneous coronary intervention: A subgroup analysis of the VALIDATE-SWEDEHEART trial. Eur Heart J Acute Cardiovasc Care 2019;8(6):502–509. doi: 10.1177/2048872618803760.
[86] Qaderdan K, Vos GA, McAndrew T, et al. Outcomes in elderly and young patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention with bivalirudin versus heparin: Pooled analysis from the EUROMAX and HORIZONS-AMI trials. Am Heart J 2017;194:73–82. doi: 10.1016/j.ahj.2017.08.009.
[87] Bikdeli B, McAndrew T, Crowley A, et al. Individual patient data pooled analysis of randomized trials of bivalirudin versus heparin in acute myocardial infarction: rationale and methodology. Thromb Haemost 2020;120(2):348–362. doi: 10.1055/s-0039-1700872.
[88] Capodanno D, Angiolillo DJ. Pooling the evidence at the patient level: end of the bivalirudin saga. Thromb Haemost 2020;120(2):191–193. doi: 10.1055/s-0039-3400743.

How to cite this article: Li Y, Li Y, Stone GW, Han Y. Bivalirudin in Primary PCI: Can Its Glory Being Restored? Cardiol Discov 2021;1(3):179–194. doi: 10.1097/CD9.0000000000000016