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

Tim Kinnaird1
Goran Medic2
Gianni Casella3
Francois Schiele4
Upendra Kaul5
Peter W Radke6
Indra Eijgelshoven2
Gert Bergman2
Derek P Chew7

1Cardiff and Vale University Health Board, Cardiff, UK; 2Mapi-Health Economics Outcomes Research and Strategic Market Access, Houten, the Netherlands; 3Ospedale Maggiore, Unità Operativa di Cardiologia, Bologna, Italy; 4Hôpital Jean Minjoz, Besançon Cedex, France; 5Fortis Escorts Heart Institute and Research Centre, Okhla Road, New Delhi, India; 6Schön Klinik Neustadt, Neustadt, Germany; 7Flinders University; Department of Cardiovascular Medicine, Southern Adelaide Health Service, Bedford Park, SA, Australia

Correspondence: Goran Medic
Mapi-Health Economics Outcomes Research and Strategic Market Access, De Molen 84, 3995AX Houten, the Netherlands
Tel +31 30 63 59 055
Email gmedic@mapigroup.com

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 guidelines3,4 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 antplatelet activation drugs (aspirin and P2Y12 inhibitors). Antiplatelet aggregation drugs such as glycoprotein IIb/IIIa inhibitors (GPIs)3 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. Thrombin is an important modulator of coagulation, activation of platelets, and inflammatory pathways.

Heparins (unfractionated heparin [UFH], low-molecular weight heparin) are indirect thrombin inhibitors and have a variety of limitations, including an unpredictable anticoagulant response, unclear pharmacokinetics, and a narrow therapeutic window. In addition, heparins provide ineffective inhibition of clot-bound thrombin and include risk for heparin-induced thrombocytopenia. Moreover, the dose of heparin in PCI and, in particular, in PPCI, has never been formally assessed. 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.

Bivalirudin inhibits thrombin directly 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. In addition, bivalirudin inhibits clot-bound thrombin in addition to plasma/free thrombin and inhibits platelet activation via thrombin.

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. These benefits were sustained at 1 year and 3 years.

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, heparin monotherapy continues to be used only in a significant minority 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 (abiximab, 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 were not picked up by the search strategy. After careful review of the meta-analysis paper, it was decided that two publications, 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). 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. 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 effect (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. The results of the ON-TIME2 study for the double-blinded phase only were reported in other publications. Furthermore, the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial had a 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 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. 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 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 and the CADILLAC substudy.

**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 mentioned in the De Luca et al 2009 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

122 full publications screened

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)

15 publications included (8 trials)

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 al23 meta-analysis

Heparin + GPI

- ASSIST23  
- ON-TIME227,28  
- ON-TIME226  
- CADILLAC29,36,37  
- BRAVE-335  
- Fu et al30  
- ACE21,22  
- Montalescot et al38

Heparin monotherapy

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

Figure 2 Evidence network diagram.  
Note: Box GPI in the right hand corner shows which GIs 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\textsuperscript{9,10} 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\textsuperscript{15–18} | | | | |
| Heparin + GPI | 1,802 | RCT, OL, SB, MC | 30 days, 1 year | Major bleeding, TIMI bleeding, combined adverse clinical events |
| Bivalirudin | 1,800 | | | |
| ASSIST\textsuperscript{14} | | | | |
| Heparin + GPI | 201 | RCT | 30 days, 6 months, and in hospital | Composite of death – any cause, recurrent MI, recurrent severe ischemia, TIMI bleeding |
| Heparin | 199 | | | |
| ON-TIME2\textsuperscript{26} | | | | |
| Heparin + GPI | 536 | RCT mixed OL, DB, PC, MC | 30 days | Death, MI, urgent TVR, TIMI major bleeding, bleeding; early stent thrombosis |
| Heparin | 537 | | | |
| ON-TIME2\textsuperscript{26,27,28} | | | | |
| Heparin + GPI | 491 | RCT, DB, PC, MC | 30 days | Primary outcomes: extent of residual ST-segment deviation at 1 hour after PPCI |
| Heparin | 493 | | | |
| BRAVE-3\textsuperscript{34} | | | | |
| Heparin + GPI | 401 | RCT, DB | 30 days | Primary outcomes: infarct size in the SPECT study |
| Heparin | 399 | | | |
| CADiLLAC\textsuperscript{36,37} | | | | |
| Heparin + GPI | 1,052 | RCT, MC | 30 days, 1 year | Death, reinfarction, urgent repeat vasculatization, stroke, bleeding, NACE, MACE |
| Heparin | 1,030 | | | |
| Fu et al\textsuperscript{39} | | | | |
| Heparin + GPI | 72 | RCT | 6 months | Death, reinfarction, MACE, thrombosis, TIMI-major/minor bleeding |
| Heparin | 78 | | | |
| ACE\textsuperscript{1,22} | | | | |
| Heparin + GPI | 200 | RCT, MC | 30 days, 6 months, and 1 year | Primary outcomes: death, reinfarction, TVR, stroke |
| Heparin | 200 | | | |
| Montalescot et al\textsuperscript{40} | | | | |
| Heparin + GPI | 149 | RCT, DB, MC | 30 days, 6 months | Primary outcomes: death, reinfarction, urgent TVR |
| Heparin | 151 | | | |

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, Acrobiximab 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                                                                                                   |
|                         |                  |        |                                          |                          | Before intervention | After intervention | Ticlopidine Before intervention | After intervention |
| HORIZONS-AMI15–18        |                  |        |                                          |                          | Y; dose: 324 mg per os or 500 mg IV | Y; dose: 75–81 mg | Y; dose: 500 mg | NR |
| Heparin + GPI           | 1802             | 76     | 61 [22–92]                               | 17                       | Y; dose: 160 mg per os | 81–325 mg | NR | NR |
| Bivalirudin             | 1800             | 77     | 60 [26–92]                               | 16                       | Y; dose: 500 mg IV | NR | NR | NR |
| ASSIST14                |                  |        |                                          |                          |                                                                                                          |
| Heparin + GPI           | 201              | 81     | 60 (12)                                  | 14                       | Y; dose: 500 mg IV | NR | NR | NR |
| Heparin                 | 199              | 72     | 61 (12)                                  | 18                       | Y; dose: 100 mg per os | NR | NR | NR |
| ON-TIME220,21,28        |                  |        |                                          |                          |                                                                                                          |
| Heparin + GPI           | 491              | 77     | 62 (12)                                  | 12                       | Y; dose: 500 mg IV | NR | NR | NR |
| Heparin                 | 493              | 75     | 62 (12)                                  | 11                       | Y; dose: 100 mg per os | NR | NR | NR |
| BRAVE-323              |                  |        |                                          |                          |                                                                                                          |
| Heparin + GPI           | 401              | 76     | 62 (12)                                  | 19                       | Y; dose: 500 mg IV | NR | NR | NR |
| Heparin                 | 399              | 73     | 62 (12)                                  | 16                       | Y; dose: 100 mg per os | NR | NR | NR |
| 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 al24              |                  |        |                                          |                          |                                                                                                          |
| Heparin + GPI           | 72               | 90     | 54 (11)                                  | 18                       | Y; dose: 300 mg | Y; dose: 300 mg | NR | NR |
| Heparin                 | 78               | 90     | 52 (10)                                  | 21                       |                                                                                                          |
| ON-TIME220,21,28 substudy |                |        |                                          |                          |                                                                                                          |
| Heparin + GPI           | 536              | 76     | 61 (12)                                  | 11                       | Y; dose: 500 mg | NR | NR | NR |
| Heparin                 | 537              | 79     | 62 (12)                                  | 9                        |                                                                                                          |
| ACE21,22                |                  |        |                                          |                          |                                                                                                          |
| Heparin + GPI           | 200              | 76     | 64 [36–90]                               | 17                       | Y; dose: 325 mg per os | 325 mg | NR | Y; dose: 500 mg |
| Heparin                 | 200              | 79     | 63 [32–90]                               | 19                       |                                                                                                          |
| Montalescot et al28     |                  |        |                                          |                          |                                                                                                          |
| 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.}

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; CrI, 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; CrI, 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; CrI, 0.47–1.52). Scenario 1 showed consistent results for TIMI major bleeding at 30 days (OR, 0.78; CrI, 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: 300 mg per os           | 2.1 (1.3–3.9)                     | 11      | 93                 | 88                |
|             |                                                               | Y; dose: 600 mg per os           | 2.2 (1.3–4.0)                     | 10      | 93                 | 90                |
|             | Y; dose: 600 mg per os                                        | Y; dose: 600 mg per os           | 1.5 (0.9–1.3)                     | 14      | 93                 | 93                |
|             |                                                               | Y; dose: 600 mg per os           | 1.5 (0.9–1.3)                     | 14      | 93                 | 92                |
|             | Y; dose: 600 mg per os                                        | Y; dose: 600 mg per os           | 1.5 (0.8–2.5)                     | 11      | 95                 | 93                |
|             |                                                               | Y; dose: 600 mg per os           | 1.5 (0.8–2.5)                     | 11      | 93                 | 92                |
|             | Y; dose: 600 mg per os                                        | Y; dose: 600 mg per os           | 3.5 (1.8–7.0)                     | 10      | NR                 | NR                |
|             |                                                               | Y; dose: 600 mg per os           | 3.6 (1.8–7.8)                     | 11      | NR                 | NR                |
|             | Y; dose: 600 mg per os                                        | Y; dose: NR                      | 1.7 (1.0–3.2)                     | 15      | NR                 | NR                |
|             |                                                               | Y; dose: NR                      | 1.9 (1.5–2.7)                     | 13      | NR                 | NR                |
|             | Y; dose: 300 mg                                               | Y; dose: 75 mg                   | NR                                | 50      | NR                 | NR                |
|             |                                                               | Y; dose: 75 mg                   | NR                                | 51      | NR                 | NR                |
|             | Y; dose: 600 mg                                               | NR                                | 7                                 | 7       | NR                 | 100               |
|             |                                                               | NR                                | 7                                 | 7       | NR                 | 100               |
|             | NR                                                             | Y; dose: 75 mg                   | 10                                | 4       | NR                 | 99                |
|             |                                                               | NR                                | 12                                | 6       | NR                 | 99                |
|             |                                                                 | 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
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.

| Outcomes and comparator | Fixed effects model | Random effects model |
|-------------------------|---------------------|---------------------|
|                         | OR      | CrL    | Probability that | OR      | CrL    | Probability that |
|                         |         |        | bivalirudin is better |         |        | bivalirudin is better |
|                         |         |        | than comparator |         |        | 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.
Bivalirudin versus heparin in STEMI

**Table 4** Absolute risk for an event by treatment option

| Outcomes at 30 days                  | Bivalirudin | Heparin monotherapy | Heparin + GPI |
|--------------------------------------|-------------|---------------------|---------------|
| % CrL                                | % CrL       | % CrL               |               |
| 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**

| % CrL                                | % CrL       | % CrL               |               |
| 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) |

**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               | 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 + GPI           | 0.55 (0.32–0.95) | 0.59 (0.33–1.03) | 0.52 (0.30–0.90) | 0.55 (0.31–0.97) |
| Heparin                 | 1.19 (0.53–2.74) | 1.19 (0.53–2.74) | N/A         | N/A         |
| Stroke                  | 0.08 (0.37–2.13) | 0.29 (0.05–1.31) | N/A         | N/A         |
| Myocardial infarction   | 1.03 (0.63–1.70) | 1.03 (0.63–1.70) | 1.03 (0.63–1.70) | 1.03 (0.63–1.70) |
| TIMI minor bleeding     | 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 major bleeding     | 0.61 (0.42–0.87) | N/A         | N/A         | N/A         |
| TIMI major and minor bleeding | 0.70 (0.41–1.18) | N/A         | N/A         | N/A         |
| Ischemic TVR            | 0.59 (0.42–0.83) | N/A         | N/A         | N/A         |
| MACE                    | 1.36 (0.87–2.13) | 1.36 (0.88–2.12) | N/A         | N/A         |
| Outcomes at 1 year      | 0.75 (0.38–1.46) | 0.79 (0.24–2.43) | N/A         | N/A         |
| Mortality               | 0.70 (0.49–0.97) | 0.70 (0.50–0.98) | N/A         | N/A         |
| Heparin + GPI           | 0.50 (0.31–0.79) | 0.54 (0.32–0.90) | N/A         | N/A         |
| Heparin                 | 1.00 (0.53–1.89) | N/A         | N/A         | N/A         |
| Stroke                  | 0.73 (0.12–4.00) | N/A         | N/A         | N/A         |
| Myocardial infarction   | 0.81 (0.57–1.14) | 0.81 (0.57–1.14) | N/A         | N/A         |
| TIMI minor bleeding     | 0.63 (0.34–1.16) | 0.53 (0.24–1.14) | N/A         | N/A         |
| TIMI major and minor bleeding | 1.00 (0.81–1.22) | N/A         | N/A         | N/A         |
| Ischemic TVR            | 0.90 (0.66–1.22) | N/A         | N/A         | N/A         |

**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.
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 trial32 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 P2Y₁₂ 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
Tim Kinnaird has received honoraria as speaker or consultant from The Medicines Company. Derek P Chew’s institution has received speaker and consultancy honoraria from Astra Zeneca and Abbott Vascular. Upendra Kaul received honoraria as a speaker and consultant from Boehringer Ingelheim and Eli Lilly. He also received a research grant from Boston Scientific Corporation. Francois Schiele received research grants from GlaxoSmithKline, St Jude Medical, Sanofi-Aventis, Servier, and Daichi-Sankyo/Lilly; was a speaker for Boehringer Ingelheim, Lilly, Novartis, Sanofi-Aventis, Servier, The Medicines Company, and AstraZeneca; and provided consulting services for Sanofi, AstraZeneca, and Lilly. Gianni Casella has received honoraria as speaker from Astra Zeneca and Merck Sharp and Dohme in 2013. Peter W Radke has received honoraria as speaker or consultant from AstraZeneca, Bayer, Bristol Myers Squibb, Daichi Sankyo, Novartis, and The Medicines Company and has received research grants from the German Heart Foundation. Gert Bergman, Indra Eijgelshoven, and Goran Medic received institutional research funding from The Medicines Company.

References
1. Aisagbonhi O, Rai M, Ryzhov S, Atria N, Feoktistov I, Hatzopoulos AK. Experimental myocardial infarction triggers canonical Wnt signaling and endothelial-to-mesenchymal transition. Dis Model Mech. 2011;4(4):469–483.
2. National Institute for Health and Clinical Excellence. Health Technology Appraisal. Bivalirudin for the treatment of ST-segment elevation myocardial infarction. July 2011. http://www.nice.org.uk/nicemedia/live/13513/55411/55411.pdf. Accessed: February 19, 2013.
3. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2012;33(20):2569–2619.
4. Levine GN, Bates ER, Blankenship JC, et al; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; Society for Cardiovascular Angiography and Interventions. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. J Am Coll Cardiol. 2011;58(24):e44–e122.
5. Brummel-Ziedins K, Undas A, Orfeo T, et al. Thrombin generation in acute coronary syndrome and stable coronary artery disease: dependence on plasma factor composition. J Thromb Haemost. 2008;6(1):104–110.
6. Jennings LK. Mechanisms of platelet activation: need for new strategies to protect against platelet-mediated atherothrombosis. Thromb Haemost. 2009;102(2):248–257.
7. Henry TD. Overcoming heparin limitations in high-risk percutaneous coronary intervention: the alternative strategy – replacing heparin with bivalirudin. *J Investig Cardiol*. 2002;14 Suppl B:19B–29B.

8. Weitz JI, Buller HR. Direct thrombin inhibitors in acute coronary syndromes: present and future. *Circulation*. 2002;105(8):1004–1011.

9. Weitz JI, Hudoba M, Massel D, Maragano J, Hirsh J. Clot-bound thrombin is protected from inhibition by heparin-antithrombin III but is susceptible to inactivation by antithrombin III-independent inhibitors. *J Clin Invest*. 1990;86(2):385–391.

10. Mascelli MA, Delargyris EN, Damaraju LV, et al. Antibodies to platelet factor 4/heparin are associated with elevated endothelial cell activation markers in patients with acute coronary ischemic syndromes. *J Thromb Thrombolysis*. 2004;18(3):171–175.

11. Hirsh J, Warkentin TE, Raschke R, Granger C, Ohman EM, Dahlen JE. Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing considerations, monitoring, efficacy, and safety. *Chest*. 1998;114(Suppl 5):489S–510S.

12. Allie DE, Litzman MD, Wyatt CH, et al. Bivalirudin as a foundation anticoagulant in peripheral vascular disease: a safe and feasible alternative for renal and iliac interventions. *J Investig Cardiol*. 2003;15(6):334–342.

13. Robson R. The use of bivalirudin in patients with renal impairment. *J Investig Cardiol*. 2000;12 Suppl F:33F-6.

14. Weitz J, Maragano J. The thrombin-specific anticoagulant, bivalirudin, completely inhibits thrombin-mediated platelet aggregation. *Am J Cardiol*. 2001;88(Suppl 5A):83G.

15. Kimmelstiel C, Zhang P, Kapur NK, et al. Bivalirudin is a dual inhibitor of thrombin and collagen-dependent platelet activation in patients undergoing percutaneous coronary intervention. *Circ Cardiovasc Interv*. 2011;4(2):171–179.

16. Stone GW, Witzenbichler B, Guagliumi G, et al; HORIZONS-AMI Trial Investigators. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med*. 2008;358(21):2218–2230.

17. Mehran R, Lansky AJ, Witzenbichler B, et al; HORIZONS-AMI Trial Investigators. Bivalirudin in patients undergoing primary angioplasty for acute myocardial infarction (HORIZONS-AMI): 1-year results of a randomised controlled trial. *Lancet*. 2009;374(9696):1149–1159.

18. Stone GW, Witzenbichler B, Guagliumi G, et al; HORIZONS-AMI Trial Investigators. Heparin plus a glycoprotein IIb/IIIa inhibitor versus bivalirudin monotherapy and paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction (HORIZONS-AMI): final 3-year results from a multicentre, randomised controlled trial. *Lancet*. 2011;377(9784):2193–2204.

19. Gitt AK, Zeymer U, Zahn R, et al. Current Practice of PCI for ACS and Stable Angina in Europe 2005–2008 – Lessons from the EHS PCI-Registry. Sophia Antipolis, France: European Society of Cardiology; 2009. Available from: http://osp.escardio.org/essources/view.aspx?ecid=33&sid=4993. Accessed February 21, 2013.

20. Sweedheart – RIKSHA, SEP’HIA, CAAR, EART SURGERY, AVI. Annual Report 2011. Stockholm, Sweden. 2011 http://www.ucr.uu.se/sweedheart/index.php/dokument/doc_download/178-sweedheart-annual-report-2011-english. Accessed: February 19, 2013.

21. Antoniucci D, Rodriguez A, Hempel A, et al. A randomized trial comparing primary infarct artery stenting with or without abciximab in acute myocardial infarction. *J Am Coll Cardiol*. 2003;42(1):1879–1885.

22. Antoniucci D, Migliorini A, Parodi G, et al. Abciximab-supported infract artery stent implantation for acute myocardial infarction and long-term survival: a prospective, multicenter, randomized trial comparing infract artery stenting plus abciximab with stenting alone. *Circulation*. 2004;109(14):1704–1706.

23. De Luca G, Navarese E, Marino P. Risk profile and benefits from Gp IIb-IIIa inhibitors among patients with ST-segment elevation myocardial infarction treated with primary angioplasty: a meta-regression analysis of randomized trials. *Eur Heart J*. 2009;30(22):2705–2713.

24. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med*. 2004;23(20):3105–3124.

25. Spiegelhalter DJ, Abrams KR, Myles JP. Bayesian Approaches to Clinical Trials and Health-Care Evaluation (Statistics in Practice). Chichester, United Kingdom: Wiley; 2004.

26. Heestermans AA, Van Werkum JW, Hamm C, et al. Marked reduction of early stent thrombosis with pre-hospital initiation of high-dose Tirofiban in ST-segment elevation myocardial infarction. *J Thromb Haemost*. 2009;7(10):1612–1618.

27. ten Berg JM, van ’t Hof AW, Dill T, et al; On-TIME 2 Study Group. Effect of early, pre-hospital initiation of high bolus dose tirofiban in patients with ST-segment elevation myocardial infarction on short- and long-term clinical outcome. *J Am Coll Cardiol*. 2010;55(22):2446–2455.

28. Van’t Hof AW, Ten Berg J, Heestermans T, et al; Ongoing Tirofiban In Myocardial infarction Evaluation (On-TIME) 2 study group. Prehospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): a multicentre, double-blind, randomised controlled trial. *Lancet*. 2008;372(9638):537–546.

29. Cox DA, Stone GW, Grines CL, et al; CADILLAC Investigators. Comparative early and late outcomes after primary percutaneous coronary intervention in ST-segment elevation and non-ST-segment elevation acute myocardial infarction (from the CADILLAC trial). *Am J Cardiol*. 2006;98(3):331–337.

30. Fu KH, Hao QQ, Jia XW, et al. Effect of tirofiban plus clopidogrel and aspirin on primary percutaneous coronary intervention via transradial approach in patients with acute myocardial infarction. *Chin Med J (Engl)*. 2008;121(6):522–527.

31. Kinnaird TD, Stable E, Mintz GS, et al. Incidence, predictors, and prognostic implications of bleeding and blood transfusion following percutaneous coronary interventions. *Am J Cardiol*. 2003;92(8):930–935.

32. Stone GW, Clayton T, Mehran R, Deliagyris M, Prats J, Pocock S. Bivalirudin reduces cardiac mortality in patients with and without major bleeding: The HORIZONS-AMI trial. *J Am Coll Cardiol*. 2012;60(17_S): Abstract TCT-52.

33. Garratt KN, Cohen HA, Fan W. Mortality Reductions Linked to Bivalirudin Use in Unselected Angioplasty Patients With and Without Bleeding Complications. *J Am Coll Cardiol*. 2010;56(Suppl 13):B28.

34. Le May MR, Wells GA, Glover CA, et al. Primary percutaneous coronary angioplasty with and without eptifibatide in ST-segment elevation myocardial infarction: a safety and efficacy study of integrilin-facilitated versus primary percutaneous coronary intervention in ST-segment elevation myocardial infarction (ASSIST). *Circ Cardiovasc Interv*. 2009;2(4):330–338.

35. Mehilli J, Kastrati A, Schulz S, et al; Bavarian Reperfusion Alternatives Clinical Trials and Health-Care Evaluation (Statistics in Practice) treatment comparisons. *Circulation*. 2009;119(14):1933–1940.

36. Ashby DT, Aymong EA, Tcheng JE, et al; CADILLAC Trial. Outcomes following bail-out abciximab administration during primary intervention in acute myocardial infarction (The CADILLAC Trial). *Am J Cardiol*. 2003;92(9):1091–1094.

37. Tcheng JE, Kandzari DE, Grines CL, et al; CADILLAC Investigators. Bivalirudin Use in Unselected Angioplasty Patients With and Without Bleeding Complications. *Circ Cardiovasc Interv*. 2010;3(2):171–179.

38. Antoniucci D, Migliorini A, Parodi G, et al. Abciximab-supported infract artery stent implantation for acute myocardial infarction and long-term survival: a prospective, multicenter, randomized trial comparing infract artery stenting plus abciximab with stenting alone. *Circulation*. 2004;109(14):1704–1706.

39. De Luca G, Navarese E, Marino P. Risk profile and benefits from Gp IIb-IIIa inhibitors among patients with ST-segment elevation myocardial infarction treated with primary angioplasty: a meta-regression analysis of randomized trials. *Eur Heart J*. 2009;30(22):2705–2713.

40. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med*. 2004;23(20):3105–3124.
