Bivalirudin for acute coronary syndromes: premises, promises and doubts

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Summary

Bivalirudin is a valuable anticoagulant option in patients with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention. Advantages over heparin as a parenteral anticoagulant include more predictable pharmacokinetics and pharmacodynamics, shorter half-life, no need for cofactors, some degree of antiplatelet effect, and the ability to inhibit clot-bound thrombin. Clinical evidence supporting the use of bivalirudin over heparin in current ACS guidelines, however, derives mostly from early randomised trials that may no longer reflect current management patterns, now including the use of oral antiplatelet agents more potent than clopidogrel (i.e. prasugrel or ticagrelor) and a broader implementation of strategies to reduce bleeding (i.e. radial access for percutaneous coronary intervention, and use of glycoprotein IIb/IIIa inhibitors only in bailout situations). Defining the fine balance between bivalirudin efficacy and safety over heparins in the context of other antithrombotic treatments remains a challenge in clinical practice, particularly in a fast-evolving scenario, such as ACS, where numerous new trials have been presented in very recent times. Here we provide an up-to-date overview of the evidence on the use of bivalirudin in ACS, with focus on new data, open issues, and future directions.

Keywords

Bivalirudin, anticoagulants, heparin, acute coronary syndromes, percutaneous coronary intervention

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Introduction

Thrombosis is the main pathophysiological mechanism in acute coronary syndromes (ACS), and involves the activation of platelets and coagulation. This latter pathogenetic mechanism is interfered with by anticoagulants (1). Direct thrombin inhibitors are a class of anticoagulants that act by directly inhibiting the thrombin active site, therefore by a mechanism different from that of heparins (►Figure 1) (1, 2). Among them, bivalirudin is a 20-aminoacid parenteral synthetic analog of hirudin that interacts directly with both the active site and the substrate binding of thrombin (1). Once combined with thrombin, the drug is slowly cleaved, hence allowing the enzyme to restore its haemostatic function (2). Clearance from plasma occurs through a combination of enzymatic degradation and renal excretion, the latter accounting for about 20% of the clearance. Because the elimination of bivalirudin is linearly related to renal function, the infusion dose needs to be adjusted in patients with advanced chronic kidney disease (3). Global coagulation tests (i.e. activated partial thromboplastin time, partial thromboplastin time) are non-linearly prolonged by bivalirudin, which makes these tests relatively unreliable to predict under- or overdosing. Although routine monitoring is not needed with bivalirudin, ecarin clotting time more reliably reflects plasma concentrations than activated clotting time. On the downside, bivalirudin lacks an established antidote, but the half-life – only 25 minutes (min) after intravenous injection – makes this an issue of relatively little relevance.

Overall, several features of bivalirudin make it a valuable alternative to heparins (either unfractionated heparin [UFH] or low-molecular-weight heparin, i.e. enoxaparin) in patients who need anticoagulation in the setting of an ACS with or without an associated percutaneous coronary intervention (PCI) (►Table 1). Unlike heparins, bivalirudin does not bind to plasma proteins, does not need combination with antithrombin III to exert its pharmacological action, and is not neutralised by platelet factor 4 antibodies, resulting in more predictable pharmacokinetics, pharmacodynamics and anticoagulant effects. Of note, direct inhibition by bivalirudin is not limited only to fluid-phase thrombin but also to fibrin-bound thrombin, resulting – theoretically – in a more effective and targeted antithrombotic action. Also, bivalirudin exerts some degree of antiplatelet effect by blocking platelet protease-activated 1 and 4 receptors (PAR-1 and -4), which are typically activated by thrombin. Finally, the lack of platelet factor 4 binding eliminates the risk of heparin-induced thrombocytopenia (1, 2).

►Table 2 summarises current recommendations for anticoagulation with bivalirudin in ACS. In the United States (US), both the 2012 non-ST-segment elevation ACS (NSTE-ACS) and the 2013 ST-segment elevation myocardial infarction (STEMI)

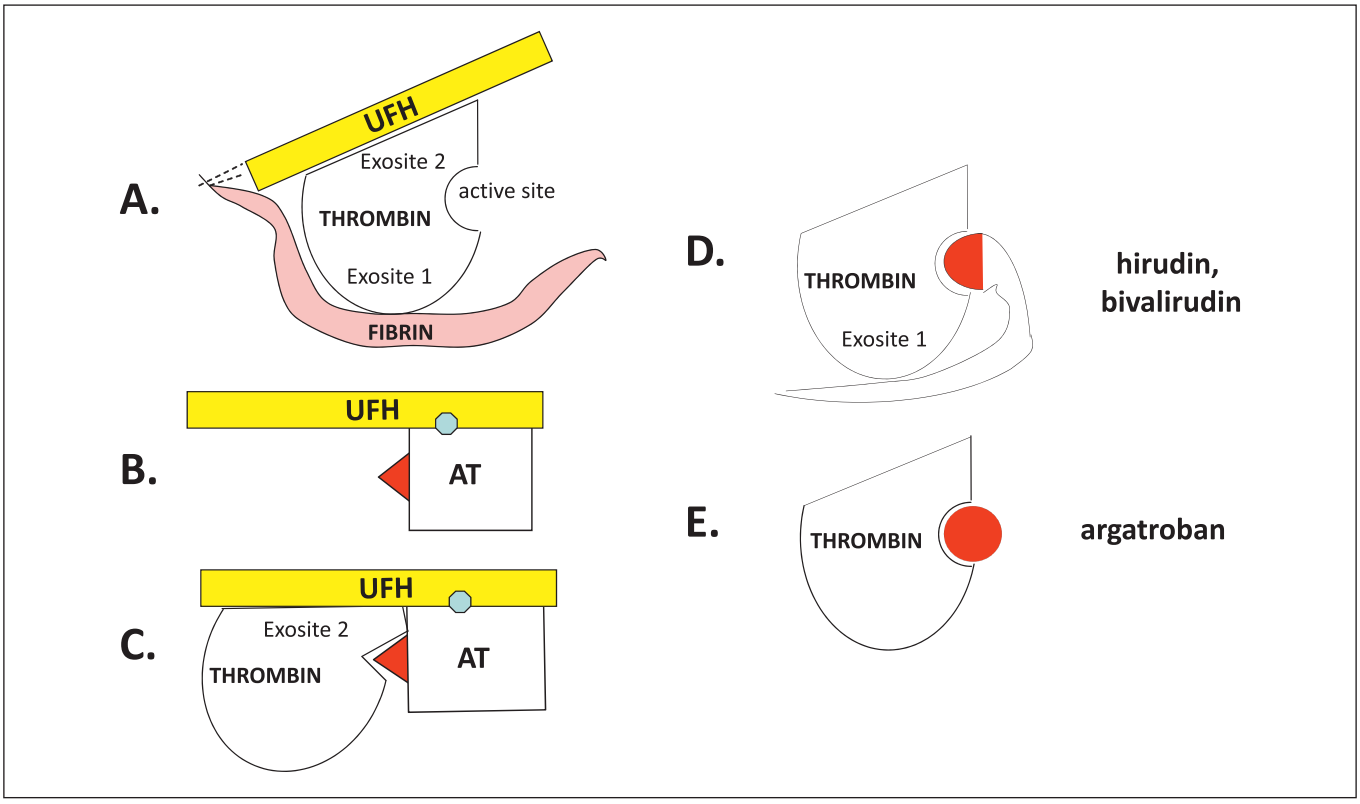

Figure 1: Mechanisms of action of different thrombin inhibitors. A) The ternary UFH/thrombin/fibrin complex increases the affinity of thrombin for its fibrin substrate and lessens the ability of the heparin-antithrombin (AT) complex to inhibit thrombin. Heparin binding to thrombin occurs through a domain of the thrombin molecule termed exosite 2, while binding of thrombin to its substrate fibrinogen, allowing the steric configuration of the complex necessary for thrombin to exert its enzymatic action, occurs through a thrombin domain known as exosite 1. UFH and LMWH (this latter not shown in this context) both possess the pentasaccharide unit (azure dot) necessary for their interaction with AT (B). The UFH/AT complex is able to block the thrombin active site, with AT blocking the active site and UFH keeping thrombin in the proper steric configuration (through its binding to exosite 2) for AT to exert its action (C). Hirudin and bivalirudin bind to thrombin via the active site as well as exosite 1, displacing thrombin from fibrin (D). The parenteral direct thrombin inhibitor argatroban only blocks the thrombin active site (E). Adapted with permission from De Caterina et al. (2).

guidelines recommend bivalirudin with a class I indication (4, 5). The level of evidence for these recommendations is B, reflecting the notion that the evidence supporting the use of bivalirudin in NSTE-ACS and STEMI, at the time of guidelines publication, came at best from a single randomised clinical trial in each setting (6, 7). In contrast, in Europe, the newer 2014 guidelines for myocardial revascularisation assign a class I (level of evidence A) recommendation for anticoagulation with bivalirudin in NSTE-ACS, but a lower class IIa (level of evidence A) in STEMI (8). Indeed, early phase III trials conducted in the ACS setting highlighted the ability of bivalirudin to reduce bleeding complications while maintaining comparable efficacy vs the combination of UFH and glycoprotein IIb/IIIa inhibitors (GPIs). Since the US guidelines publication, however, at least four new randomised clinical trials have been published (9–12). Such trials in some cases reinforce the evidence for using bivalirudin in ACS, whereas in other cases, particularly in STEMI, cast doubts on the superior safety-efficacy balance of the drug as compared with heparin in combination with routine or bailout use of GPIs. Hence, the different time of publication explains most of the current discrepancy between US and European guidelines regarding recommendations and/or levels of evidence for bivalirudin. A 2014 European Expert Consensus Document for orally anticoagulated patients with atrial fibrillation who present with an ACS and/or undergo PCI has been recently made available, assigning a IIa class of recommendation (level of evidence B) to bivalirudin as an alternative to UFH in NSTE-ACS undergoing PCI, regardless of the bleeding risk (13).

Overall, the available trials of bivalirudin in NSTE-ACS and STEMI differ for a number of considerations that include the study design, control arms, patient populations, drug dosages, the use (upstream or downstream) of GPIs, arterial access (i.e. femoral or radial), and adjunctive oral antiplatelet agents (i.e. clopidogrel, prasugrel, or ticagrelor). Two recent meta-analyses consistently concluded that in patients undergoing PCI across the broad spectrum of coronary artery disease, bivalirudin appears to reduce the risk of bleeding at the expense of a higher risk of stent thrombosis when compared with a heparin-based regimen (14, 15). On this background, defining the fine balance between efficacy and safety of different alternatives for anticoagulation remains a challenge in clinical practice, and particularly the role of bivalirudin as the default anticoagulant to support PCI in ACS patients remains controversial in an era of economic constraints (16). This article

Attribute	UFH	Enoxaparin	Bivalirudin
Target	FXa > thrombin	FXa >>> thrombin	Thrombin
Action independent of antithrombin III	No	No	Yes
Inhibition of fibrin-bound thrombin	No	No	Yes
Protein binding	Yes	Yes	No
Bioavailability*	Low	High	High**
Variable PK-PD	Yes	No	No
Need for renal adjustment	No	Yes	Yes
Neutralising agent	Protamine sulfate	Protamine sulfate	Not available
Activation of platelets	Yes	Yes	No
PF-4 complexing and risk of HIT	Yes	Yes	No
$t_{1/2}$	30–150 min	4.5 hours*	25 min

*subcutaneous route. **for bivalirudin the only approved route of administration is intravenous. FXa = activated Factor X; HIT = heparin-induced thrombocytopenia; PD = pharmacodynamics; PK = pharmacokinetics; UFH = unfractionated heparin.

Table 1: Key differences between heparins and bivalirudin.

provides an up-to-date overview of the currently available evidence on the use of bivalirudin in ACS. In particular, the most recent randomised clinical trials and large registries of bivalirudin in NSTE-ACS and STEMI are put in perspective. Open issues of bivalirudin will be also discussed.

Bivalirudin in patients with non ST-segment elevation acute coronary syndromes

Details of trials of bivalirudin in NSTE-ACS are listed in ▶Table 3. In the open-label Acute Catheterization and Urgent Intervention Triage strategY (ACUITY) trial, 13,819 patients with NSTE-ACS were randomised 1:1:1 to bivalirudin, bivalirudin plus GPIs or heparin (either UFH or enoxaparin) plus GPIs (6). The trial was powered for three primary endpoints, including a composite ischaemic endpoint (all-cause death, reinfarction, or unplanned revascularisation for ischaemia), major bleeding; and a net clinical benefit endpoint, defined as the combination of the composite ischaemic endpoint and major bleeding. Compared with the combination of heparins plus GPIs, bivalirudin was associated with a non-inferior rate of the composite ischaemic endpoint at 30 days; and significant 47 % and 14 % relative reductions in major bleeding and in the net clinical benefit endpoint, respectively. Conversely, the use of bivalirudin in combination with GPIs was associated with non-inferior 30-day rates of the composite ischaemic endpoint, major bleeding and the net clinical benefit endpoint compared with heparins plus GPIs (6).

The Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 4 (ISAR-REACT 4) trial (n=1,721) compared bivalirudin and the combination of heparin plus GPIs in NSTE-ACS but, differently from ACUITY 1) included only high-risk patients with positive biomarkers undergoing PCI (whereas ACUITY also included patients with unstable angina); 2) UFH was the only heparin used in the control arm (whereas in ACUITY the use of enoxaparin was allowed in the heparin plus GPIs arm); 3) GPIs were administered only after the guidewire had crossed the lesion (whereas in ACUITY, patients assigned to heparin plus GPIs or bivalirudin plus GPIs were randomly assigned, in a two-by-two factorial design, to upstream or

Table 2: Recommendations for bivalirudin use in acute coronary syndromes.

	Europe	United States
NSTE-ACS	Bivalirudin (0.75 per kg i. v. bolus, followed by i. v. infusion 1.75 mg/kg/h for up to 4 h after the procedure) is recommended as alternative to UFH plus GPI during PCI. (Class I, LOE A).	For patients in whom an invasive strategy is selected, regimens with established efficacy include [omissis] bivalirudin (class I, LOE B).
STEMI	Bivalirudin (0.75 per kg i. v. bolus, followed by i. v. infusion 1.75 mg/kg/hour for up to 4 h after the procedure (Class IIa, LOE A).	To support reperfusion with primary PCI: bivalirudin 0.75 mg/kg i.v. bolus, then 1.75 mg/kg/h infusion with or without prior treatment with UFH. An additional bolus of 0.3 mg/kg may be given if needed. Reduce infusion to 1 mg/kg/h with estimated creatinine clearance <30 mL/min (class I, LOE B).

GPI = glycoprotein IIb/IIIa inhibitors; i.v.= intravenous; LOE = level of evidence; NSTE-ACS = non-ST-segment elevation acute coronary syndromes; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; UFH = unfractionated heparin.

Table 3: Randomised clinical trials of bivalirudin in NSTE-ACS.

	ACUITY (6)		ISAR-REACT 4 (9)	
Centres	450		8	
Population	UA/NSTEMI		NSTEMI	
Primary endpoint	1)All-cause death, reinfarction, unplanned revascularisation at 30 days 2)Major bleeding at 30 days 3)Net composite of ischaemia and major bleeding at 30 days		All-cause death, large reinfarction, urgent TVR, or major bleeding at 30 days	
Major bleeding definition	Intracranial or intraocular bleeding, haemorrhage at the access site requiring intervention, haematoma with a diameter of at least 5 cm, a reduction in haemoglobin levels of at least 4 g/dl without an overt bleeding source or at least 3 g/dl with such a source, reoperation for bleeding, or transfusion of a blood product		Intracranial, intraocular, or retroperitoneal haemorrhage; a decrease in the haemoglobin level of more than 40 g/l plus either overt bleeding or the need for transfusion of 2 or more units of packed red cells or whole blood	
Treatment	**Bivalirudin arms:** 0.1 mg/kg bolus followed by 0.25 mg/kg/h infusion before angiography; before PCI 0.75 mg/kg bolus followed by 1.75 mg/kg/h infusion for the duration of PCI **Heparin arm:** UFH 60 UI/kg; enoxaparin 0.3–0.75 mg/kg bolus		**Bivalirudin arm:** 0.75 mg/kg bolus followed by 1.75 mg/kg/h infusion for the duration of PCI **Heparin arm:** UFH 70 UI/kg	
GPI type	Any (abciximab, eptifibatide or tirofiban)		abciximab	
GPI timing	Upstream or downstream		Downstream	
Clopidogrel dose	At the discretion of the investigator		600 mg	
Clopidogrel timing	At the discretion of the investigator		Before any study drug	
	Bivalirudin	**Bivalirudin+GPI**	**Bivalirudin**	**Heparin+GPI**
Patients (N)	4612	4604	860	861
Age (Year)	63	63	67.5	67.5
Female	30.7 %	30.1 %	23.1 %	23.2 %
Positive biomarkers	60.3 %	58.5 %	100 %	100 %
Clopidogrel	100 %	100 %	100 %	100 %
GPI (upstream)	0.7 %	48.8 %	0 %	0 %
GPI (downstream)	9.1 %	96.7 %	0 %	100 %
GPI (bailout)	NA	NA	0 %	0 %
Angiography performed	98.9 %	98.8 %	100 %	100 %
PCI performed	56.8 %	56.7 %	99.8 %	99.8 %

CABG = coronary artery bypass grafting; CVA = cerebrovascular accidents; GPI = glycoprotein IIb/IIIa inhibitors; NA = not available; NSTEMI = non ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; TLR = target-lesion revascularisation; TVR = target-vessel revascularization; UA = unstable angina; UFH = unfractionated heparin.

downstream treatment with GPIs); 4) abciximab was the only GPI used in the control arm (whereas in ACUITY the use of tirofiban or eptifibatide was permitted); 5) clopidogrel 600 mg was given before any study drug (whereas in ACUITY the initial dose and timing of clopidogrel were left to the discretion of the investigator); 6) the definition of major bleeding was less sensitive (Table 3) (9). The primary endpoint was a composite of death, large recurrent myocardial infarction, urgent target-vessel revascularisation, or major bleeding within 30 days. There were no differences between bivalirudin and UFH plus GPIs in the primary endpoint at 30 days, and no differences were described in ischaemic endpoints up to one year (9, 17). However, bivalirudin was associated with significantly less major bleeding at 30 days (2.6 % vs 4.6 %, p=0.02) (8). Interestingly, on-clopidogrel high platelet reactivity was found to affect significantly the ischaemic outcomes of patients treated with bivalirudin, but did not affect those of patients treated with UFH plus GPIs, a finding that underscores the importance of potent in-lab platelet inhibition coupled with anticoagulation (18).

A pooled analysis of 3,798 patients with NSTEMI undergoing PCI in the ACUITY and ISAR-REACT 4 trials recently showed a 46 % reduction in major bleeding at 30 days with bivalirudin compared with heparin plus GPIs, whereas the risk of ischaemic

complications was not affected (19). The treatment effect of bivalirudin was consistent across multiple subgroups and independent of the type of heparins (i.e. UFH or enoxaparin) and GPIs (i.e. abciximab, eptifibatide or tirofiban) used in the control group. A recent report from the Evaluation of Drug-Eluting Stents and Ischaemic Events (EVENT) registry found similar results in 1,036 propensity-matched pairs of patients treated with bivalirudin or UFH monotherapy (20).

Overall, the net composite outcome of ischaemia and bleeding seems not to be significantly different between bivalirudin and heparins plus a GPI in patients with NSTE-ACS undergoing PCI after clopidogrel pretreatment. Although no significant differences in efficacy are seen in terms of reduction of adverse ischaemic events, bivalirudin has been consistently shown to be superior to heparins plus GPIs in terms of reducing bleeding events. Evidence from a single relatively large registry suggests that even compared with heparin monotherapy bivalirudin might result in potential reduction of bleeding in NSTEMI patients undergoing PCI.

Bivalirudin in patients with ST-segment elevation myocardial infarction

Bivalirudin characteristics theoretically make it an attractive option for anticoagulation of patients with STEMI undergoing fibrinolysis. Indeed, inadequate thrombin inhibition at the thrombus site may be partly responsible for the potential procoagulant effect of fibrinolysis despite the use of heparin (21). In the Hirulog Early Reperfusion/Occlusion (HERO) trial, 412 STEMI patients were randomised to UFH, low-dose bivalirudin (at that time termed "hirulog") or high-dose bivalirudin on top of aspirin and streptokinase (22). The primary endpoint was Thrombolysis In Myocardial Infarction (TIMI) grade 3 flow of the infarct-related artery at 90 to 120 min, which occurred less frequently with UFH compared with low-dose or high-dose bivalirudin. Bivalirudin significantly reduced major bleeding, and there were no differences among groups in the rates of re-occlusion at 48 hours (h) and of death, cardiogenic shock or reinfarction at 35 days. In the subsequent and larger HERO-2 trial, 17,073 STEMI patients undergoing fibrinolysis with streptokinase were randomised to an intravenous bolus and a 48-h infusion of either bivalirudin or UFH (23). There were no differences in the primary endpoint of all-cause mortality at 30 days between patients treated with bivalirudin and those treated with UFH. However, patients treated with bivalirudin had significantly fewer reinfarctions within 96 h, suggesting that early and more efficient inhibition of thrombin may play a role against reocclusion. Despite numerically less severe bleeding and intracranial haemorrhages with bivalirudin, small absolute increases were seen in mild and moderate bleeding events.

►Table 4 and ►Table 5 illustrate key features and differences in trials of bivalirudin conducted in patients with STEMI mainly referred to primary PCI. The landmark Harmonizing Outcomes with Revascularisation and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial (n=3,602) demonstrated that bivalirudin plus provisional GPIs is more effective than the combination of UFH and routine GPIs in reducing major bleeding and the combined endpoint of all-cause death, re-infarction, repeat revascularisation, definite stent thrombosis, stroke, or major bleeding both at 30 days and 1 year (7, 24). Although the trial highlighted a worrisome increase in acute stent thrombosis with bivalirudin (1.3% vs 0.3%, p<0.001), all-cause death and cardiac death were both higher with UFH plus GPIs at 30 days. Notably, the develop-

Table 4: Randomised clinical trials of bivalirudin in STEMI.

	HORIZONS AMI (7)	EUROMAX (10)	BRIGHT	HEAT PPCI (12)	BRAVE-4 (11)
Centres	123	65	82	1	3
Primary endpoint	All-cause death, re-infarction, TVR, definite stent thrombosis, stroke, or major bleeding at 30 days	All-cause death or non-CABG related major bleeding at 30 days	All-cause death, re-infarction, TVR, ischaemic stroke and bleeding events at 30 days	All-cause death, CVA, re-infarction or TLR at 28 days	All-cause death, re-infarction, TVR, definite stent thrombosis, stroke, or major bleeding at 30 days
Treatment	**Bivalirudin arm:** 0.75 mg/kg bolus followed by 1.75 mg/kg/h infusion for the duration of the procedure and optional 0.25 mg/kg/h after the procedure **Heparin arm:** UFH 60 UI/kg	**Bivalirudin arm:** 0.75 mg/kg bolus followed by 1.75 mg/kg/h infusion for the duration of the procedure and 0.25–1.75 mg/kg/h for at least 4 hours after the procedure **Heparin arm:** UFH 100 UI/kg without a GPI or 60 UI/kg with a GPI; enoxaparin 0.5 mg/kg bolus **GPI:** optional in both groups	**Bivalirudin arm:** 0.75 mg/kg bolus followed by 1.75 mg/kg/h infusion for the duration of the procedure **Heparin arm:** UFH 100 UI/kg without a GPI or 60 UI/kg with a GPI Heparin+GPI arm: UFH 60 UI/kg + tirofiban 10 µg/kg bolus followed by 0.15 µg/kg/min for the duration of the procedure	**Bivalirudin arm:** 0.75 mg/kg bolus followed by 1.75 mg/kg/h infusion for the duration of the procedure **Heparin arm:** UFH 70 UI/kg GPI: only for bailout use in both groups	**Bivalirudin arm:** 0.75 mg/kg bolus followed by 1.75 mg/kg/h infusion for the duration of the procedure **Heparin arm:** UFH 70–100 UI/kg

CABG = coronary artery bypass grafting; CVA = cerebrovascular accidents; GPI = glycoprotein IIb/IIIa inhibitors; TLR = target-lesion revascularisation; TVR = target-vessel revascularisation; UFH = unfractionated heparin.

Table 5: Baseline and procedural characteristics of patients included in randomised clinical trials of bivalirudin in STEMI.

	HORIZONS AMI (7)		EUROMAX (10)		BRIGHT		HEAT PPCI (12)		BRAVE-4 (11)	
	Bivalirudin	Heparin	Bivalirudin	Heparin	Bivalirudin	Heparin	Bivalirudin	Heparin	Bivalirudin	Heparin
Patients (N)	1800	1802	1089	1109	728	1450	914	915	271	277
Age (Year)	59.8	60.7	61	62	57	58	62.9	63.6	61.4	61.4
Female	22.9 %	23.9 %	25.3 %	22.4 %	17 %	18 %	28.5 %	26.9 %	24 %	21 %
Clopidogrel	99 %	99 %	50.0 %	51.5 %	100 %	100 %	11.8 %	10.0 %	3.7 %	90.2 %
Prasugrel	0 %	0 %	30.8 %	28.9 %	0 %	0 %	27.3 %	27.6 %	94.6 %	7.1 %
Ticagrelor	0 %	0 %	19.2 %	19.4 %	0 %	0 %	61.2 %	62.7 %	0 %	0 %
GPI (upstream)	0 %	97.7 %	3.9 %	58.5 %	0 %	50.1 %	0 %	0 %	0 %	0 %
GPI (bailout)	7.5 %	0 %	7.9 %	25.4 %	4.4 %	5.7 %	13.5 %	15.5 %	3.0 %	6.1 %
Radial access	NA	NA	47.7 %	46.3 %	78.5 %	78.8 %	80.3 %	82.0 %	0 %	0 %
STEMI	100 %	100 %	100 %	100 %	89 %	87 %	100 %	100 %	100 %	100 %
PCI performed	91.3 %	90.3 %	86.6 %	85.3 %	100 %	100 %	83.0 %	81.6 %	88.6 %	86.6 %

NA = not available; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction.

ment of intra-procedural thrombotic events was associated with subsequent adverse outcomes, including death at 30 days, thus underscoring the need for investigating additional strategies to decrease acute stent thrombosis during primary PCI (25).

In the European Ambulance Acute Coronary Syndrome Angiography (EUROMAX) trial (n=2,218), the comparative effectiveness of bivalirudin and heparin was re-assessed in a more contemporary practice setting characterised by prehospital initiation of treatment, use of newer oral antiplatelet agents and radial artery access (10). GPI use in the bivalirudin arm was recommended only in the presence of a large thrombus or of microvascular obstruction, while in the heparin arm was left to the operator's preference. Overall, the upstream use of GPIs occurred in 3.9 % and 58.5 % of patients randomised to bivalirudin and heparin, respectively, and bailout use occurred in 7.9 % and 25.4 %, respectively. Differently from HORIZONS-AMI, the protocol specified that the infusion of bivalirudin was to be continued for at least 4 h after PCI, either at the higher dose used during PCI (which occurred in 22.5 % of patients) or at the lower maintenance dose. The primary outcome was a composite of death or major bleeding not associated with coronary artery bypass grafting (CABG) at 30 days. There was a 40 % relative reduction with bivalirudin in the 30-day risk of the primary outcome, driven by a significant reduction in major bleeding. However, the risk of stent thrombosis remained higher with bivalirudin (1.1 % vs 0.2 %, p=0.007) (10). A subanalysis of EUROMAX focused on the interaction between the treatment effect of bivalirudin and the mode (routine vs bailout) of GPI administration in the heparin arm (26). Patients who received bivalirudin (n=1,089) were compared with those who received heparin and routine GPIs (n=649) and with those who received heparin with bailout GPIs (n=460). There was a significant 33 % relative risk reduction in the primary endpoint with bivalirudin vs heparin plus routine GPIs (5.1 % vs 7.6 %, P=0.034) and a 48 % significant relative risk reduction vs heparin plus bailout GPIs (5.1 % vs 9.8 %, p=0.0006), whereas no differences were noted between the two heparin plus GPIs groups. Similar to the main study, the benefit of bivalirudin was driven by significant reductions in major bleeding. Stent thrombosis was numerically more frequent with bivalirudin, irrespective of the heparin control. Although prespecified, this subanalysis represents a post-randomisation comparison within the context of an open-label trial; hence its conclusions should be regarded only as hypothesis-generating. A second subanalysis explored the impact of prolonging the infusion of bivalirudin at the higher dose given during PCI (1.75 mg/kg/h) instead of the reduced dose (0.25 mg/kg/h) (27). The rates of acute stent thrombosis were 0.2 % in the arm with heparin with or without GPIs, 1.6 % in the reduced-dose bivalirudin arm, and 0.4 % in the extended PCI bivalirudin dose arm. On multivariable analysis, the use of low-dose bivalirudin was independently associated with an almost eight-fold increased risk of stent thrombosis, whereas the use of prasugrel or ticagrelor was found to have no impact. Major bleeding was lower with bivalirudin compared with heparin irrespective of the post-PCI infusion strategy. This analysis suggests that the risk of acute stent thrombosis in EUROMAX was confined to the first few hours after PCI, with low-dose bivalirudin and newer $P2Y_{12}$ inhibitors exerting no protective effect. In contrast, a prolonged infusion of bivalirudin at the PCI dose was shown to be safe and was not associated with a higher risk of acute stent thrombosis compared with heparin with or without GPIs.

Another three-arm trial named Bivalirudin foR acute myocardial Infarction underGoing angioplasty in CHinese patienTs (BRIGHT) randomised Chinese patients with acute myocardial infarction (mostly STEMI, occurring in 90 % of the population) to bivalirudin alone, UFH alone or UFH plus tirofiban (unpublished data, presented at Chinese Interventional Therapeutics 2014 Scientific Session, Shanghai, and updated at Transcatheter Cardio-

vascular Therapeutics 2014 Scientific Sessions, Washington DC). The primary endpoint was the net composite of ischaemic and bleeding events at 30 days, which occurred less frequently with bivalirudin compared with UFH alone or UFH plus tirofiban, driven by a significant reduction in bleeding endpoints, including Bleeding Academic Research Consortium (BARC) class 3 or 5 bleeding events. In contrast, there were no differences across groups in the ischaemic components of the primary endpoint, and no differences in acute stent thrombosis. Patients treated with UFH alone had similar outcomes compared with those treated with UFH plus tirofiban.

The How Effective are Antithrombotic Therapies in Primary PCI (HEAT-PPCI) trial recently challenged the paradigm of bivalirudin as the safest anticoagulant in the setting of primary PCI by focusing on its relative performance vs UFH with no confounding effect arising from differential GPI use (12). Specifically, GPIs were allowed only for bailout use in both patients randomised to bivalirudin (n=905) and those randomised to UFH (n=907). Due to a strategy of delayed informed consent (i.e. patients were randomised and treated with no discussion in the acute phase and later approached in the recovery phase for full informed consent), all eligible patients were randomised, thereby reflecting, despite the contentions raised by a policy of later acquisition of the informed consent, a representative real-world population. Prasugrel and ticagrelor were used in about 90% of patients, a radial approach was used in 80%, and GPIs were given to 13% and 15% of patients treated with bivalirudin and UFH, respectively. The primary outcome was the composite of all-cause mortality, cerebrovascular accidents, recurrent infarction (both in hospital and after discharge [28]), and additional, unplanned target lesion revascularisation. The trial showed a significant 52% higher rate of the primary efficacy outcome with bivalirudin, with event curves separating early as a reflection of the substantial early hazard occurring with bivalirudin. The advantage of heparin was noted in all the components of the primary endpoint, and definite or probable stent thrombosis, mostly acute, was significantly higher with bivalirudin (3.4% vs 0.9%, p=0.001). There were no differences in major (BARC 3 or 5) and minor bleeding between the bivalirudin and heparin groups. Concerns over the findings from the HEAT-PPCI trial have been raised, including its open-label, single-centre design, the fact that only 82% of patients randomised underwent primary PCI, possible under-dosing of bivalirudin, and the lack of concordance with previous trials of bivalirudin in which a safety benefit was consistently noted in the comparison with heparin. However, these latter findings may be partly explained by the notion that previous trials used high doses of heparin and/or GPIs followed by prolonged infusion (►Table 4), two factors that are expected to increase the risk of bleeding complications in the control group (29).

The Bavarian Reperfusion Alternatives Evaluation 4 (BRAVE-4) trial aimed at assessing the putative synergistic effects of the combination of prasugrel and bivalirudin in reducing ischaemic and bleeding complications through a comparison with the combination of UFH and clopidogrel (11). However, the study was prematurely interrupted for the slow recruitment rate at about 46% of the originally planned sample size, thereby its results should be regarded as exploratory only. In this perspective, there was no difference in the primary endpoint, a composite of death, myocardial infarction, unplanned revascularisation of the infarct-related artery, stent thrombosis, stroke or major bleeding, between prasugrel plus bivalirudin and clopidogrel plus UFH.

Overall, the evidence supporting the preferential use of bivalirudin in STEMI over UFH is mixed, with GPIs possibly exerting a confounding role. In studies where GPIs were mostly routinely combined with UFH/LMWH in the control group (i.e. HORIZONS-AMI and EUROMAX), bivalirudin was shown to reduce the incidence of bleeding at the price of an increased risk of intraprocedural thrombotic complications. In EUROMAX this occurred despite the use of more potent $P2Y_{12}$ receptor inhibition in a significant proportion of patients. There is increasing evidence that the onset of action of clopidogrel or even newer antiplatelet agents remains slower in ACS patients than in healthy volunteers or patients with stable coronary artery disease (30, 31). GPIs are rapidly active in ACS patients by being given intravenously and not needing biotransformation, whereas the majority of primary PCI procedures with bivalirudin monotherapy are likely performed without adequate platelet inhibition due to the short time of pretreatment with $P2Y_{12}$ antagonists, some of which (clopidogrel and prasugrel) needing bioactivation to generate the active metabolites. This may contribute to explain why patients on bivalirudin monotherapy experience higher rates of stent thrombosis than those who receive GPIs in combination with heparins. Interestingly, a continued low-dose infusion of bivalirudin did not appear to offer protection against very early stent thrombosis in both EUROMAX and a 968-patients registry (where the lower maintenance dose was used) (32). In contrast, the high-dose infusion of bivalirudin was shown to be protective in a subanalysis of EUROMAX (where it was used in 22.5% of patients). In BRIGHT, GPI use in combination with UFH significantly increased the rates of BARC 1 or 2 bleeding and, numerically, those of BARC 3 or 5 bleeding, further contributing to explain the safety of bivalirudin when compared with a combination therapy of UFH and GPIs. Indeed, in HEAT-PPCI, GPIs were not routinely administered to patients randomised to UFH, resulting in similar bleeding compared with bivalirudin, and more ischaemic complications. These results are consistent with those of a recently reported 2,317-patients Canadian registry, where the primary outcome of non-CABG-related major bleeding was significantly reduced with bivalirudin vs UFH plus GPIs, but was not significantly reduced vs UFH alone (33). Importantly, the results of HEAT-PPCI are in contrast with those of the EUROMAX subanalysis showing no evidence of an interaction between the treatment effect of bivalirudin and the mode of GPIs use in the heparin arm (26).

Bivalirudin cost-effectiveness

Confronting with cost-effectiveness is becoming a must for physicians and decision-makers struggling between a paucity of resources and the need of giving ACS patients access to beneficial

pharmacological therapies. Since the cost of bivalirudin is quite significantly higher than that of heparin, its use should be justified by a clear incremental benefit (i.e. either superior efficacy or reduced bleeding, with subsequent shortening of hospitalisation). In economic analyses, bivalirudin has been suggested to be cost-effective and possibly a dominant strategy compared with heparin plus GPIs in patients with ACS (34). In a cost-effectiveness study of the ACUITY trial data carried on from the perspective of the United Kingdom Health Service, the higher costs for bivalirudin compared with heparin were partially offset by lower hospitalisation and bleeding costs, resulting in an incremental cost-effectiveness ratio (ICER) of £9,906 per quality-adjusted life year (QALY) gained. In probabilistic sensitivity analyses, 72 % of simulation results were more cost-effective than the ICER typically used for reimbursement in the United Kingdom (£20,000/QALY) (35). A similar cost-effectiveness analysis of the HORIZONS-AMI trial showed that the ICER of bivalirudin was lower (therefore acceptable by current standard) than the £20,000/QALY in 99 % of simulations (36). It must be emphasised that these economic analyses were based on early trials of bivalirudin in NSTE-ACS and STEMI. An updated assessment of the cost-effectiveness of bivalirudin vs heparins should take into account current practices where GPIs are increasingly used only as bailout therapies. Indeed, based on the results of HEAT-PPCI, bivalirudin would hardly be considered cost-effective. Notably, in their publication, the HEAT-PPCI investigators hypothesise a £500,000 saving with heparin per 1,000 primary PCI cases (12). On this basis, an updated cost-effectiveness analysis that incorporates the latest result from trials of bivalirudin is warranted. Since trials are different in design and outcomes, it is unlikely that such analyses can be based on meta-analytical data.

Open issues and future directions

Despite the evidence of benefit provided in reducing bleeding complications in ACS and the high level of recommendation received by guidelines, bivalirudin has not replaced the combination of heparin and GPIs in routine clinical practice (37, 38). Adding to safety concerns regarding acute stent thrombosis in STEMI and the unavailability of an antidote, other sources of uncertainty (including costs) may contribute to explain the underuse of bivalirudin. Open issues involve the optimal duration of administration after PCI (i.e. 2 or 4 h), the maintenance dose (ranging between 0.25 and 1.75 mg/kg/h after PCI in the available trials, with no head-to-head comparison available among different strategies), and the actual need for prolonging bivalirudin infusion beyond the procedure. In addition, many physicians advocate that the efficacy and safety profile or bivalirudin over UFH should be re-assessed in the light of the increasing transition to radial access and the use of newer antiplatelet agents in ACS. A two-by-two comparison of trans-radial vs trans-femoral access routes and bivalirudin monotherapy vs UFH plus provisional GPIs in ACS patients undergoing PCI is underway in the multicentre, open-label, multifactorial Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX (MATRIX) trial (39). Here patients randomly assigned to bivalirudin or UFH will be further randomised to stop the infusion at the end of PCI or to continue it at an infusion rate of 0.25 mg/kg/h for at least 6 h after completion of PCI, or optionally at an infusion rate of 1.75 mg/kg/h up to 4 h. Primary outcome measures will be the composite of death, non-fatal myocardial infarction or stroke at 30 days for both the access and drug treatment randomisations, and the composite of death, non-

Table 6: Details of the ongoing MATRIX trial.

Trial name	MATRIX
Clinicaltrials.gov identifier	NCT01433627
Masking	Single-blind
Design	Randomised, multifactorial, 2 by 2
Target population	ACS patients undergoing PCI
Estimated enrollment	6800 patients
Treatment arm (pharmacological randomisation)	Bivalirudin 0.75 mg/kg bolus prior to PCI, followed by 1.75 mg/kg/h infusion for the duration of the procedure. After PCI, the infusion will be stopped (short-duration bivalirudin sub-randomization) or reduced to 0.25 mg/kg/h for at least 6 hours (prolonged infusion sub-randomization). An optional higher-dose infusion of 1.75 mg/kg/h is also permitted for up to 4 hours in the prolonged infusion arm but prohibited in the short-duration bivalirudin group.
Control arm (pharmacological randomisation)	UFH 100 IU/kg with no GPIs and 60 IU/kg with GPIs.
PCI approach	1:1 radial or femoral
Primary endpoint	Access and pharmacology randomizations: Death, non-fatal myocardial infarction or stroke. Duration of bivalirudin infusion post-PCI sub-randomisation: Death, non-fatal myocardial infarction, stroke, stent thrombosis or BARC-defined type 3 or 5 bleedings.

ACS = acute coronary syndromes; BARC = Bleeding Academic Research Consortium; GPI = glycoprotein IIb/IIIa inhibitors; IU = International Units; PCI = percutaneous coronary intervention; UFH = unfractionated heparin.

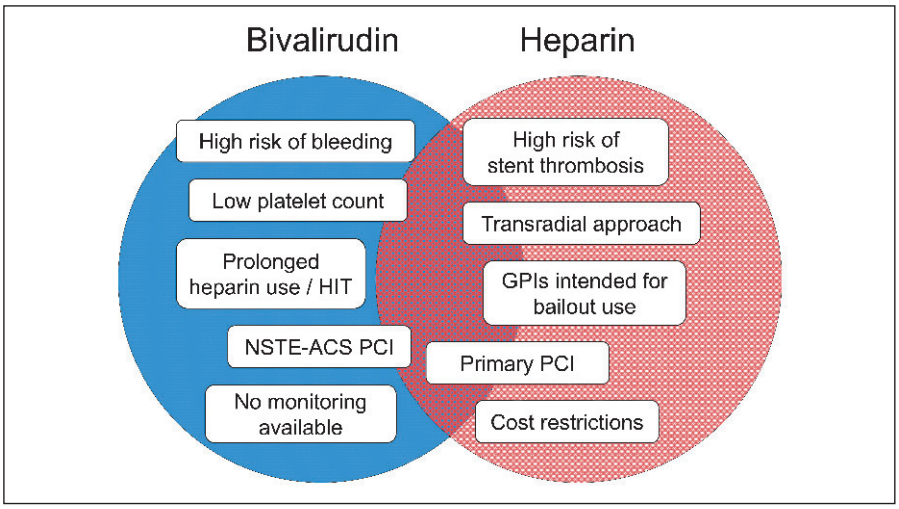

Figure 2: Venn's diagram of proposed preferential subgroups for treatment with bivalirudin or heparin.

fatal myocardial infarction, stroke, stent thrombosis or BARC 3 or 5 bleeding events at 30 days for the bivalirudin duration sub-randomisation (▶Table 6).

As far as the use of newer $P2Y_{12}$ inhibitors together with bivalirudin is concerned, the results of the BRAVE-4 trial do not support a clear advantage of combining bivalirudin and prasugrel vs UFH and clopidogrel, but this finding must be interpreted in view of the premature termination of the trial. Although there was no evidence of a significant interaction between the treatment effect of bivalirudin vs heparin and the use of different $P2Y_{12}$ inhibitors in the EUROMAX trial, only a specifically designed randomised trial of bivalirudin vs heparin in patients treated with prasugrel or ticagrelor may fully elucidate this topic. In the HORIZONS II AMI trial, >7,500 patients with STEMI will undergo primary PCI under anticoagulation with bivalirudin and will receive antiplatelet treatment with aspirin, cangrelor in the peri-PCI period and ticagrelor thereafter. At 30 days, patients with no major adverse cardiac events or bleeding will be randomised to continuing ticagrelor or switching to clopidogrel. This trial will provide interesting data on the combination of bivalirudin and ticagrelor as adjunctive antithrombotic therapy for primary PCI, although no comparison vs heparin has been planned.

Conclusions

Suggested areas of application for bivalirudin and heparin are depicted in ▶Figure 2. Bivalirudin has shown a favourable net outcome compared with heparins in both patients with NSTE-ACS and STEMI, driven by a significant reduction in bleeding complications. Because bleeding carries per se a high risk of death, myocardial infarction and stroke, pharmacological strategies aimed at preventing bleeding are of outmost importance in ACS (35). It should be noted that reducing bleeding complications with bivalirudin over the combination of UFH and GPIs has been accompanied by significant one-year and three-year mortality reductions in STEMI patients from the HORIZONS-AMI trial, but not in NSTE-ACS patients from the ACUITY trial. The reasons for the differential impact of bivalirudin on mortality in STEMI and NSTE-ACS remain unclear. The paradigm of bivalirudin as a dominant strategy for anticoagulation in ACS under every circumstance has been, however, recently challenged by new studies and may require further appraisal in view of the significant changes occurring in ACS management patterns worldwide. The safety benefit of bivalirudin vs UFH plus GPIs has been demonstrated by multiple randomised clinical trials, but it should not be accepted tout-court if it comes at the price of a significant increase in life-threatening thrombotic complications (i.e. stent thrombosis), particularly when ACS patients are denied fast-acting antiplatelet agents (i.e. GPIs, which in turn may be responsible for the observed increase in bleeding in the control arms of bivalirudin studies). The impact of the mode of GPI use with heparin on the treatment effect of bivalirudin remains undefined: the EUROMAX GPIs subanalysis and the HEAT-PPCI trial provide discordant results in this regard, but both studies have limitations (namely, the EUROMAX subanalysis is non-randomised, the HEAT-PPCI is a single-centre study). A multicentre randomised trial of bivalirudin vs heparin, with GPIs restricted to bailout in both groups on top of best-in-class procedural and antiplatelet strategies, is needed to ultimately settle the question. In view of the above, and until new data will be available to dissipate unsolved questions on bivalirudin, it remains critical that clinicians weigh the relative importance of the bleeding and ischaemic risks in each individual patient, as well as the additive or synergistic role of concurrent antithrombotic strategies, before selecting a parenteral anticoagulant for ACS.

Conflicts of interest

D. Capodanno has received modest honoraria from AstraZeneca, Eli Lilliy/Daiichi-Sankyo and Bayer. R. De Caterina has received honoraria and/or research grants from Boehringer Ingelheim, Bayer, BMS/Pfizer, Daiichi-Sankyo and Novartis.

References

1. De Caterina R, et al. General mechanisms of coagulation and targets of anticoagulants (Section I). Position Paper of the ESC Working Group on Thrombosis--Task Force on Anticoagulants in Heart Disease. Thromb Haemost 2013; 109: 569–579.
2. De Caterina R, et al. Parenteral anticoagulants in heart disease: current status and perspectives (Section II). Position paper of the ESC Working Group on Thrombosis-Task Force on Anticoagulants in Heart Disease. Thromb Haemost 2013; 109: 769–786.
3. Capodanno D, Angiolillo DJ. Antithrombotic therapy in patients with chronic kidney disease. Circulation 2012; 125(21): 2649–2661.
4. O'Gara PT, 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: e78–140.
5. Anderson JL, et al. 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non-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: e179–347.
6. Stone GW, et al. Bivalirudin for patients with acute coronary syndromes. N Engl J Med 2006; 355: 2203–2216.
7. Stone GW, et al. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med 2008; 358: 2218–2230.
8. Windecker S, et al. 2014 ESC/EACTS Guidelines on myocardial revascularisation: The Task Force on Myocardial Revascularisation 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; Epub ahead of print.
9. Kastrati A, et al. Abciximab and heparin versus bivalirudin for non-ST-elevation myocardial infarction. N Engl J Med 2011; 365: 1980–1989.
10. Steg PG, et al. Bivalirudin started during emergency transport for primary PCI. N Engl J Med 2013; 369: 2207–2217.
11. Schulz S, et al. Prasugrel plus bivalirudin vs. clopidogrel plus heparin in patients with ST-segment elevation myocardial infarction. Eur Heart J 2014; Epub ahead of print; Epub ahead of print.
12. Shahzad A, et al. Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. Lancet 2014; Epub ahead of print.
13. Lip GY, et al. Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventions: a joint consensus document of the European Society of Cardiology Working Group on Thrombosis, European Heart Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular Interventions (EAPCI) and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS) and Asia-Pacific Heart Rhythm Society (APHRS). Eur Heart J 2014; Epub ahead of print.
14. 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.
15. Cassese S, et al. Bivalirudin versus heparin in patients treated with percutaneous coronary intervention: a meta-analysis of randomised trials. EuroIntervention 2014; Epub ahead of print.
16. De Servi S, et al. The bivalirudin paradox: high evidence, low use. J Cardiovasc Med 2013; 14: 334–341.
17. Schulz S, et al. One-year outcomes with abciximab and unfractionated heparin vs bivalirudin during percutaneous coronary interventions in patients with non-ST-segment elevation myocardial infarction: updated results from the ISAR-REACT 4 trial. Eurointervention 2013; 9: 430–436.
18. Sibbing D, et al. Prognostic value of a high on-clopidogrel treatment platelet reactivity in bivalirudin vs abciximab treated non-ST-segment elevation myocardial infarction patients. ISAR-REACT 4 (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment-4) platelet substudy. J Am Coll Cardiol 2012; 60: 369–377.
19. Ndrepepa G, et al. Bivalirudin vs heparin plus a glycoprotein IIb/IIIa inhibitor in patients with non-ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention after clopidogrel pretreatment: pooled analysis from the ACUITY and ISAR-REACT 4 trials. Circ Cardiovasc Interv 2012; 5: 705–712.
20. Bangalore S, et al. Heparin Monotherapy or Bivalirudin During Percutaneous Coronary Intervention in Patients With Non-ST-Segment-Elevation Acute Coronary Syndromes or Stable Ischaemic Heart Disease: Results From the Evaluation of Drug-Eluting Stents and Ischaemic Events Registry. Circ Cardiovasc Interv 2014 Epub ahead of print.
21. Krishnaswamy A, et al. The use and limitations of unfractionated heparin. Crit Pathw Cardiol 2010; 9: 35–40.
22. White HD, et al. Randomized, double-blind comparison of hirulog versus heparin in patients receiving streptokinase and aspirin for acute myocardial infarction (HERO). Hirulog Early Reperfusion/Occlusion (HERO) Trial Investigators. Circulation 1997; 96: 2155–2161.
23. White H, Hirulog, Early Reperfusion or Occlusion –2 Trial I. Thrombin-specific anticoagulation with bivalirudin versus heparin in patients receiving fibrinolytic therapy for acute myocardial infarction: the HERO-2 randomised trial. Lancet 2001; 358: 1855–1863.
24. Mehran R, 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: 1149–1159.
25. Kirtane AJ, et al. Association between intraprocedural thrombotic events and adverse outcomes after primary percutaneous coronary intervention for ST-segment elevation myocardial infarction (a Harmonizing Outcomes With RevascularisatioN and Stents in Acute Myocardial Infarction [HORIZONS-AMI] Substudy). Am J Cardiol 2014; 113: 36–43.
26. Zeymer U, et al. Bivalirudin is superior to heparins alone with bailout GP IIb/IIIa inhibitors in patients with ST-segment elevation myocardial infarction transported emergently for primary percutaneous coronary intervention: a prespecified analysis from the EUROMAX trial. Eur Heart J 2014 Epub ahead of print.
27. Clemmensen P, et al. Predictors associated with acute stent thrombosis after primary PCI: the EUROMAX trial. J Am Coll Cardiol 2014; 63: 1_S.
28. Zimarino, et al. Isolated troponin increase after percutaneous coronary interventions: Does it have prognostic relevance? Atherosclerosis. 2012;221(2):297–302.
29. Berger PB, Blankenship JC. Is the heat on HEAT-PPCI appropriate? Lancet 2014 Epub ahead of print.
30. Parodi G, et al. Comparison of double (360 mg) ticagrelor loading dose with standard (60 mg) prasugrel loading dose in ST-elevation myocardial infarction patients: the Rapid Activity of Platelet Inhibitor Drugs (RAPID) primary PCI 2 study. Am Heart J 2014; 167: 909–914.
31. Alexopoulos D, et al. Randomized assessment of ticagrelor versus prasugrel antiplatelet effects in patients with ST-segment-elevation myocardial infarction. Circ Cardiovasc Interv 2012; 5: 797–804.
32. Shelton R, 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: 118–124.
33. Hibbert B, et al. Bivalirudin for primary percutaneous coronary interventions: outcome assessment in the Ottawa STEMI registry. Circ Cardiovasc Interv 2012; 5: 805–812.
34. Latour-Perez J, de-Miguel-Balsa E. Cost effectiveness of anticoagulation in acute coronary syndromes. Pharmacoeconomics 2012; 30: 303–321.
35. Schwenkglenks M, et al. Cost-effectiveness of bivalirudin versus heparin plus glycoprotein IIb/IIIa inhibitor in the treatment of non-ST-segment elevation acute coronary syndromes. Value Health 2011; 14: 24–33.
36. Schwenkglenks M, et al. Cost-effectiveness of bivalirudin versus heparin plus glycoprotein IIb/IIIa inhibitor in the treatment of acute ST-segment elevation myocardial infarction. Heart 2012; 98: 544–551.
37. Steg PG, et al. Bleeding in acute coronary syndromes and percutaneous coronary interventions: position paper by the Working Group on Thrombosis of the European Society of Cardiology. Eur Heart J 2011; 32: 1854–1864.
38. Kadakia MB, et al. Use of anticoagulant agents and risk of bleeding among patients admitted with myocardial infarction: a report from the NCDR ACTION Registry--GWTG (National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network Registry--Get With the Guidelines). JACC Cardiovasc Interv 2010; 3: 1166–1177.
39. Valgimigli M, et al. Scientific foundation and possible implications for practice of the Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of AngioX (MATRIX) trial. J Cardiovasc Transl Res 2014; 7: 101–111.

