



Bivalirudin in stable angina and acute coronary syndromes[☆]



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ABSTRACT

A parenteral anticoagulant is indicated in patients with acute coronary syndromes. Which anticoagulant should be preferred in each setting is not clearly established. Bivalirudin administration was considered in acute coronary syndromes after several clinical trials showed decreased bleeding risk with its use compared with the association of unfractionated heparin (UFH) with glycoprotein IIb/IIIa inhibitors (GPIs). Most recent data demonstrate that the bleeding benefit identified in the previous studies was not due to bivalirudin's properties but to higher bleeding incidence in the comparator arm due to the disproportional use of GPIs with heparin. This paper reviews clinical evidence on bivalirudin as anticoagulant in stable angina and acute coronary syndromes.

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1. Introduction: acute coronary syndrome management in 2015

Coronary artery disease (CAD) constitutes the most common cause of death worldwide. The spectrum of acute coronary syndromes (ACS) includes ST-segment elevation myocardial infarction (STEMI) diagnosed on the basis of the characteristic electrocardiographic findings, non-ST-segment elevation myocardial infarction (NSTEMI) in patients without those findings but positive cardiac biomarkers, and unstable

angina if it is new-onset, crescendo or at rest, and the cardiac biomarkers are negative (Thygesen et al., 2012).

Patients with STEMI need immediate reperfusion. They should be preferably directed to a percutaneous coronary intervention (PCI) – capable hospital within 90 min of the first medical contact, or treated with fibrinolytics if primary PCI referral will significantly delay time to reperfusion (Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology, ESC et al., 2012). According to the current practice guidelines (Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology, ESC et al., 2012; Authors/Task Force members, et al., 2014), all STEMI patients should be treated with oral aspirin and an ADP receptor blocker. The novel ADP receptor blockers prasugrel and ticagrelor have proven to be superior to clopidogrel (Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology, ESC et al., 2012). The STEMI patients should also receive a parenteral anticoagulant, i.e. unfractionated heparin (UFH), low molecular weight heparin (LMWH), fondaparinux, or bivalirudin. However, fondaparinux

Abbreviations: ACS, acute coronary syndromes; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; UFH, unfractionated heparin; GPIs, glycoprotein IIb/IIIa inhibitors; NSTEMI-ACS, non-ST-segment elevation acute coronary syndromes; DTI, direct thrombin inhibitors; CABG, coronary artery bypass grafting.

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is not an option in patients undergoing primary PCI. Glycoprotein IIb/IIIa inhibitors (GPIs) may be used peri-procedurally as bailout therapy in case of certain angiographic criteria (large thrombus, slow flow, no re-flow, or other thrombotic complications). Routine GPI use is not indicated in patients on bivalirudin and is at least debatable on patients treated with UFH. Routine post-procedural anticoagulation is not indicated.

Patients with non-ST-segment elevation acute coronary syndromes (NSTEMI-ACS) should all receive anti-ischemic treatment, aspirin, an ADP receptor blocker (ticagrelor or prasugrel in patients without contra-indications proceeding to PCI), and a parenteral anticoagulant (fondaparinux, enoxaparin, UFH, or bivalirudin) (Hamm et al., 2011; Authors/Task Force members, et al., 2014). All patients should also have their risk calculated with one of the available risk scores (GRACE or TIMI). Patients with high-risk profile should benefit from an early invasive strategy (within 24 h). The anticoagulant should not be changed during PCI. However, if the patient was initially treated with fondaparinux, UFH has to be added before PCI. Anticoagulants are usually discontinued after PCI. GPIs can be considered based on angiographic criteria but are rarely used upstream.

Which anticoagulant should be preferred in each setting is not clearly established. Bivalirudin administration was identified as having potential value after several clinical trials that showed decreased bleeding risk with its use in comparison with heparin. However, an increased risk for early stent thrombosis was also identified. This paper considers available evidence for selecting bivalirudin as an anticoagulant for ACS.

2. The pharmacological profile of bivalirudin

Thrombin has a central role in the coagulation cascade. It converts fibrinogen to fibrin and is also a potent platelet agonist. Direct thrombin inhibitors (DTI) were developed in order to overcome heparin's inability to inactivate the clot-bound thrombin (Serruys et al., 2006).

Bivalirudin is one of the available parenteral DTIs, the others being hirudin, lepirudin, and desirudin (not available in the US). It is an oligopeptide analog of hirudin with one third of its size (a 20-amino acid peptide) (Fig. 1 top). Its molecular weight is 2,180 Da. Bivalirudin binds specifically to thrombin at two sites, with an affinity intermediate between hirudin and the synthetic DTI argatroban. Binding of bivalirudin to thrombin is transient and not irreversible as occurs with hirudin (Fig. 1 bottom) (Warkentin et al., 2008). Bivalirudin prevents

both initiation and continuation of clot formation (Reed & Bell, 2002) (Fig. 2). Additional features that make bivalirudin an attractive option in clinical practice include its lack of binding to plasma proteins and its lack of neutralization by platelet factors (Serruys et al., 2006). Bivalirudin was also found to block in vitro thrombin-mediated and ADP-mediated platelet aggregation (Leger et al., 2006; Curran, 2010). It can be used for heparin-induced thrombocytopenia treatment, as its immunogenic potential is negligible (Warkentin et al., 2008).

Its half-life is short (25 min). The drug has an extracellular distribution with a volume of distribution of 0.24 l/kg. Its bioavailability following intravenous administration is immediate and complete. Its pharmacokinetic properties do not seem to be significantly affected by age or gender (The Medicines Company, 2009). Most of the drug is eliminated after proteolytic cleavage into its constituent amino acids, which are recycled in protein synthesis. Only 20% of the drug is excreted unchanged in the urine (Table 1). Renal failure prolongs bivalirudin half-life up to four hours in dialysis-dependent patients (Warkentin et al., 2008). The currently recommended dose for patients undergoing PCI is a bolus of 0.75 mg/kg followed by an infusion of 1.75 mg/kg/h for the duration of the procedure (Authors/Task Force members, et al., 2014).

Several drugs must never be administered in the same intravenous line with bivalirudin because they cause microparticulate formation or gross precipitation. These drugs are alteplase, amiodarone, amphotericin B, chlorpromazine, diazepam, prochlorperazine edisylate, reteplase, streptokinase, and vancomycin (Reed & Bell, 2002).

Among the various coagulation assays, the prothrombin time (PT), activated thromboplastin time (aPTT), thrombin time (TT), and activated clotting time (ACT) all rise linearly with increasing doses of bivalirudin (Fox et al., 1993). No specific antidote exists for bivalirudin intoxication/overdosage. Hemodialysis, hemofiltration, or plasmapheresis has been reported to be helpful in case of overdosage (Koster et al., 2003).

3. Bivalirudin in clinical trials for patients with stable angina and acute coronary syndromes

3.1. Bivalirudin in stable and unstable angina

Table 2 summarizes trials, registries, and ongoing trials for bivalirudin in stable or unstable angina. Bivalirudin was first evaluated in ACS in the Hirulog Angioplasty Study (Bittl et al., 1995). This double-blinded study

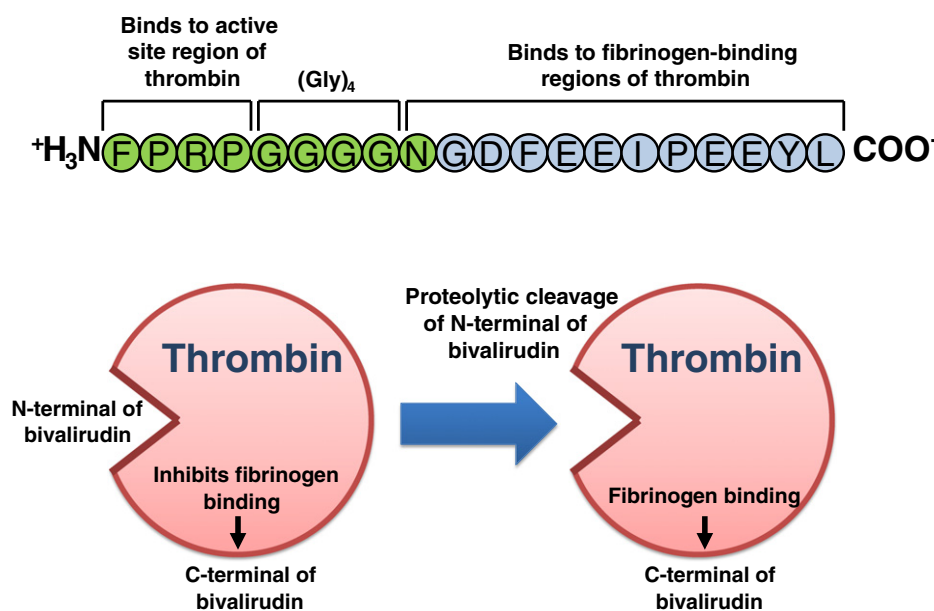


Fig. 1. Top: The molecule of bivalirudin, Bottom: Initially, bivalirudin binds specifically to thrombin at two sites. Following proteolytic cleavage, the N-terminal sequence of bivalirudin does not bind to thrombin and the bivalirudin remnant is transformed to a competitive thrombin inhibitor that can be displaced by other substrates.

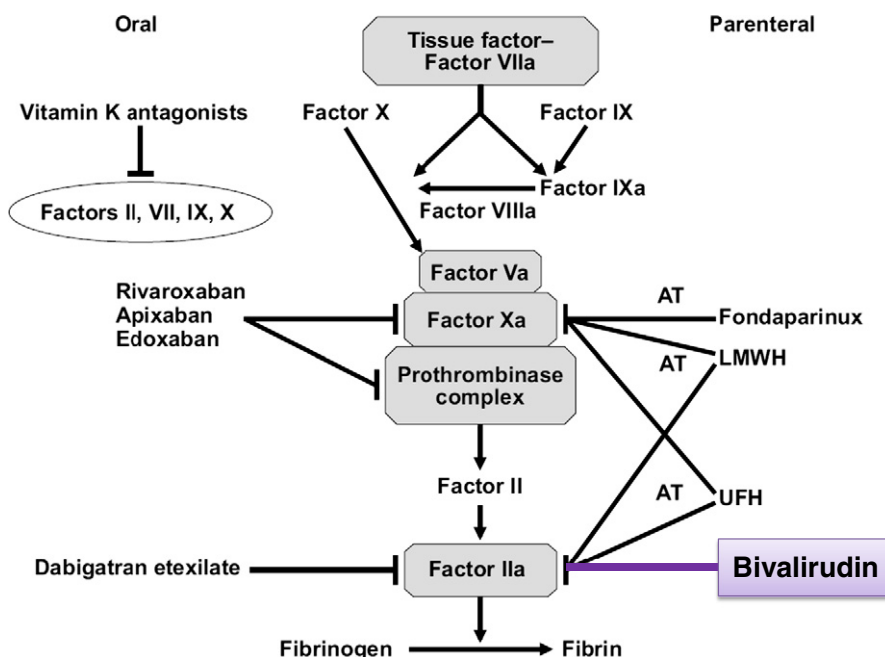


Fig. 2. Target of bivalirudin in the coagulation cascade.

[Adapted with permission from Mavranakas, T. & Bounameaux, H. (2011). The potential role of new oral anticoagulants in the prevention and treatment of thromboembolism. *Pharmacology & Therapeutics* 130, 46–58].

enrolled patients with unstable angina or post-infarction angina (less than two weeks after myocardial infarction) urgently scheduled for PCI. They were randomized to receive either bivalirudin (intravenous bolus followed by a 18–24 hour infusion) or UFH at a high-dose bolus followed by a 18–24 hour infusion. The primary outcome was a composite of death, myocardial infarction, abrupt closure of the dilated vessel or rapid clinical deterioration of cardiac origin requiring repeated angioplasty, intra-aortic balloon counterpulsation, or coronary artery bypass grafting (CABG) during hospitalization. The primary outcome occurred in 11.8% of patients treated with bivalirudin and 12.9% of patients treated with UFH ($p = 0.26$, intention-to-treat population). Bivalirudin was associated with a lower incidence of major hemorrhage (3.8% vs. 9.8%, $p < 0.001$). After this study, bivalirudin was approved for use in Europe and the United States as an alternative to heparin for patients with unstable angina during percutaneous coronary intervention (PCI). However, this trial excluded patients scheduled to undergo coronary stenting. Thienopyridines were not used at that time and heparin doses were much higher than the currently suggested.

Meanwhile, GPI use became widespread during PCI and novel antiplatelet agents were developed. Two pilot trials (CACHET and REPLACE-1), in patients undergoing elective or urgent coronary angioplasty or stenting, suggested that, by replacing heparin with bivalirudin,

Table 1

Summary of pharmacological properties of bivalirudin versus heparin (Kandrotas 1992). AT, antithrombin; HIT, heparin induced thrombocytopenia.

Property	Heparin	Bivalirudin
Mechanism	Potentiates AT activity	Direct thrombin inhibitor
Effect on clot-bound thrombin	No effect	Inactivation
Administration	Subcutaneous or intravenous	Intravenous
Molecular weight	3,000–30,000 Da	2,180 Da
Half-life	90 min	25 min
Plasma proteins	Binds to plasma proteins	No binding
Renal excretion	No significant renal excretion	20%
Antidote	Protamine	No specific antidote
HIT	Cause of HIT	Can be used for HIT treatment

adjunctive GPI use may not be indicated for all patients but only in the event of massive thrombus, slow or no-reflow, or a thrombotic complication (provisional or bail-out GPI use) (Lincoff et al., 2002; Lincoff et al., 2004a). REPLACE-2 was a double blind double-dummy trial designed to determine whether bivalirudin with provisional GPI had comparable efficacy to UFH with routine GPI for patients undergoing urgent or elective PCI (Lincoff et al., 2003). Patients undergoing PCI as reperfusion therapy for acute myocardial infarction were excluded. The primary outcome, a composite of death, myocardial infarction, severe ischemia requiring surgical or percutaneous revascularization, or major bleeding episodes by 30 days, was observed in 10% of patients in the UFH/GPI group and in 9.2% of patients in the bivalirudin arm (odds ratio [OR] 0.92; 95% confidence interval (CI) 0.77–1.09). Major bleeding events occurred less frequently in the bivalirudin arm (2.4%) compared with UFH/GPI (4.1%; $p < 0.001$). The authors concluded that bivalirudin was comparable (non-inferior) to UFH/GPI concerning the acute ischemic end points and was associated with less bleeding episodes. Long-term clinical outcomes were equivalent at 6 months (death, myocardial infarction, repeat revascularization) and at 12 months (death) (Lincoff et al., 2004b).

After the encouraging results of these trials, the ISAR-REACT 3 study was designed to compare bivalirudin with UFH in patients undergoing PCI for stable or unstable angina, with normal biomarkers (troponin T and CK-MB) (Kastrati et al., 2008). In the REPLACE-2 trial, only 84% of patients received 300 mg of clopidogrel and a stent was placed in 85% of patients. The rest of the patients did not receive any clopidogrel and did not have any stent placed. In the ISAR-REACT 3 study, all patients were treated with stent placement after a loading dose of 600 mg of clopidogrel. Bolus UFH dose was higher (140 UI/kg instead of the usual bolus dose of 70 UI/kg) but GPI use was marginal (0.2% of patients in each group). The primary outcome, a composite of ischemic complications and major bleeding similar to the REPLACE-2 trial, occurred in 8.3% of patients in the bivalirudin group and 8.7% of patients in the UFH group (relative risk (RR) 0.94, 95% CI 0.77–1.15). Major bleeding was observed in 3.1% of patients treated with bivalirudin and 4.6% of patients treated with UFH (RR 0.66, 95% CI 0.49–0.90). Therefore, bivalirudin did not provide a net clinical benefit but reduced the incidence of bleeding.

Table 2

Summary of trials, registries, and ongoing trials for bivalirudin in stable or unstable angina. N, number of participants in the trial; NSTE-ACS, non-ST segment elevation acute coronary syndrome; CAD, coronary artery disease; UFH, unfractionated heparin; MI, myocardial infarction; IABC, intra-aortic balloon counterpulsation; CABG, coronary artery bypass grafting; GPIs, glycoprotein IIb/IIIa inhibitors; *, concerns the propensity score-matched cohort. Caveat: definition of major bleeding is not uniform throughout the studies. All p values are for superiority.

Study	Reference	N	Indication	Groups	Efficacy outcome	Efficacy	Major bleeding
HIRULOG	(Bittl et al., 1995)	4098	Unstable or postinfarction angina	Bivalirudin vs. UFH	Death, MI, repeated angioplasty, IABC or CABG during hospitalization	11.8% vs. 12.9% (p = 0.26)	3.8 vs. 9.8% (p < 0.001)
REPLACE-2	(Lincoff et al., 2003)	5966	Urgent or elective PCI	Bivalirudin & provisional GPI vs. UFH & planned GPI	Death, MI, ischemia requiring revascularization, major bleeding at day 30	9.2% vs. 10% (p = 0.32)	2.4% vs. 4.1% (p < 0.001)
ISAR-REACT 3	(Kastrati et al., 2008)	4570	Stable or unstable angina	Bivalirudin vs. UFH	Death, MI, revascularization at day 30 or in-hospital major bleeding	8.3% vs. 8.7% (p = 0.57)	3.1% vs. 4.6% (RR 0.66; 95% CI 0.49–0.90)
NAPLES	(Tavano et al., 2009)	335	Elective PCI in diabetics	Bivalirudin vs. UFH plus tirofiban	Death, MI, urgent revascularization at day 30 or in-hospital bleeding	18% vs. 31.5% (p = 0.004)	0.6% vs. 2.4% (p = 0.37)
ARMYDA-7 BIVALVE	(Patti et al., 2012)	401	NSTE-ACS or stable angina	Bivalirudin vs. UFH	Cardiac death, MI, revascularization or stent thrombosis at 30 days	11.1% vs. 8.9% (p = 0.56)	0.5% vs. 1% (p = 0.98)
NAPLES III	NCT01465503	837	Stable or unstable angina	Bivalirudin vs. UFH	Death, MI, revascularization, stent thrombosis or major bleeding at 30 days	6.5% vs. 4.3% (p = 0.17)	3.3% vs. 2.6% (p = 0.54)
EVENT registry	(Bangalore et al., 2011)	3022*	Stable angina or ACS	Bivalirudin vs. UFH	In-hospital death or MI	5.6% vs. 5.7% (p = 0.88)	No data only for major bleeding
EUROVISION registry	(Hamon et al., 2014)	2018	Stable CAD or ACS	Bivalirudin. No control group	Death, MI, revascularization, or stroke at 30 days	2.9%	1.6%

The NAPLES study was a single center trial focusing on the management of diabetic patients undergoing elective PCI (Tavano et al., 2009). All patients received 300 mg of clopidogrel the day before PCI. They were randomized to receive bivalirudin monotherapy (intravenous bolus with infusion during the procedure) or UFH bolus plus routine tirofiban (bolus followed by a 12 hour infusion). The primary end point, a composite of death, myocardial infarction, urgent revascularization within 30 days, or in-hospital bleeding occurred in 31.5% of patients in the UFH/GPI group and 18% of patients in the bivalirudin group (p = 0.004). However, this result was due to minor bleeding events that were more frequent in the UFH/tirofiban group.

ARMYDA-7 BIVALVE was a small randomized open-label trial in patients with documented coronary artery disease undergoing PCI and had at least one of the following risk factors for bleeding complications: age >75 years, diabetes mellitus, or chronic kidney disease (estimated creatinine clearance of 30 to 60 ml/min by the Cockcroft–Gault formula) (Patti et al., 2012). Patients undergoing primary PCI for STEMI were excluded. Patients were randomized to receive UFH bolus before the procedure or bivalirudin bolus followed by infusion during PCI. GPIs were available in both arms at the operator's discretion. Although UFH use was associated with more bleeding events, their incidence was mainly driven by large entry-site hematomas. Major bleeding events were similar in both groups. The primary efficacy end point, a composite outcome of cardiac death, myocardial infarction, target-vessel revascularization, or stent thrombosis at 30 days, was similar in both groups (11.1% for bivalirudin vs. 8.9% for UFH; p = 0.56).

The NAPLES III trial was a single-center double-blind study comparing UFH to bivalirudin in patients undergoing elective PCI who had negative biomarkers but a high bleeding risk (defined as a Nikolsky score superior or equal to 10). The primary outcome was the rate of in-hospital major bleeding. The NAPLES III study has been recently completed but the results have not been published yet (NCT01465503). Preliminary results recently presented at the American College of Cardiology Scientific Sessions in Washington, DC in March 2014 showed a similar bleeding rate in both groups (2.6% for UFH vs. 3.3% for bivalirudin, p = 0.54). The rate of major cardiovascular events was similar in both groups.

3.2. Bivalirudin in non-ST-segment elevation acute coronary syndromes

Table 3 summarizes trials and registries for bivalirudin in NSTE-ACS. The ACUITY trial was a prospective, open-label study enrolling patients with moderate- or high-risk NSTE-ACS (59% of whom had NSTEMI) (Stone et al., 2006). Patients were randomly assigned to UFH or enoxaparin plus a GPI, bivalirudin plus a GPI, or bivalirudin alone (with provisional use of GPI during PCI). All patients had angiography within 72 h after randomization (median of 19.5–19.8 h). Patients on GPI were further randomized in a two-by-two factorial design to receive the GPI either immediately after randomization (upstream) or to defer administration only during PCI starting in the catheterization laboratory. Three endpoints were evaluated at 30 days: a composite ischemia endpoint (death from any cause, myocardial infarction or unplanned revascularization for ischemia), major bleeding (non-related to CABG), and a net clinical outcome combining ischemic and bleeding events. Bivalirudin plus GPI was non-inferior to UFH plus GPI for the composite ischemia end point (7.7% vs. 7.3%; RR 1.07, 95% CI 0.92–1.23), for major bleeding events (5.3% vs. 5.7%; RR 0.93, 95% CI 0.78–1.10), and for the net clinical outcome (11.8% vs. 11.7%; RR 1.01, 95% CI 0.90–1.12). Bivalirudin alone was non-inferior to UFH plus GPI for the composite ischemia end point (7.8% vs. 7.3%; RR 1.08, 95% CI 0.93–1.24), but was superior to UFH plus GPI for major bleeding (3% vs. 5.7%; RR 0.53, 95% CI 0.43–0.65) and the net clinical outcome.

Similar results were observed when the follow up was extended to 1 year (Stone et al., 2007a). Composite ischemia was observed in 16% of patients in the bivalirudin/GPI group, 15.4% in the UFH/GPI group, and 16.2% in the bivalirudin alone group. All cause mortality was similar

Table 3
 Summary of trials and registries for bivalirudin in non-ST segment elevation acute coronary syndromes (NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; UFH, unfractionated heparin; GPIs, glycoprotein IIb/IIIa inhibitors; MI, myocardial infarction; #, concerns the propensity score-matched cohort; *, p for the comparison of UFH/enoxaparin plus GPI vs. bivalirudin plus GPI; **, p for the comparison of UFH/enoxaparin plus GPI vs. bivalirudin alone; N/A, not available. Caveat: definition of major bleeding is not uniform throughout the studies. All p values are for superiority.

Study	Reference	N	Indication	Groups	Efficacy outcome	Efficacy	Major bleeding
ACUITY	(Stone et al., 2006) (Stone et al., 2007a)	13,819	Moderate or high risk NSTEMI-ACS	UFH/enoxaparin plus GPI vs. bivalirudin plus GPI vs. bivalirudin alone	Death, MI, or unplanned revascularization at 30 days Death, MI, or unplanned revascularization at 1 year	7.3% vs. 7.7% vs. 7.8% (p = 0.39* & p = 0.32**) 15.4% vs. 16% vs. 16.2% (p = 0.35* & p = 0.29**)	5.7% vs. 5.3% vs. 3% (p = 0.38* & p < 0.001**) N/A
PROTECT TIMI-30	(Gibson et al., 2006)	797	NSTEMI-ACS with ≥ 1 risk factor	Eptifibatide (with UFH or enoxaparin) vs. bivalirudin	Death, MI, or ischemia on Holter through 48 h	14.2% vs. 18% (p = 0.15)	0.7% vs. 0% (p = 0.308)
ISAR-REACT 4	(Kastrati et al., 2011)	1721	NSTEMI	UFH plus abciximab vs. bivalirudin	Death, large MI, urgent revascularization or major bleeding	10.9% vs. 11% (p = 0.94)	4.6% vs. 2.6% (p = 0.02)
SWITCH III	(Waksman et al., 2013)	100	NSTEMI-ACS undergoing PCI	UFH vs. bivalirudin	-	-	0 vs 2% (p = 0.49)
GRAPE registry	(Alexopoulos et al., 2014)	740*	Moderate to high risk ACS	Standard treatment vs. bivalirudin	In-hospital or 30 days death, MI, revascularization, stroke	5.1% vs. 4.1% (p = 0.6)	4.3% vs. 3.5% (p = 0.7)

at 1 year in all three groups. Deferred selective use of GPIs compared with routine upstream use was not associated with statistical differences in mortality or composite ischemia.

A subgroup analysis of the ACUITY trial, including only the patients who were pre-treated with either UFH or enoxaparin before randomization (White et al., 2008), demonstrated that patients could be safely switched from UFH or enoxaparin to bivalirudin monotherapy before coronary angiography. Another subgroup analysis, in the 56% of patients of the ACUITY trial who underwent PCI following angiography (Stone et al., 2007b), showed that bivalirudin alone was not associated with more composite ischemia (death from any cause, myocardial infarction or unplanned revascularization for ischemia) than UFH/GPI but significantly lowered the rate of major bleeding.

The PROTECT TIMI-30 trial was a randomized trial enrolling patients presenting with NSTEMI-ACS who had at least one high-risk feature (diabetes mellitus, positive cardiac biomarkers, ST-segment deviation > 0.5 mm, TIMI risk score ≥ 3) and were anticipated to undergo PCI (Gibson et al., 2006). They were assigned randomly to UFH plus eptifibatide, enoxaparin plus eptifibatide or bivalirudin with provisional eptifibatide. No significant difference was detected between bivalirudin and both eptifibatide arms with regard to the composite of death, MI, or ischemia on Holter through 48 h, or the rate of TIMI major bleeding. However, the study had an angiographic primary end point and was not adequately powered for clinical outcomes.

The ISAR-REACT 4 trial was a double blind double-dummy study comparing UFH plus abciximab with bivalirudin in patients undergoing PCI for NSTEMI (Kastrati et al., 2011). All patients were given 325–500 mg of aspirin and 600 mg of clopidogrel. The primary outcome, a composite of death, large recurrent myocardial infarction, urgent target-vessel revascularization, or major bleeding within 30 days, was observed in 10.9% of patients in the UFH/abciximab group and 11% of patients in the bivalirudin group (RR 0.99, 95% CI 0.74–1.32). The rate of death or ischemic complications did not differ between the two groups. Major bleeding events were more common with UFH plus abciximab compared with bivalirudin (4.6% vs. 2.6%; RR 1.84, 95% CI 1.10–3.07). The authors concluded that UFH and abciximab failed to provide a net clinical benefit and increased the risk of bleeding. Comparable clinical outcomes for mortality or the ischemic complications were observed at one year (Schulz et al., 2013).

A pooled analysis of the ACUITY and ISAR-REACT 4 trials included only the subset of patients with NSTEMI treated with PCI who received ticlopidine or clopidogrel load before the intervention (Ndrepepa et al., 2012). The efficacy end point at 30 days, a composite of death, recurrent myocardial infarction, or urgent target vessel revascularization, occurred in 10.6% in the bivalirudin arm vs. 10.2% in the UFH/GPI arm (OR 1.04, 95% CI 0.85–1.27). Definite stent thrombosis rates were similar in both arms. The safety end point of non-CABG-related major bleeding events was significantly lower in the bivalirudin arm (3.4% vs. 6.3%; OR 0.54, 95% CI 0.40–0.72).

SWITCH III was an open-label pilot trial comparing UFH to bivalirudin in patients with NSTEMI-ACS undergoing PCI who were pretreated with fondaparinux 2.5 mg subcutaneously and a loading dose of 600 mg of clopidogrel (Waksman et al., 2013). Patients were randomized to receive either UFH boluses or bivalirudin bolus followed by infusion for the duration of the PCI. GPIs were used in 3.9% of patients in the bivalirudin group and 12.2% of patients in the UFH group. The number of events (ischemic or hemorrhagic) was very low and the study was not powered to detect intergroup differences.

3.3. Bivalirudin in ST-segment elevation myocardial infarction

Table 4 summarizes trials, registries, and ongoing trials for bivalirudin in STEMI. The HORIZONS-AMI trial (Stone et al., 2008) was the first trial to assess bivalirudin efficacy and safety in patients with STEMI undergoing primary PCI. It was a prospective, randomized, open-label study that compared treatment with intravenous boluses

Table 4
 Summary of trials, registries, and ongoing trials for bivalirudin in ST-segment elevation acute myocardial infarction (STEMI). N, number of participants in the trial; NSTEMI, non-ST-segment elevation myocardial infarction; ACS, acute coronary syndrome; UFH, unfractionated heparin; GPIs, glycoprotein IIb/IIIa inhibitors; MI, myocardial infarction; #, estimated enrollment; *, p for the comparison of UFH vs. bivalirudin; **, p for the comparison of GPI vs. bivalirudin; ***, p for the comparison of GPI vs. bivalirudin; \$, combined outcome for short- and long-term bivalirudin administration. Caveat: definition of major bleeding is not uniform throughout the studies. All p values are for superiority.

Study	Reference	N	Indication	Groups	Efficacy outcome	Efficacy	Major bleeding
HORIZONS-AMI	(Stone et al., 2008)	3602	STEMI	UFH plus GPI vs. bivalirudin	Death, reinfarction, stroke, revascularization or major bleeding at 30 days	12.1% vs. 9.2% (p = 0.005)	8.3% vs. 4.9% (p < 0.001)
	(Mehran et al., 2009)				Death, reinfarction, stroke, revascularization or major bleeding at 1 year	18.3% vs. 15.6% (p = 0.022)	9.2% vs. 5.8% (p < 0.0001)
	(Stone et al., 2011)				Death, reinfarction, stroke, revascularization or major bleeding at 3 years	27.6% vs. 25.5% (p = 0.09)	10.5% vs. 6.9% (p = 0.0001)
EUROMAX	(Steg et al., 2013)	2198	STEMI	UFH vs. bivalirudin	Death or major bleeding at 30 days	8.5% vs. 5.1% (p = 0.001)	6% vs. 2.6% (p < 0.001)
HEAT-PPCI	(Shahzad et al., 2014)	1812	STEMI	UFH vs. bivalirudin	Death, stroke, reinfarction, or revascularization at 28 days	5.7% vs. 8.7% (p = 0.01)	3.1% vs. 3.5% (p = 0.59)
BRAVE 4	(Schulz et al., 2014)	548	STEMI	UFH plus clopidogrel vs. bivalirudin plus prasugrel	Death, MI, revascularization, stent thrombosis, stroke, or bleeding at 30 days	14.5% vs. 15.6% (p = 0.68)	2.9% vs. 2.6% (p = 0.97)
OTTAWA registry	(Hibbert et al., 2012)	2123	STEMI	UFH vs. GPI vs. bivalirudin	In-hospital death, stroke, reinfarction, and major bleeding	9.5% vs. 11.4% vs. 7.6% (p = 0.88* & p = 0.06**)	3.6% vs. 7.4% vs. 3.1% (p = 0.68* & p < 0.001**)
BRIGHT	(Han et al., 2015)	2194	STEMI & NSTEMI	UFH vs. UFH plus tirofiban vs. bivalirudin	Death, MI, revascularization, stroke, or bleeding at 30 days	13.2% vs. 17.0% vs. 8.8% (p = 0.008* & p < 0.001**)	7.5% vs. 12.3% vs. 4.1% (p < 0.001***)
MATRIX	(Valgimigli et al., 2014)	8404	ACS	UFH vs. bivalirudin vs. prolonged bivalirudin	Death, non-fatal MI, or stroke at 30 days	10.9% vs. 10.3% (p = 0.45)	2.5% vs. 1.4% (p = 0.001)
SWEDHEART	NCT02311231	6000#	STEMI & NSTEMI	UFH vs. bivalirudin	Death, MI, or major bleeding at 180 days	-	-

of UFH plus a GPI (abciximab bolus followed by a 12 hour infusion or double-bolus eptifibatide followed by a 12–18 hour infusion), both started before PCI, to treatment with bivalirudin alone (intravenous bolus followed by an infusion discontinued at the completion of PCI). Two thirds of patients in the bivalirudin arm had also received a UFH bolus before cardiac catheterization. GPIs were administered to 7.2% of patients in the bivalirudin arm mainly because of a giant thrombus or no reflow after PCI. The primary outcome of combined adverse clinical events at 30 days (a composite of major bleeding events and major adverse cardiovascular events) occurred in 9.2% of the intention to treat population in the bivalirudin arm and 12.1% in the UFH/GPI arm (relative risk [RR] of 0.76, 95% confidence interval [CI] 0.63 to 0.92). The co-primary end point of major bleeding (non-CABG-related) occurred in 4.9% of the intention to treat population in the bivalirudin arm and 8.3% in the UFH/GPI arm (p < 0.001). Mortality from cardiac causes and all-cause mortality were significantly lower in the bivalirudin arm at 30 days. Reinfarction rate did not differ between the two groups. The same results were observed not only in the intention to treat but also in the primary PCI population. In a pre-specified analysis, stent thrombosis in the first 24 h occurred more frequently in the bivalirudin group (1.3%) compared with the UFH/GPI arm (0.3%, p < 0.001).

A pre-specified analysis of the same outcomes at 1 year from the HORIZONS-AMI trial was published in 2009 (Mehran et al., 2009). The primary outcome of adverse clinical events was observed in 15.6% of patients in the bivalirudin group versus 18.3% in the control group (intention-to-treat population, hazard ratio [HR] of 0.83, 95% CI 0.71–0.97). This difference was due to less non-CABG-related major bleeding events in the bivalirudin arm (5.8% versus 9.2%, HR 0.61, 95% CI 0.48–0.78), as the rate of major adverse cardiovascular events was similar in both groups. Cardiac and all-cause mortality were lower in the bivalirudin group at 1 year. This benefit was also observed at 30 days and the difference in survival widened between 30 days and 1 year. The rate of stent thrombosis did not differ between study groups at 1 year.

The results were sustained at 3 years (Stone et al., 2011). Major bleeding events (non-CABG related) increased at the same rate in both groups between the 30th day and the end of the third year, maintaining bivalirudin's superiority observed at 30 days. Differences in cardiac mortality, all-cause mortality and reinfarction continued to increase throughout the follow-up period and all became significant in favor of bivalirudin at 3 years. Between 24 h and 3 years, stent thrombosis occurred less frequently in the bivalirudin arm and, at the end of the follow-up, there was no significant difference in the stent thrombosis rate between the study groups.

The aforementioned reduction in mortality with bivalirudin may be attributed to a lower risk of major hemorrhagic complications in bivalirudin treated patients. However, a recently published analysis from the HORIZONS-AMI trial demonstrated that bivalirudin was also associated with reduced mortality at 3 years in patients without major bleeding events (Stone et al., 2014).

The SWITCH analysis of the same trial concerned only the patients treated with UFH before study enrollment (Dangas et al., 2011). In the group subsequently switched to bivalirudin, bivalirudin was started 30 min after the last UFH bolus, but always before PCI. The same outcomes were observed in this population: the SWITCH group compared with the group maintained on UFH and GPI had lower rates of major bleeding events and lower cardiac mortality at 30 days, but stent thrombosis was more common in the SWITCH group in the first 24 h. At 2 years, patients in the switch group had lower rates of cardiac mortality or reinfarction, and similar rates of all-cause mortality and stent thrombosis. Therefore, this analysis demonstrated that bivalirudin can be safely administered in STEMI before PCI even if the patient has already received a UFH bolus.

A subgroup analysis was performed in patients from the HORIZONS-AMI trial who underwent left anterior descending artery PCI (Wöhrle et al., 2013). Bivalirudin treatment was associated with significantly

lower rates of non-CABG-related major bleeding events, reinfarction, or cardiac mortality at 3 years, compared with UFH and GPI. Subacute, late, and very late stent thrombosis was also observed significantly less frequently in the bivalirudin arm.

The EUROMAX trial was an open label study that randomized patients with a presumed diagnosis of STEMI scheduled for primary PCI to receive either bivalirudin (intravenous bolus followed by an infusion for at least 4 h after PCI) or heparin bolus (UFH or enoxaparin) (Steg et al., 2013). Study drugs were started in the ambulance or a non-PCI hospital. GPI use was allowed routinely or for bailout use with heparin (decision left to treating physician) but only for bailout use in the bivalirudin group (69.1% vs. 11.5%). The primary outcome of death from any cause or non-CABG-related major bleeding at 30 days (intention to treat analysis) was observed in 5.1% of patients in the bivalirudin arm and 8.5% of patients in the control arm (RR 0.6; 95% CI 0.43–0.82). Reinfarction rate and all-cause or cardiac mortality were similar in both groups. Stent thrombosis occurred more frequently in the bivalirudin arm during the first 24 h (1.1% vs. 0.2%; RR 6.11, 95% CI 1.37–27.24) but stent thrombosis rates were similar during the period from 24 h to 30 days. The composite outcome of net adverse clinical events (death, reinfarction, ischemia-driven revascularization, or stroke) occurred in 7.8% of patients in the bivalirudin group and 10.6% of patients in the heparin group (RR 0.73, 95% CI 0.56–0.96).

This study confirmed the reduced risk of bivalirudin administration for causing major bleeding events but not cardiac mortality in the era of radial access for PCI and of novel P2Y₁₂ inhibitors, as clopidogrel or prasugrel. However, the lower risk of major bleeding was due to differences in access site hemorrhage, drop in hemoglobin or hematocrit, and blood transfusion, whereas the rate of TIMI major bleeding was similar in both groups. Long-term outcomes from this trial are not yet available to compare with the HORIZONS-AMI trial findings. Acute stent thrombosis post bivalirudin seems to remain an important issue despite the availability and use of more potent thienopyridine agents.

A recent article reported on the pooled analysis of the 30-day HORIZONS-AMI and EUROMAX databases (Stone et al., 2015). 5,800 patients were included in the analysis. A GPI was used in 84.8% of patients assigned to heparin and 8.8% of patients assigned to bivalirudin. The radial access was used in 21.3% of patients. Non-CABG related major bleeding was lower with bivalirudin (4.2% vs. 7.8%; RR 0.53, 95% CI 0.43–0.66). Cardiac mortality at 30 days decreased with bivalirudin (2% vs 2.9%; RR 0.7, 95% CI 0.5–0.97). However, acute stent thrombosis rate was higher with bivalirudin (1.2% vs. 0.2%; RR 6.04, 95% CI 2.55–14.31). No significant heterogeneity was detected between the 2 studies and the results were consistent across the different subgroups.

The HEAT-PPCI trial was an open-label randomized study that used a delayed consent approach in order to recruit a higher proportion of the potentially eligible population and avoid selective inclusion that limits the generalization of study findings (Shahzad et al., 2014). All consecutive patients presenting with STEMI and scheduled for emergency angiography were randomized to receive either UFH (intravenous boluses) or bivalirudin (intravenous bolus followed by infusion for the duration of PCI). GPI use was allowed selectively in both groups in the event of massive thrombus, slow or no-reflow, or a thrombotic complication (13% in the bivalirudin and 15% in the UFH group). The primary efficacy outcome, a composite of all-cause mortality, cerebrovascular accident, reinfarction, or additional unplanned target lesion revascularization at 28 days, occurred in 8.7% of patients in the bivalirudin group versus 5.7% of patients in the heparin group (RR 1.52, 95% CI 1.09–2.13). The heparin advantage was primarily due to higher reinfarction or revascularization rate in the bivalirudin arm. Most of these events could be explained by acute stent thrombosis incidence that was also higher in bivalirudin treated patients. The primary safety outcome, the major bleeding event rate by 28 days, did not differ between the two groups (3.5% vs. 3.1%, $p = 0.59$). The major advantage of this trial is that 97% of the eligible population was randomized in the trial. Limitations of

this trial include its open-label, single-center design; long-term outcomes will be very interesting to follow-up.

The BRAVE 4 trial was a randomized, open-label, multicenter study in Germany comparing prasugrel plus bivalirudin to clopidogrel plus UFH in STEMI patients planned for primary PCI (Schulz et al., 2014). The primary outcome, a composite of death, myocardial infarction, unplanned revascularization, stent thrombosis, stroke, or bleeding occurred in 15.6% of patients treated with prasugrel and bivalirudin, and in 14.5% of patients treated with clopidogrel and UFH (RR 1.07; 95% CI 0.70–1.64). There was no significant difference between the two groups in the composite ischemic endpoint, bleeding events, cardiac mortality, or definite stent thrombosis. However, the trial was not adequately powered for the aforementioned outcomes as it was prematurely stopped due to slow recruitment.

The BRIGHT study was a multi-center study in China that randomized patients with acute myocardial infarction (1925 patients with STEMI and 269 patients with NSTEMI) undergoing PCI to receive UFH monotherapy, bivalirudin monotherapy or UFH with tirofiban (Han et al., 2015). Bailout use of tirofiban was allowed in the monotherapy groups for no reflow or other thrombotic complications (4.4% of patients in the bivalirudin group and 5.6% in the UFH group). The primary outcome was a composite of all-cause mortality, reinfarction, target vessel revascularization, stroke, and any bleeding events at 30 days. It occurred in 8.8% of patients treated with bivalirudin, 13.2% of patients treated with UFH, and 17% of patients treated with UFH plus tirofiban (RR for bivalirudin vs. UFH 0.67, 95% CI 0.50–0.90). This difference was driven from a higher incidence of bleeding events in the UFH group. No significant difference in acute stent thrombosis was detected between the three groups. The results were similar in the STEMI subgroup.

The MATRIX trial (NCT01433627) enrolled patients with ACS intended for invasive management. Participants were randomized for trans-radial versus trans-femoral intervention, and to receive bivalirudin stopped at the end of PCI or prolonged bivalirudin infusion for at least 4–6 h or UFH with provisional GPI (Valgimigli et al., 2014). The primary outcome was the composite of death, non-fatal myocardial infarction, or stroke at 30 days. The trial's results were presented in March 2015 at the ACC.15 meeting in San Diego. Major adverse cardiovascular events occurred in 10.3% of bivalirudin-treated patients and 10.9% of patients treated with UFH ($p = 0.45$). Major bleeding events occurred in 1.4% of patients who received bivalirudin and 2.5% of UFH-treated patients ($p = 0.001$). Stent thrombosis occurred in 1% and 0.6% of patients who received bivalirudin and UFH, respectively ($p = 0.048$). All cause mortality was higher in the UFH arm (2.3%) compared with bivalirudin arms (1.7%, $p = 0.042$).

3.4. Registries

The OTTAWA STEMI Registry trial reported on the outcomes on 2123 patients who underwent PCI for STEMI between 2004 and 2010 (Hibbert et al., 2012). 748 patients were treated with bivalirudin, 699 with GPIs, and 676 with heparin. In a propensity score-matched logistic regression analysis, bleeding complications in the bivalirudin arm occurred with similar frequency when compared with heparin alone (OR 1.21, 95% CI 0.60–2.43). In contrast, major bleeding events were more frequent with GPIs when compared with bivalirudin (OR 2.96, 95% CI 1.60–5.45). There was no benefit from bivalirudin use on the composite outcome of in-hospital death, stroke, reinfarction, and major bleeding compared with heparin alone (OR 0.97, 95% CI 0.62–1.51). Acute stent thrombosis was observed in 1.6% of patients with bivalirudin, 0.6% with GPIs, and 0.3% with heparin alone.

The EVENT Registry report evaluated 7777 patients from more than 50 centers in the United States who underwent attempted PCI for stable angina or ACS and were treated with UFH monotherapy, bivalirudin monotherapy or UFH plus GPI during PCI (Bangalore et al., 2011). A propensity score matching technique was used to assemble a cohort for each comparison. Bivalirudin therapy was associated with a lower risk

of in-hospital major or minor bleeding compared with UFH (OR 0.70, 95% CI 0.57–0.85). In-hospital death or myocardial infarction rate was similar in both groups (OR 0.88, 95% CI 0.89–1.15). Ischemic outcomes did not differ at 12 months including stent thrombosis. Similar results were obtained for all outcomes with the comparison of the bivalirudin and the UFH/GPI group.

The EUROVISION registry reported on the outcomes of 2018 consecutive patients from 58 sites in five European countries (Hamon et al., 2014). All patients received bivalirudin either for an ACS or during PCI for stable CAD. Death or a major adverse cardiovascular event (myocardial infarction, revascularization, stroke) was observed in 1.7% of patients at 7 days and 2.9% at 30 days. A major bleeding event occurred in 1.4% and 1.6% of patients respectively. The composite outcome combining both adverse cardiovascular and major bleeding events was observed in 4.4% of patients at 30 days. However, there was no control group in this study.

The GRAPE registry included 2047 patients undergoing PCI for moderate to high risk ACS in 8 Greek hospitals (Alexopoulos et al., 2014). Bivalirudin was used in 404 patients. To assess the effect of bivalirudin on short-term outcomes, propensity score matching was used resulting in 370 pairs of patients. There was no difference between the two groups in adverse cardiovascular or bleeding events.

3.5. Meta-analyses

Three meta-analyses were recently published seeking to define the role of bivalirudin for patients undergoing PCI. The first one included seven published randomized trials comparing bivalirudin with provisional use of GPI to UFH or enoxaparin with provisional or routine GPI in patients with elective or urgent PCI (Nairouz et al., 2014). Bivalirudin use was associated with significantly decreased TIMI major bleeding rates (RR 0.58, 95% CI 0.46–0.74). All-cause mortality and repeat revascularization rates were similar with both treatment strategies. However, bivalirudin administration was associated with a trend toward more myocardial infarctions or stent thrombosis at 30 days compared with UFH/GPI. This trend was driven primarily by the HORIZONS-AMI and the EUROMAX trials in patients with STEMI. Routine use of GPI in association to UFH in the REPLACE-2, ISAR REACT-4, and HORIZONS-AMI trials may have overestimated the bleeding risk reduction observed with bivalirudin.

The second meta-analysis included 16 studies that enrolled individuals for planned PCI and randomly assigned patients to bivalirudin or heparin (UFH or low-molecular weight heparin) with or without a GPI (Cavender & Sabatine, 2014). The primary efficacy endpoint was the incidence of major adverse cardiac events at 30 days and occurred in 7% of patients treated with heparin and 8% of patients treated with bivalirudin (RR 1.09, 95% CI 1.01–1.17). These findings were consistent regardless of the type of patients the trial enrolled or GPI use. The increase in cardiac adverse events with bivalirudin was driven by an increase in myocardial infarctions and ischemia-driven revascularizations. The risk of acute stent thrombosis was also higher with bivalirudin (RR 3.86, 95% CI 2.11–7.07), and highest in patients with STEMI. Major bleeding events were less frequent with bivalirudin-based anticoagulation (RR 0.62, 95% CI 0.49–0.78). However, the bleeding risk significantly differed depending on concomitant GPI use. Among the trials in which GPI use was provisional for the bivalirudin group but planned in the heparin group, the relative risk for bleeding events favored bivalirudin-based anticoagulation (RR 0.53, 95% CI 0.47–0.61). On the contrary, if GPIs were used on a provisional basis in both arms, there was no significant difference in bleeding events between the two groups (RR 0.78, 95% CI 0.51–1.19). In the studies using routinely GPIs in both arms, no significant difference was identified in regard to bleeding events (RR 1.07, 95% CI 0.87–1.31).

The third meta-analysis included 22 randomized trials comparing the available anticoagulant regimens in patients with STEMI undergoing primary PCI with stent implantation (Bangalore et al., 2014). Five of

these trials used bivalirudin in one of the comparator arms. If more than 50% of patients in the arm were treated with a GPI, the trial arm was considered as anticoagulant plus GPI. Short-term major adverse cardiovascular events, a composite of 30 days or in-hospital mortality, MI, revascularization, or stroke, were observed in 6.45% of patients treated with bivalirudin and in 5.97% of patients treated with UFH (without GPI) (RR 1.08; 95% CI 0.87–1.33). However, when compared with UFH (without GPI), bivalirudin use was associated with increased stent thrombosis (1.6% vs. 0.76%; RR 2.19, 95% CI 1.25–3.82). Major bleeding events were less frequent with bivalirudin compared with UFH (without GPI): 2.36% vs. 3.19% (RR 0.68, 95% CI 0.50–0.93). The authors concluded that bivalirudin was the safest agent but was associated with more ischemic events. They proposed an individualized approach weighing the risk of bleeding against the risk of ischemic outcomes in order to optimize the anticoagulant regimen.

3.6. Ongoing trials

The SWEDEHEART trial (NCT02311231) is a randomized open-label study in patients with NSTEMI or STEMI scheduled for invasive management and pretreated with ticagrelor or prasugrel. The patients are randomized to receive UFH bolus or bivalirudin bolus followed by intravenous infusion. The primary outcome is the composite of death, myocardial infarction, or major bleeding events at 180 days. The study is actively recruiting participants.

4. Conclusions and future perspectives

The first trials with bivalirudin in STEMI used the association of UFH with GPIs as the comparator arm. They showed promising results: bleeding complications were significantly lower with bivalirudin, and cardiac or all-cause mortality also improved. However, in the era of more potent P2Y₁₂ inhibitors, the routine use of a GPI became less common and is no longer considered as beneficial as it used to be. The HEAT-PPCI trial, and the recent meta-analysis by Cavender & Sabatine, demonstrated that the bleeding benefit identified in the first studies was not due to bivalirudin's properties but to the disproportional use of GPIs in the studied groups. When GPIs were allowed only for bailout use, UFH was not inferior to bivalirudin for major bleeding. However, the most recent meta-analysis by Bangalore et al., including only trials in patients with STEMI, showed that bivalirudin was superior to UFH/GPI for major bleeding events. The recently published BRIGHT and MATRIX trials also suggest a significant benefit from bivalirudin use for reducing bleeding events as compared with UFH. Cardiac mortality reduction seen with bivalirudin in STEMI in the first studies was probably due to the prevention of iatrogenic hemorrhagic complications and might no longer be present in the era of provisional GPI use. In the HEAT-PPCI trial, a UFH advantage was identified and was primarily due to higher reinfarction or revascularization rate in the bivalirudin arm. Most of these events could be explained by acute stent thrombosis, a finding also present in the HORIZONS-AMI and EUROMAX trials. However, the MATRIX trial, including a prolonged bivalirudin infusion arm, showed that bivalirudin use may be associated with lower mortality rates, despite a slightly higher acute stent thrombosis rate in the bivalirudin arm.

Therefore, on the basis of the current evidence bivalirudin use in STEMI appears to be associated with a small safety benefit. Whether this is at the expense of lower efficacy is still unclear. Studies in NSTEMI-ACS were in support of bivalirudin use in this setting. However, the comparator arm in the ACUITY and the ISAR REACT 4 trials was the association of UFH with GPI, a combination that is no longer routinely applied.

Further randomized clinical trials are needed to better understand the safety and efficacy of bivalirudin in the era of PCI through radial artery with the use of more potent P2Y₁₂ inhibitors. The substantially higher cost of bivalirudin compared to heparin is another factor that should be also taken into consideration.

Conflict of interest

None.

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