REVIEW

Relative efficacy of bivalirudin versus heparin monotherapy in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention: a network meta-analysis

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Abstract: In the absence of head-to-head clinical data, the objective of this study was to indirectly compare the efficacy and safety of a bivalirudin-based anticoagulation strategy with that of heparin monotherapy in patients with ST-elevation myocardial infarction (STEMI) intended for primary percutaneous coronary intervention. A systematic literature review was performed to identify randomized controlled trials to build a network of bivalirudin and heparin monotherapy strategies in STEMI patients using heparin, with glycoprotein IIb/IIIa inhibitor as a common reference strategy. At 30 days, the bivalirudin-based strategy was expected to result in lower mortality rates than heparin monotherapy (odds ratio [OR], 0.55; credible limit [CrL], 0.32–0.95). This relationship was sustained at 1 year. At 30 days, the risk for stroke (OR, 0.88; CrL, 0.37–2.13), myocardial infarction (OR, 0.79; CrL, 0.40–1.55), and thrombolysis in myocardial infarction major and minor bleedings (OR, 0.66; CrL, 0.45–0.98) tended to be numerically reduced with bivalirudin in comparison with heparin monotherapy. For patients with STEMI intended for primary percutaneous coronary intervention, bivalirudin is associated with lower mortality rates in comparison with heparin monotherapy. This study suggests that bivalirudin is more effective and safer than heparin monotherapy and should therefore be preferred over heparin monotherapy.

Keywords: primary angioplasty, STEMI, pharmacology

Introduction

Myocardial infarction is the leading cause of death for both men and women worldwide.[1] For patients with ST-segment elevation myocardial infarction (STEMI), standard treatment is intended to quickly reopen the blocked artery.[2] According to the guidelines[3,4] the use of primary percutaneous coronary intervention (PPCI) is recommended for patients with STEMI who have an onset of symptoms of less than 12 hours when presenting to hospitals capable of performing PPCI within 90–120 minutes.

Guidelines recommend the use of adjunctive therapies during PPCI, including anticoagulants (heparins and bivalirudin) and antiplatelet activation drugs (aspirin and $P2Y_{12}$ inhibitors). Antiplatelet aggregation drugs such as glycoprotein IIb/IIIa inhibitors (GPIs)[2] may also be used.

Thrombin inhibition is a key target for pharmacotherapy in patients with STEMI who are undergoing PPCI. STEMI is characterized by a high thrombotic burden and

a highly prothrombotic environment, thereby necessitating powerful and predictable thrombin inhibition.[5] Thrombin is an important modulator of coagulation, activation of platelets, and inflammatory pathways.[6]

Heparins (unfractionated heparin [UFH], low-molecular weight heparin) are indirect thrombin inhibitors and have a variety of limitations,[7] including an unpredictable anticoagulant response, unclear pharmacokinetics, and a narrow therapeutic window.[8] In addition, heparins provide ineffective inhibition of clot-bound thrombin[9] and include risk for heparin-induced thrombocytopenia.[10] Moreover, the dose of heparin in PCI and, in particular, in PPCI, has never been formally assessed.[11] There are no placebo-controlled randomized clinical trials (RCTs) evaluating the use of heparins in PPCI, although American College of Cardiology/American Heart Association and European Society of Cardiology guidelines recommend its use based on expert consensus.[3,4]

Bivalirudin inhibits thrombin directly[12] and has an immediate effect, a linear dose response, and a short half-life, resulting in a predictable anticoagulant effect, with less risk for bleeding.[13] In addition, bivalirudin inhibits clot-bound thrombin in addition to plasma/free thrombin[14] and inhibits platelet activation via thrombin.[15]

In contrast to heparins, bivalirudin has been studied in a series of RCTs and significantly reduces major and minor bleeding and thrombocytopenia across a broad range of patients with coronary artery disease (Bivalirudin Angioplasty Trial, Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events 2, Acute Catheterization and Urgent Intervention Strategy, Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction [HORIZONS-AMI]) while maintaining ischemia protection. Specifically, bivalirudin has been studied in a large RCT in STEMI patients undergoing PPCI, in which bivalirudin provided comparable ischemic protection and reduced bleeding as well as mortality rates when compared with a heparin and GPI-based strategy.[16] These benefits were sustained at 1 year[17] and 3 years.[18]

Although several RCTs have shown a heparin + GPI-based strategy to be superior over heparin only, and heparin + GPI is a commonly used and guideline-recommended strategy in Europe and the United States,[3,4] heparin monotherapy continues to be used only in a significant minority[19,20] of STEMI patients undergoing PPCI. However, no clinical trial as yet has been performed comparing a heparin-only strategy versus bivalirudin in PPCI. In the absence of a head-to-head RCT comparing heparin monotherapy and bivalirudin monotherapy, the objective of the current study was to indirectly compare the efficacy of bivalirudin with that of heparin monotherapy for the treatment of STEMI patients undergoing PPCI.

Methods
Study identification and selection

A systematic literature search was performed to identify RCTs evaluating the efficacy and safety of bivalirudin and heparin monotherapy in the treatment of STEMI with PPCI. Patients were allowed to use aspirin+clopidogrel or ticlopidine as background treatment. The search was performed using a prespecified search strategy in Medline, Medline-In Progress, and EMBASE simultaneously, using OVID. In addition, a search of the Cochrane Library was performed to identify trials from the Cochrane Controlled Trials Registry, and reference lists of relevant meta-analyses were scanned. The search was performed capturing publications until January 23, 2012.

Search terms included a combination of free-text and MeSH terms relevant to STEMI, bivalirudin, heparin, GPIs (abciximab, tirofiban, eptifibatide), and RCTs. Two reviewers independently evaluated each identified study against predetermined inclusion criteria. For an article to be included, at least one of the conditions under each PICOS (population, intervention, comparison, outcome, and study design) point must be fulfilled (ie, at least one listed outcome must be present in the publication). The population of interest included all patients having had STEMI, presented within 12 hours after the onset of symptoms, and having undergone PPCI. A mixed acute coronary syndrome and STEMI population of patients was of interest if STEMI outcomes were reported separately.

Interventions of interest included bivalirudin at the recommended dosage, an intravenous bolus of 0.75 mg/kg followed by an intravenous infusion at a rate of 1.75 mg/kg/hour, in combination with aspirin and thienopyridine (clopidogrel or ticlopidine); heparin at the dosage of intravenous bolus 60 IU/kg, with subsequent boluses as required to achieve a target activated clotting time of 200–250 seconds, in combination with aspirin, and thienopyridine (clopidogrel or ticlopidine); or heparin at the dosage of intravenous bolus 60 IU/kg, with subsequent boluses as required to achieve a target activated clotting time of 200–250 seconds, in combination with aspirin, thienopyridine (clopidogrel or ticlopidine), and a GPI (abciximab, tirofiban, or eptifibatide).

Comparators of interest are listed under interventions. Studies that only compared treatment within the same class (ie, GPIs) were excluded; only comparative RCTs in English

were included. Outcomes of interest were all-cause mortality, bleeding, stroke, recurrent myocardial infarction, thrombosis, need for revascularization (ie, urgent target vessel revascularization [TVR]), net adverse clinical events, and major adverse cardiovascular events (MACE). Outcomes of interest were evaluated at 30 days and 1 year.

Despite very broad search criteria, two relevant publications[21,22] were not picked up by the search strategy. After careful review of the meta-analysis paper,[23] it was decided that two publications,[21,22] both from the Abciximab and Carbostent Evaluation trial, were to be included in the analysis. None of the key search terms was reported in the abstract or keywords of these publications.

Statistical analysis

The availability of trials comparing both treatment strategies with a common reference strategy (heparin + GPI) offered the possibility of comparing the efficacy and safety of bivalirudin and heparin monotherapy indirectly, using Bayesian network meta-analyses (NMA).[24] NMA have been presented as an extension of traditional meta-analysis, in which all studies compare the same intervention with the same comparator.

Bayesian NMA include data, a likelihood distribution, a model with parameters, and prior distributions. A regression model with a binominal likelihood distribution was used, and both fixed and random effect models were tested. The deviance information criterion (DIC) is used to compare the fixed and random effects model and provides a measure of model fit.[25] Because the analysis was performed using the Bayesian Statistical Framework, the *P*-value was not used to compare efficacy or safety of treatments.

WinBUGS 1.4.1 software (BUGS Project, Cambridge, United Kingdom) was used for the statistical analysis. Summary statistics are presented for the relative treatment effects (ie, odds ratio [OR] for occurrence of events) and the 95% credible limit (CrL), which reflect the range of true underlying effects with 95% probability.

Two studies were different by design or evaluated patients. In the Ongoing Tirofiban In Myocardial Infarction Evaluation 2 (ON-TIME2) study, a mixed population was recruited during an open-label and a blinded phase, and the combined findings for this study were reported.[26] The results of the ON-TIME2 study for the double-blinded phase only were reported in other publications.[27,28] Furthermore, the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial had 2 × 2 factorial randomization. The CADILLAC trial is, in fact, a comparison of four different treatment groups: heparin monotherapy with or without stents and heparin + GPI with or without stents.

A sensitivity analysis was performed to test whether these differences in trial design or evaluated patients had an influence on the outcomes. For the base case analysis, the intention to treat (ITT) population of all trials was used.

In addition to base case analysis, three different scenarios regarding the CADILLAC and ON-TIME2 studies were performed for each outcome (one or all depending on the outcome): in scenario 1, ITT population was used from all randomized studies, but this scenario only included a subpopulation of the CADILLAC trial[29] of 426 patients for heparin + GPI and 428 patients for heparin alone. This group of patients consists only of STEMI patients who had a stent implanted and were separated according to abciximab (GPI) use (heparin + abciximab versus heparin alone). Patients from a double-blinded phase of ON-TIME2 trial were used.[27,28] In scenario 2, the ITT population was used from all randomized studies except an ON-TIME2 substudy, in which the subpopulation from the Heestermans et al 2009[26] publication was used. This scenario includes a population of patients from the double-blinded and open-label phases in the ON-TIME2 study. Therefore, the number of ON-TIME2 patients analyzed is higher than that of the randomized trial because of the addition of patients from the open-label phase. Finally, in scenario 3, both scenario 1 and 2 study populations were combined, thereby using both the ON-TIME2 substudy[26,28] and the CADILLAC substudy.[29]

Results
Study selection

The systematic literature review identified 841 potentially relevant abstracts, of which 719 were excluded on the basis of their abstracts (Figure 1). Of the remaining 122 studies, 109 publications were excluded after a full text review, resulting in 13 relevant identified publications. Two full-text publications[21,22] mentioned in the De Luca et al 2009[23] meta-analysis were of interest and were not retrieved by the systematic literature search. These publications were manually added to the 13 systematically identified articles. In total, 15 publications were included, covering eight individual studies including a total of 8,807 adult patients.

The network of evidence is presented in Figure 2. Only a single study (HORIZONS-AMI) was identified that directly compared bivalirudin with heparin in combination with GPI; other studies compared heparin monotherapy with heparin in combination with GPI.
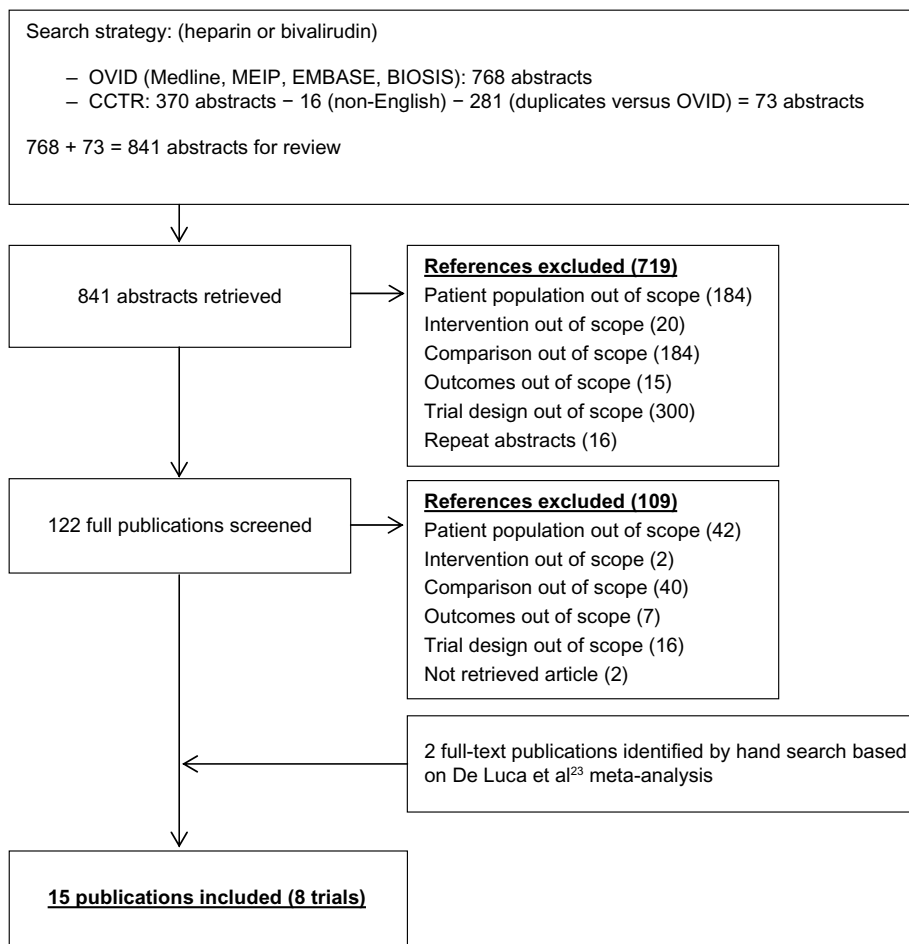
Search strategy: (heparin or bivalirudin)

    – OVID (Medline, MEIP, EMBASE, BIOSIS): 768 abstracts
    – CCTR: 370 abstracts − 16 (non-English) − 281 (duplicates versus OVID) = 73 abstracts

768 + 73 = 841 abstracts for review

841 abstracts retrieved

References excluded (719)
Patient population out of scope (184)
Intervention out of scope (20)
Comparison out of scope (184)
Outcomes out of scope (15)
Trial design out of scope (300)
Repeat abstracts (16)

122 full publications screened

References excluded (109)
Patient population out of scope (42)
Intervention out of scope (2)
Comparison out of scope (40)
Outcomes out of scope (7)
Trial design out of scope (16)
Not retrieved article (2)

2 full-text publications identified by hand search based on De Luca et al[23] meta-analysis

15 publications included (8 trials)

Figure 1 Flow chart of the selected studies.
Abbreviations: MEIP, Medline in Progress; CCTR, Cochrane Controlled Trials Registry.

ASSIST[34]
ON-TIME2[27,28]
ON-TIME2[26]
CADILLAC[29,36,37]
BRAVE-3[35]
Fu et al[30]
ACE[21,22]
Montalescot et al[38]

Heparin + GPI   Heparin monotherapy

HORIZONS-AMI[16–18]

GPI used in each relevant study:
• HORIZONS-AMI: abciximab or eptifibatide
• ASSIST: eptifibatide
• ON-TIME2: tirofiban
• BRAVE-3: abciximab
• CADILLAC: abciximab
• Fu et al: tirofiban
• ACE: abciximab
• Montalescot et al: abciximab
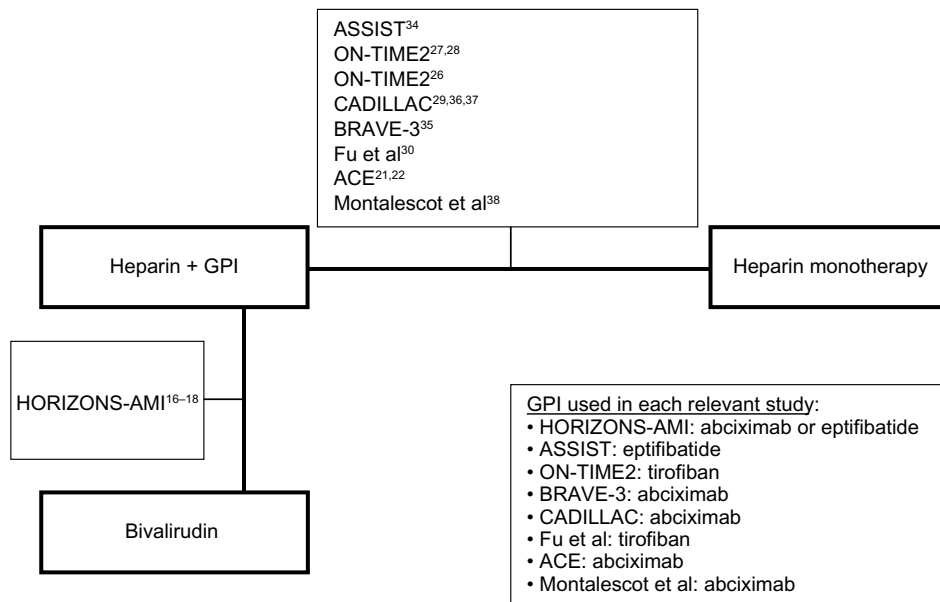
Bivalirudin

Figure 2 Evidence network diagram.
Note: Box GPI in the right hand corner shows which GPIs were used in which trials.
Abbreviations: ACE, Abciximab and Carbostent Evaluation; ASSIST, Revascularization Strategies for ST Elevation Myocardial Infarction Trial; BRAVE-3, Bavarian Reperfusion Alternatives Evaluation 3; CADILLAC, Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications; GPI, glycoprotein IIB/IIIa inhibitor; HORIZONS-AMI, Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction; ON-TIME2, Ongoing Tirofiban In Myocardial Infarction Evaluation 2.

Comparability of study designs

Two studies[18,30] reported outcomes at 6 months and 3 years, respectively, and were for this reason not further considered in the analysis. The general patient characteristics (sex, age, diabetes) and background treatment were comparable across the studies included (Tables 1 and 2).

Results of the network meta-analysis

The results of the base case analysis are presented in Table 3. The expected incidence of mortality at 30 days within the population included in this analysis was 1.9% with a bivalirudin treatment strategy, versus 3.4% with heparin monotherapy (OR, 0.55; CrL, 0.32–0.95). This effect was sustained at 1 year, when bivalirudin resulted in an incidence of mortality of 3.3%, compared with 6.4% for heparin monotherapy (OR, 0.50; CrL, 0.31–0.79; Tables 3 and 4). Mortality at 30 days for bivalirudin versus heparin monotherapy in scenario 1 had an OR of 0.59 (CrL, 0.33–1.03); for scenario 2 it was 0.52 (CrL, 0.30–0.90), and for scenario 3 it was 0.55 (CrL, 0.31–0.97; Table 5). Mortality at 1 year for bivalirudin versus heparin monotherapy in scenario 1 had an OR of 0.54 (CrL, 0.32–0.90; Table 5).

Table 1 Overview of the design of the included studies

Study and treatment group	Patients randomized, n	Study design	Outcomes	Summary of outcomes
HORIZONS-AMI[16–18]				
Heparin + GPI	1,802	RCT, OL, SB, MC	30 days, 1 year	Major bleeding, TIMI bleeding, combined adverse
Bivalirudin	1,800			clinical events
ASSIST[34]				
Heparin + GPI	201	RCT	30 days, 6 months,	Composite of death – any cause, recurrent MI,
Heparin	199		and in hospital	recurrent severe ischemia, TIMI bleeding
ON-TIME2*,[26]				
Heparin + GPI	536	RCT mixed OL,	30 days	Death, MI, urgent TVR, TIMI major bleeding,
Heparin	537	DB, PC, MC		bleeding; early stent thrombosis
ON-TIME2*,[27,28]				
Heparin + GPI	491	RCT, DB, PC, MC	30 days	Primary outcomes: extent of residual ST-segment
Heparin	493			deviation at 1 hour after PPCI
				Secondary outcomes: death, MI, urgent TVR, blinded
				bail-out use of tirofiban at 30 days, TIMI bleeding
BRAVE-3[35]				
Heparin + GPI	401	RCT, DB	30 days	Primary outcomes: infarct size in the SPECT study
Heparin	399			Secondary outcomes: death, MI, stroke, urgent IRA
				revascularization, TIMI bleeding
CADILLAC[29,36,37]				
Heparin + GPI	1,052	RCT, MC	30 days, 1 year	Death, reinfarction, urgent repeat vascularization,
Heparin	1,030			stroke, bleeding, NACE, MACE
Fu et al[30]				
Heparin + GPI	72	RCT	6 months	Death, reinfarction, MACE, thrombosis,
Heparin	78			TIMI-major/minor bleeding
ACE[21,22]				
Heparin + GPI	200	RCT, MC	30 days, 6 months,	Primary outcomes: death, reinfarction, TVR, stroke
Heparin	200		and 1 year	Secondary outcomes: ST-segment reduction,
				postprocedural corrected TIMI, infarct size, death,
				reinfarction and composite of death, reinfarction and
				TVR at 6 months; angiographic restenosis
Montalescot et al[38]				
Heparin + GPI	149	RCT, DB, MC	30 days, 6 months	Primary outcomes: death, reinfarction, urgent TVR
Heparin	151			Secondary outcomes: death, reinfarction,
				revascularization (percutaneous coronary or CABG)

Notes: *In the base case analysis and scenario 1, data from ON-TIME2 trial by Van't Hof et al 2008 and ten Berg et al 2010 were used, as they only report data from the double-blinded phase, which has a higher internal validity. In a scenario 2 and 3 analysis, the open-label phase patients from ON-TIME2, as reported by Heestermans et al 2009, were included as well. To avoid double counting of patients, both Heestermans et al 2009 and Van't Hof et al 2008 were not combined, at the same time, in an individual analysis.
Abbreviations: ACE, Abciximab and Carbostent Evaluation; CABG, coronary artery bypass graft; DB, double blind; GPI, glycoprotein IIB/IIIa inhibitor; IRA, infarct related artery; MACE, major adverse cardiovascular events; MC, multicenter; MI, myocardial infarction; NACE, net adverse clinical events; OL, open label; ON-TIME2, Ongoing Tirofiban In Myocardial Infarction Evaluation 2; PC, placebo controlled; PPCI, primary percutaneous coronary intervention; RCT, randomized controlled trial; SB, single blind; TIMI, thrombolysis in MI; TVR, target vessel revascularization; HORIZONS-AMI, Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction; ASSIST, Revascularization Strategies for ST Elevation Myocardial Infarction Trial; BRAVE-3, Bavarian Reperfusion Alternatives Evaluation 3; CADILLAC, Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications; SPECT, Single Photon Emission Computed Tomography study.

Table 2 Overview of the patient characteristics at baseline

Study, treatment groups	ITT population, n	Men, %	Age in years, mean (SD) or median [range]	Patients with diabetes, %	Y/N (yes/no), dose (once daily unless otherwise specified), and ticlopidine or clopidogrel is used (not at the same time)			
					Aspirin		Ticlopidine	
					Before intervention	After intervention	Before intervention	After intervention
HORIZONS-AMI[16–18]								
Heparin + GPI	1802	76	61 [22–92]	17	Y; dose: 324 mg per os or 500 mg IV	Y; dose: 75–81 mg	Y; dose: 500 mg	NR
Bivalirudin	1800	77	60 [26–92]	16				
ASSIST[34]								
Heparin + GPI	201	81	60 (12)	14	Y; dose: 160 mg per os	Y; dose: 81–325 mg	NR	NR
Heparin	199	72	61 (12)	18				
ON-TIME2*[,27,28]								
Heparin + GPI	491	77	62 (12)	12	Y; dose: 500 mg IV	NR	NR	NR
Heparin	493	75	62 (12)	11				
BRAVE-3[35]								
Heparin + GPI	401	76	62 (12)	19	Y; dose: 500 mg IV	Y; dose: 100 mg per os twice daily	NR	NR
Heparin	399	73	62 (12)	16				
Heparin + GPI	1052	74	60 [24–94]	18	Y; dose: NR	Y; dose: NR	Y; dose: NR	Y; dose: NR
Heparin	1030	72	59 [21–95]	16				
Fu et al[30]								
Heparin + GPI	72	90	54 (11)	18	Y; dose: 300 mg	Y; dose: 300 mg	NR	NR
Heparin	78	90	52 (10)	21				
ON-TIME2*[,26] substudy								
Heparin + GPI	536	76	61 (12)	11	Y; dose: 500 mg	NR	NR	NR
Heparin	537	79	62 (12)	9				
ACE[21,22]								
Heparin + GPI	200	76	64 [36–90]	17	Y; dose: 325 mg per os or 250 mg IV	Y; dose: 325 mg	NR	Y; dose: 500 mg
Heparin	200	79	63 [32–90]	19				
Montalescot et al[38]								
Heparin + GPI	149	85	60 (13)	15	Y	NR	NR	Y; dose: 250 mg twice daily
Heparin	151	78	62 (13)	20				

Notes: *In the base case analysis and scenario 1, data from the ON-TIME2 trial by Van't Hof et al 2008 and ten Berg et al 2010 were used since they only report data from the double-blinded phase, which has a higher internal validity. In a scenario 2 and 3 analysis, the open-label phase patients from ON-TIME2, as reported by Heestermans et al 2009, were included as well. To avoid double counting of patients both Heestermans et al 2009 and Van't Hof et al 2008 were not combined, at the same time, in an individual analysis.
Abbreviations: ACE, Abciximab and Carbostent Evaluation; GPI, glycoprotein IIB/IIIa inhibitor; ITT, intention to treat; IV, intravenous; MI, myocardial infraction; n, number of patients; N, no; NR, not reported; ON-TIME2, Ongoing Tirofiban In Myocardial Infarction Evaluation 2; per os, orally; PPCI, primary percutaneous coronary intervention; SD, standard deviation; Y, yes; HORIZONS-AMI, Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction; ASSIST, Revascularization Strategies for ST Elevation Myocardial Infarction Trial; BRAVE-3, Bavarian Reperfusion Alternatives Evaluation 3; os, orally; IQR, interquartile range.

Other ischemic outcomes tended to be numerically reduced by the use of bivalirudin in comparison with heparin monotherapy. It is expected that at 30 days, 1.4% of patients suffer from a myocardial infarction after treatment with bivalirudin in comparison with 1.8% after treatment with heparin monotherapy (OR, 0.79; CrL, 0.40–1.55). At 1 year, the incidence of myocardial infarction was 2.4% for bivalirudin versus 3.7% for heparin monotherapy (OR, 0.63; CrL, 0.34–1.16).

The occurrence of stroke at 1 year is uncertain, especially in comparison with other outcomes. The wide credibility interval is likely a result of the low number of studies included (only the CADILLAC and Abciximab and Carbostent Evaluation trials reported data on this outcome) and the low incidence of events (<5) in the different trials. For example, the Abciximab and Carbostent Evaluation trial reported no cases of stroke in the heparin + GPI strategy and only one case of stroke after using heparin monotherapy.

Furthermore, the incidence of thrombolysis in myocardial infarction (TIMI) major bleeding was 2.6% with bivalirudin, versus 3.1% for heparin monotherapy (OR, 0.85; CrL, 0.47–1.52). Scenario 1 showed consistent results for TIMI major bleeding at 30 days (OR, 0.78; CrL, 0.42–1.47). The risk for a TIMI minor bleeding was

Table 2 (*Continued*)

Clopidogrel		Time from symptom onset to hospital arrival, median [IQR] in hours	Patients who previously had MI, %	Patients who previously had PPCI, %	PPCI, %	Stent implanted, %
Before intervention	**After intervention**					
Y; dose: 300 or 600 mg	Y; dose: 75 mg per os	2.1 (1.3–3.9)	11	11	93	88
		2.2 (1.3–4.0)	10	10	93	90
Y; dose: 600 mg per os	Y; dose: 75 mg per os	1.5 (0.8–2.5)	11	8	95	93
		1.5 (0.9–1.3)	14	8	93	92
Y; dose: 600 mg per os	NR	NR	9	10	87	90
		NR	8	8	89	90
Y; dose: 600 mg per os	Y; dose: 75 mg per os	3.5 (1.8–7.0)	10	NR	NR	NR
		3.6 (1.8–7.8)	11	NR	NR	NR
Y; dose: NR	Y; dose: NR	1.7 (1.0–3.2)	15	12	NR	56
		1.9 (1.5–2.7)	13	10	NR	58
Y; dose: 300 mg	Y; dose: 75 mg	NR	50	NR	NR	NR
		NR	51	NR	NR	NR
Y; dose: 600 mg	NR	NR	7	7	NR	100
		NR	7	7	NR	100
NR	Y; dose: 75 mg	NR	10	4	NR	99
		NR	12	6	NR	99
NR	NR	NR	14	18	NR	NR
		NR	7	10	NR	NR

numerically lower, with bivalirudin 3.4% compared with heparin monotherapy 4.7% (OR, 0.70; CrL, 0.41–1.18). Only the base case analysis was performed for TIMI minor bleeding. The incidence of combined TIMI major and minor bleeding at 30 days was significantly lower with bivalirudin than with heparin monotherapy (5.9% versus 8.6%; OR, 0.66; CrL, 0.45–0.98).

Other outcomes that were reported were ischemic TVR at 30 days and MACE at 1 year. Bivalirudin results in a 2.9% risk for ischemic TVR versus 3.9% with heparin monotherapy (OR, 0.75; CrL, 0.38–1.46). The incidence of MACE is 14% with a bivalirudin treatment strategy in

comparison with 15.4% with heparin monotherapy (OR, 0.90; CrL, 0.66–1.22).

For all outcomes, the fixed-effect model was chosen because of lower DIC values, a limited number of studies included in the NMA, and smaller confidence intervals. The results of scenario analyses were in line with the base case analyses (Table 5).

Discussion

The main body of evidence of bivalirudin in STEMI patients undergoing PPCI is derived from RCTs that have demonstrated bivalirudin to be superior to UFH + GPI, which in

Table 3 Overview of effectiveness and probabilities of bivalirudin in comparison to heparin + GPI or heparin monotherapy (base case)

Outcomes and comparator	Fixed effects model			Random effects model		
	OR	CrL	Probability that bivalirudin is better than comparator	OR	CrL	Probability that bivalirudin is better than comparator
Outcomes at 30 days						
Mortality						
Heparin + GPI	0.65	0.43–1.00	98.0%	0.65	0.22–1.88	90.7%
Heparin	0.55	0.32–0.95	98.8%	0.55	0.17–1.86	93.6%
Stroke						
Heparin + GPI	1.19	0.53–2.74	35.6%	1.17	0.09–15.43	47.0%
Heparin	0.88	0.37–2.13	98.1%	0.52	0.02–6.99	95.3%
Myocardial infarction						
Heparin + GPI	1.03	0.63–1.70	51.6%	1.03	0.16–6.35	57.8%
Heparin	0.79	0.40–1.55	91.5%	0.76	0.09–5.52	87.7%
TIMI minor bleeding						
Heparin + GPI	0.61	0.42–0.87	99.9%	0.61	0.07–4.99	92.3%
Heparin	0.70	0.41–1.18	90.9%	0.76	0.07–9.04	68.8%
TIMI major bleeding						
Heparin + GPI	0.59	0.42–0.83	>99.9%	0.59	0.11–3.14	96.1%
Heparin	0.85	0.47–1.52	71.0%	0.83	0.12–5.89	65.6%
TIMI major and minor bleeding						
Heparin + GPI	0.59	0.46–0.76	>99.9%	0.59	0.08–4.48	92.5%
Heparin	0.66	0.45–0.98	98.0%	0.70	0.07–7.65	72.5%
Ischemic TVR						
Heparin + GPI	1.36	0.87–2.13	9.7%	1.35	0.10–17.65	49.4%
Heparin	0.75	0.38–1.46	99.2%	0.75	0.02–29.07	80.7%
Outcomes at 1 year						
Mortality						
Heparin + GPI	0.70	0.49–0.97	98.3%	0.70	0.12–4.04	79.9%
Heparin	0.50	0.31–0.79	99.9%	0.47	0.06–3.34	94.4%
Stroke						
Heparin + GPI	1.00	0.53–1.89	67.1%	0.99	0.08–12.96	66.3%
Heparin	0.73	0.12–4.00	70.3%	0.58	0.01–16.65	76.2%
Myocardial infarction						
Heparin + GPI	0.81	0.57–1.14	90.8%	0.79	0.05–12.53	67.3%
Heparin	0.63	0.34–1.16	94.4%	0.39	0.01–10.18	88.4%
MACE						
Heparin + GPI	1.00	0.81–1.22	60.5%	0.99	0.08–12.05	71.8%
Heparin	0.90	0.66–1.22	87.70%	0.89	0.03–31.74	68.5%

Abbreviations: CrL, credible limit; GPI, glycoprotein IIB/IIIa inhibitor; MACE, major adverse cardiovascular events; OR, odds ratio; TIMI, thrombolysis in myocardial infarction; TVR, target vessel revascularization.

turn had previously been shown to be superior to heparin monotherapy in this setting. Because bivalirudin has not directly been compared with heparin monotherapy in PPCI in a contemporary RCT, the objective of the current study was to indirectly compare the efficacy of bivalirudin with heparin monotherapy for the treatment of STEMI patients undergoing PPCI in the coronary stenting era. Even though network meta-analysis has limitations in comparison with the outcomes of randomized controlled trials, the evidence from this study is currently the only available option for indirect comparison of bivalirudin with heparin monotherapy.

A key question is whether the included trials were comparable enough to yield meaningful results. Scenario analyses were developed to measure the effect of the different designs of the ON-TIME2 and CADILLAC trials, but these findings did not influence base case results. These results should therefore be seen on the basis of a directional likelihood or probability, rather than certainty.

A fixed-effects model was used for all outcomes based on DIC criteria; a random-effects model may have been preferable over a fixed effects approach for myocardial infarction at 1 year, but this analysis resulted in noninformative outcomes due to nonconvergence.

Table 4 Absolute risk for an event by treatment option

	Bivalirudin		Heparin monotherapy		Heparin + GPI	
	%	CrL	%	CrL	%	CrL
Outcomes at 30 days						
Mortality	1.9	1.2–2.9	3.4	2.6–4.2	2.8	2.3–3.5
Stroke	0.5	0.2–1.4	0.6	0.3–1.1	0.4	0.2–0.8
Myocardial infarction	1.4	0.8–2.4	1.8	1.3–2.5	1.4	1.0–2.9
TIMI minor bleeding	3.4	2.3–4.8	4.7	3.5–6.2	5.4	4.4–6.5
TIMI major bleeding	2.6	1.8–3.8	3.1	2.1–4.3	4.3	3.4–5.4
TIMI major and minor bleeding	5.9	4.5–7.6	8.6	6.9–10.5	9.6	8.2–11.1
Ischemic TVR	2.9	2.0–4.2	3.9	2.6–5.6	2.2	1.7–2.8
Outcomes at 1 year						
Mortality	3.3	2.3–4.6	6.4	5.1–7.8	4.6	3.8–5.6
Stroke	0.4	0.1–1.1	0.6	0.1–1.8	0.4	0.1–1.0
Myocardial infarction	2.4	1.6–3.5	3.7	2.5–5.3	2.9	2.2–3.8
MACE	14.0	12.0–16.3	15.4	13.0–18.0	14.1	12.8–15.4

Abbreviations: %, percentage of patients; CrL, credible limit; GPI, glycoprotein IIB/IIIa inhibitor; MACE, major adverse cardiovascular events; TIMI, thrombolysis in myocardial infarction; TVR, target vessel revascularization.

Table 5 Overview of effectiveness of bivalirudin in compared heparin + GPI or heparin monotherapy for base case and scenarios

Outcomes and comparator	Base case	Scenario 1	Scenario 2	Scenario 3
	OR (95% CrL)	OR (95% CrL)	OR (95% CrL)	OR (95% CrL)
Outcomes at 30 days				
Mortality				
Heparin + GPI	0.65 (0.43–1.00)	0.65 (0.43–1.00)	0.65 (0.43–0.99)	0.65 (0.43–0.99)
Heparin	0.55 (0.32–0.95)	0.59 (0.33–1.03)	0.52 (0.30–0.90)	0.55 (0.31–0.97)
Stroke				
Heparin + GPI	1.19 (0.53–2.74)	1.19 (0.53–2.74)	N/A	N/A
Heparin	0.88 (0.37–2.13)	0.29 (0.05–1.31)	N/A	N/A
Myocardial infarction				
Heparin + GPI	1.03 (0.63–1.70)	1.03 (0.63–1.70)	1.03 (0.63–1.70)	1.03 (0.63–1.70)
Heparin	0.79 (0.40–1.55)	0.83 (0.41–1.67)	0.69 (0.34–1.37)	0.71 (0.34–1.45)
TIMI minor bleeding				
Heparin + GPI	0.61 (0.42–0.87)	N/A	N/A	N/A
Heparin	0.70 (0.41–1.18)	N/A	N/A	N/A
TIMI major bleeding				
Heparin + GPI	0.59 (0.42–0.83)	0.59 (0.42–0.83)	N/A	N/A
Heparin	0.85 (0.47–1.52)	0.78 (0.42–1.47)	N/A	N/A
TIMI major and minor bleeding				
Heparin + GPI	0.59 (0.46–0.76)	N/A	N/A	N/A
Heparin	0.66 (0.45–0.98)	N/A	N/A	N/A
Ischemic TVR				
Heparin + GPI	1.36 (0.87–2.13)	1.36 (0.88–2.12)	N/A	N/A
Heparin	0.75 (0.38–1.46)	0.79 (0.24–2.43)	N/A	N/A
Outcomes at 1 year				
Mortality				
Heparin + GPI	0.70 (0.49–0.97)	0.70 (0.50–0.98)	N/A	N/A
Heparin	0.50 (0.31–0.79)	0.54 (0.32–0.90)	N/A	N/A
Stroke				
Heparin + GPI	1.00 (0.53–1.89)	N/A	N/A	N/A
Heparin	0.73 (0.12–4.00)	N/A	N/A	N/A
Myocardial infarction				
Heparin + GPI	0.81 (0.57–1.14)	0.81 (0.57–1.14)	N/A	N/A
Heparin	0.63 (0.34–1.16)	0.53 (0.24–1.14)	N/A	N/A
MACE				
Heparin + GPI	1.00 (0.81–1.22)	N/A	N/A	N/A
Heparin	0.90 (0.66–1.22)	N/A	N/A	N/A

Abbreviations: CrL, credible limit; GPI, glycoprotein IIB/IIIa inhibitor; MACE, major adverse cardiovascular events; N/A, not applicable; OR, odds ratio; TIMI, thrombolysis in myocardial infarction; TVR, target vessel revascularization.

As suggested in this analysis, treatment with bivalirudin is expected to result in lower mortality rates in comparison with heparin monotherapy in STEMI patients undergoing PPCI, consistent with observations from the HORIZONS-AMI trial, in which bivalirudin therapy led to a mortality reduction compared with patients treated with UFH + GPI. In the combined TIMI major and minor bleeding analysis, bivalirudin resulted in the reduction of bleeding compared with heparin monotherapy, with an OR of 0.66 (CrL, 0.45–0.98). A common interpretation of these trial results is that GPIs increase bleeding rates, which in turn are associated with higher mortality rates. On the basis of previous trials with bivalirudin, it indeed could be conceivable that the bleeding reduction drove a substantial part of the difference in mortality, which is consistent with previous observations that suggest a strong association between bleeding and mortality.[31] Bleeding avoidance strategies should therefore be a cornerstone of appropriate pharmacotherapy during PCI, as recommended by guidelines.

Although bleeding reduction may be a mechanism through which bivalirudin reduces mortality compared with a heparin or heparin + GPI strategy, a post hoc analysis of the HORIZONS-AMI trial[32] suggested that bivalirudin reduced mortality in both patients with and without major bleeding, an observation that was similarly seen in a large registry.[33] An alternative explanation for the mortality reduction may be the potent inhibition of thrombin by bivalirudin compared with UFH, thus more effectively inhibiting thrombin's role as a critical modulator of coagulation, activation, and inflammation and potentially exerting effects beyond bleeding. Thus, effective and predictable thrombin inhibition may result in a bleeding reduction, as well as an efficacy benefit beyond bleeding and its consequences.

All other procedural characteristics and techniques (ie, radial access, use of P2Y$_{12}$ inhibitors such as prasugrel and ticagrelor) were not the subject of this analysis because the trials included did not provide data to assess the effect of these factors. Finally, a network meta-analysis has clear limitations in comparison with a randomized controlled trial and should not be viewed as a substitute for such trial data. However until such time as a randomized study is performed, the current analysis provides useful data in the comparison of bivalirudin with heparin monotherapy for patients undergoing primary PCI. The findings from this NMA are in line with the RCTs included in the analysis.

In conclusion, for patients with STEMI intended for PPCI, treatment with bivalirudin is expected to result in lower mortality rates and lower bleeding rates in comparison with heparin monotherapy. Thus, bivalirudin should be recommended over heparin monotherapy in STEMI patients undergoing PPCI.

Disclosure

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