Bivalirudin as compared to unfractionated heparin among patients undergoing coronary angioplasty
A meta-analysis of randomised trials

Giuseppe De Luca; Ettore Cassetti; Monica Verdoia; Paolo Marino
Division of Cardiology, Maggiore della Carità Hospital, Eastern Piedmont University A. Avogadro, Novara, Italy

Summary
It has been shown that bleeding complications are associated with higher mortality rates among patients undergoing coronary angioplasty. Due to its properties, bivalirudin may provide benefits in terms of bleeding and thrombotic complications as compared to unfractionated heparin (UFH). The aim of the current study was to perform a meta-analysis of randomised trials to evaluate whether bivalirudin might offer benefits in terms of mortality as compared to UFH.

We obtained results from all randomised trials evaluating the benefits of adjunctive bivalirudin as compared to UFH with or without Gp IIb-IIIa inhibitors among patients undergoing coronary angioplasty. The literature was scanned by formal searches of electronic databases (MEDLINE and CENTRAL) from January 1990 to October 2008. The following keywords were used: randomised trial, coronary angioplasty, stent, reperfusion, primary angioplasty, bivalirudin, direct thrombin inhibitors, hirulog. Primary endpoint was mortality. Secondary endpoint was infarction. Safety endpoint was the risk of major bleeding complications. No language restriction was applied.

Keywords
Antithrombin, clinical trials, direct antithrombin agents, acute myocardial infarction, coronary angioplasty, bivalirudin

Introduction
A great improvement has been observed in the last few years in the percutaneous treatment of coronary artery disease due to advances in mechanical devices and antithrombotic therapies (1–7). However, bleeding complications still represent the achille’s heel of coronary angioplasty, and are related to the strength of anticoagulation and antithrombotic therapies. Despite the low costs, several potential disadvantages of unfractionated heparin (UFH) should be mentioned: 1) dependency on antithrombin III for inhibition of thrombin activity; 2) inability to inhibit clot-bound thrombin; 3) sensitivity to platelet factor 4 and risk of heparin-induced thrombocytopenia (8); 4) marked inter-individual variability in therapeutic response; 5) the need for frequent aPTT monitoring. In order to overcome these limitations several new antithrombotic therapies have been proposed (9). Direct thrombin inhibitors have important biologic and pharmacokinetic advantages over heparins (10–12). Direct thrombin

A total of nine randomised trials were included in the meta-analysis, with 15655 patients randomised to bivalirudin and 13104 patients randomised to UFH. We did not observe any difference in mortality between bivalirudin and UFH (1.73% vs 1.67%, p = 0.15) without any relationship between the baseline risk of mortality (r = 0.17, p = 0.71) or the reduction in major bleeding complications (r = −0.29, p = 0.53) and the benefits in mortality with bivalirudin. A trend in higher risk of myocardial infarction was observed with bivalirudin (6.9% vs 5.9%, p = 0.07, p het = 0.65). Bivalirudin was associated with a significant reduction in major bleeding complications (1.7% vs 3.4%, p < 0.0001), as compared to UFH.

This meta-analysis shows that among patients undergoing coronary angioplasty, bivalirudin is associated with significant reduction in major bleeding complications. However, these benefits did not translate into benefits in mortality, with even a trend in higher risk of myocardial infarction.
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inhibitors are able to specifically block both fluid-phase and tissue-bound thrombin and, therefore, reduce thrombin activity more effectively than UFH and low molecular weight heparin (LMWH). Because they do not bind to plasma proteins and are not inactivated by heparinas, direct thrombin inhibitors also produce a more predictable anticoagulant response than UFH. Experimental results have shown that direct thrombin inhibitors are highly effective in the prevention of thrombus formation in models of arterial thrombosis (13–14). In addition, Bivalirudin has been shown to reduce platelet and monocyte activation in patients undergoing elective percutaneous coronary intervention (PCI), as compared to UFH (15). Bivalirudin is the direct antithrombin inhibitor so far mostly investigated among patients undergoing coronary angioplasty, and it has been shown to provide benefits in terms of major bleeding complications (7, 16–24). Despite the significant impact of bleeding complications on mortality observed among patients undergoing coronary angioplasty, and it has been shown to provide benefits in terms of major bleeding complications (7, 16–24). Despite the significant impact of bleeding complications on mortality observed among patients undergoing coronary angioplasty (25–27), the benefits from bivalirudin in terms of mortality are still unclear. Thus, the aim of the current study was to perform a meta-analysis of randomised trials to evaluate whether bivalirudin, as compared to UFH, might offer benefits in terms of mortality.

**Methods**

**Eligibility and search strategy**

We obtained results from all RCTs (randomised controlled trials) on adjunctive bivalirudin as compared to UFH with or without Gp IIb-IIIa inhibitors among patients undergoing coronary angioplasty. The literature was scanned by formal searches of electronic databases (MEDLINE and CENTRAL) from January 1990 to October 2008, the scientific session abstracts in Circulation, Journal of College of Cardiology, European Heart Journal and American Journal of Cardiology from January 1990 to October 2008. Furthermore, oral presentations and/or expert slide presentations were included (searched on the TCT (www.tctmd.com), EuroPCR (www.europcr.com), ACC (www.acc.org), AHA (www.aha.org), and ESC (www.escardio.org) websites from January 2002 to October 2008. The following keywords were used: randomised trial, bivalirudin, hirulog, anticoagulation, acute coronary syndrome, myocardial infarction, reperfusion, primary angioplasty, coronary angioplasty, stent. No language restrictions were enforced.

**Data extraction and validity assessment**

Data were independently abstracted by the investigators. In case of incomplete or unclear data, authors, where possible, were contacted. Disagreements were resolved by consensus. Data were managed according to the intention-to-treat principle.

**Outcome measures**

Clinical endpoints assessed were mortality (primary endpoint) and infarction (secondary endpoint) at follow-up, whereas major bleeding complications (according TIMI [thromolysis in myocardial infarction] major bleeding definition when available, or according to study definition) were assessed as safety endpoint.

**Data analysis**

Statistical analysis was performed using the Review Manager 4.27 freeware package, SPSS 11.5 statistical package. Odds ratio (OR) and 95% confidence intervals (95% CI) were used as summary statistics. The pooled odds ratio was calculated by using a fixed effect model (the Mantel-Haenszel method) and the random effect model. Study weight calculation was based on the inverse variance of the effects estimates. Between study heterogeneity was analysed by means of $I^2 = [(Q - df) / Q] \times 100\%$, where $Q$ is the $\chi^2$ statistic, and $df$ is its degrees of freedom. This describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). A value greater than 50% may be considered substantial heterogeneity. The potential publication bias was examined by constructing a “funnel plot”, in which the standard error (SE) of the ln odds ratio was plotted against the odds ratio (mortality). In addition, a linear regression approach to measure funnel plot asymmetry was used (28).

A meta-regression analysis was carried out, as previously described (29), to evaluate the relationship between 1) mortality benefits from bivalirudin (as odds ratio) and baseline risk of...
STUDY | Period | n | Population | FU (days) | Age | Diabetes | Renal failure | Gp Iib-Illa | Study-drug design | Bleeding definition | Primary endpoint
--- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | ---
BAS | 1993–1994 | 4312 | Unstable angina – Post-MI angina | 180 | 63 | 62 | 21 | 21 | n.d. | n.d. | 0 | Overt bleeding with a decrease in Hb ≥ 3 gr/dl, the need of transfusion, intracranial or retroperitoneal bleeding | In-hospital death, MI, abrupt vessel closure, repeat revascularisation, IABP.
CA-CHET | 1998–2000 | 153 | Elective | 7 | 65 | 62 | n.d. | n.d. | n.d. | n.d. | 31 | 100 | Bivalirudin (bolus 0.75 mg/Kg) followed by infusion at 1.75 mg/kg/h) + provisional abciximab (n = 59) vs UFH (bolus 70 IU/kg) + planned abciximab (n = 94) | Overt bleeding with a decrease in Hb ≥ 3 gr/dl or transfusion of ≥ 2 units of blood, intracranial, intraocular or retroperitoneal bleeding | Combined death, Myocardial infarction, or revascularisation at 7 days.
REPLACE-1 | 2000–2001 | 1056 | Elective | 2 | 64.3 | 64.4 | 31.4 | 28.9 | n.d. | n.d. | 71.1 | 72.5 | Periprocedural bivalirudin (bolus 0.75 mg/Kg, followed by infusion at 1.75 mg/kg/h) (n = 532) vs UFH (Bolus 60–70 IU/Kg) (n = 524) | Overt bleeding with a decrease in Hb ≥ 3 gr/dl or transfusion of ≥ 2 units of blood, intracranial, intraocular or retroperitoneal bleeding | Composite death, MI, repeat revascularisation at 48 hours
REPLACE-2 | 2001–2002 | 6002 | Elective | 180 | 62.6 | 62.6 | 28.1 | 26.1 | n.d. | n.d. | 7.2 | 96.5 | Periprocedural bivalirudin (bolus 0.75 mg/Kg, followed by infusion at 1.75 mg/kg/h) (n = 2994) vs UFH (Bolus 65 IU/Kg) and Gp Iib-Illa inhibitors infused for 12–18 hours (n = 3008) | Overt bleeding with a decrease in Hb ≥ 3 gr/dl, any decrease in Hb ≥ 4 gr/dl, or transfusion of ≥ 2 units of blood, intracranial, intraocular or retroperitoneal bleeding | Combined MACE and major bleedings at 30 days
ACUITY | 2003–2005 | 7789 | ACS | 30 | 63 | 63 | 28 | 28 | 18 | 19 | 53 | 97 | Periprocedural bivalirudin (bolus 0.75 mg/Kg, followed by infusion at 1.75 mg/kg/h) (n = 2619) vs Periprocedural bivalirudin (bolus 0.75 mg/Kg, followed by infusion at 1.75 mg/kg/h) and Gp Iib-Illa inhibitors infused for 12–18 hours (n = 2609) vs UFH (Bolus 65 IU/Kg) and Gp Iib-Illa inhibitors infused for 12–18 hours (n = 2561) | Intracranial, intraocular bleeding, haemorrhage at the access site requiring intervention, haematoma > 5 cm, overt bleeding with a decrease in Hb ≥ 3 gr/dl, any decrease in Hb ≥ 4 gr/dl, reoperation for bleeding, or transfusion of blood products | MACE, major bleedings and net clinical outcome (combined MACE or major bleedings)
HORIZONS | 2005–2007 | 3602 | STEMI | 30 | 59.8 | 60.7 | 15.6 | 17.3 | 15.8 | 17.4 | 7.2 | 94.5 | Periprocedural Bivalirudin (bolus 0.75 mg/Kg, followed by infusion at 1.75 mg/kg/h) (n = 1800) vs UFH (Bolus 60 IU/Kg) + Gp Iib-Illa inhibitors (Bolus plus 12–18 hours infusion) (n = 1802) | ACUITY definition | Major bleedings and net clinical outcome (combined MACE or major bleedings)

Table 1: Characteristics of randomised trials on bivalirudin among patients undergoing coronary angioplasty.
MI = Myocardial Infarction; ACS = Acute Coronary Syndromes; UFH = Unfractionated Heparin.

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### Table 1: Continued

<table>
<thead>
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<th>Combined MACE and major bleeding complications</th>
<th>In-hospital major bleeding complications</th>
<th>Combined MACE and major bleeding complications</th>
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<td>REPLACE-2 definition</td>
<td>REPLACE-2 definition</td>
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<td>Study-drug design</td>
<td>UFH (70 IU/Kg) + Tirofiban (bolus 12 µg/Kg, followed by infusion 0.15 µg/Kg/min) vs bivalirudin (Bolus 0.75 mg/Kg, followed by infusion 1.75 Kg/h)</td>
<td>Periprocedural Bivalirudin (Bolus 0.75 mg/Kg, followed by infusion 1.75 Kg/h) vs UFH</td>
<td>Periprocedural Bivalirudin (Bolus 0.75 mg/Kg, followed by infusion 1.75 Kg/h) vs UFH</td>
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<td>FU (days)</td>
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<td>Isolated myocardial infarction (TIMI 3 flow) or high-dose Tirofiban.</td>
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<td>ISAR-REACT 3</td>
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Results

A total of 10 RCTs were initially identified (Figure 1) (7, 16–24). One trial (22) was excluded because substudy of a RCT (21). Thus, a total of nine RCTs were finally evaluated, including 15,655 patients randomised to bivalirudin and 13,104 patients randomised to UFH. Characteristics of included trials are reported on Table 1. The BAS trial (16) was the first conducted trial, including patients with unstable angina or postinfarction angina with high-dose of both UFH (175 mg/Kg) and bivalirudin (Bolus of 1 mg/Kg followed by infusion of 2.5 mg/Kg/hour). In the REPLACE-2 trial (19) elective patients were randomly assigned to bivalirudin or UFH and planned Gp IIb-IIIa inhibitors, whereas in the ISAR-REACT 3 (21) patients received UFH alone. In the HORIZONS trial (7) bivalirudin was compared to UFH and Gp IIb-IIIa inhibitors (Abciximab or Eptifibatide) in patients undergoing primary angioplasty. Patients were additionally randomised to DES (drug eluting stent) (Taxus) or BMS (bare metal stent). In the ACUITY trial, NSTEMI (non ST-segment elevation myocardial infarction) patients undergoing planned early angiography were randomised according to a more complex study design to three different strategies: bivalirudin, bivalirudin plus Gp IIb-IIIa inhibitors or UFH plus Gp IIb-IIIa inhibitors. Patients receiving Gp IIb-IIIa inhibitors were additionally randomised to early (upstream) or late (downstream) administration of Gp IIb-IIIa inhibitors. We included in our meta-analysis only patients undergoing coronary angioplasty (20). The ARNO (24) trial tested the hypothesis whether the additional postprocedural administration of protamine to neutralise the effects of UFH may be equivalent to bivalirudin in elective patients. The Naples trial (23) was the only trial dedicated to diabetic patients, who were randomised to bivalirudin or UFH + high-dose Tirofiban.

### Primary endpoint

A total of 481 patients died at follow-up. We did not observe any difference in mortality between bivalirudin and UFH (1.73% vs 1.67%, OR [95% CI] = 0.88 [0.73, 1.06], p = 0.18, p het = 0.06 [fixed effect], OR [95% CI] = 0.88 [0.73, 1.06], p = 0.18, p het = 0.03 [random effect]) (Figure 2). As shown in Figure 3, no publication bias was observed. In addition, the intercept of the regression line did not significantly deviate from 0 (α [95% CI] –0.09 [-1.89 – 1.72], p = 0.90).

By meta-regression analysis we observed no relationship between the benefits in mortality with bivalirudin and the baseline risk of mortality (r = 0.17, p = 0.71) (Figure 4).

### Secondary endpoint

A total of 1,765 patients had myocardial infarction. We observed a trend in higher risk of myocardial infarction (MI) with bivalirudin mortality (as odds) in the UFH group; 2) Benefits in major bleeding complications from bivalirudin (as odds ratio) and baseline risk of major bleeding complications in the UFH group (as odds). Results are reported as regression coefficients with associated 95% CI and two-sided p-values.

The study was performed in compliance with the Quality of Reporting of Meta-Analyses (QUOROM) guidelines (30).
Figure 2: Mortality at follow-up, with odds ratios and 95\% confidence intervals (CI). The size of the data markers (squares) is approximately proportional to the statistical weight of each trial. UFH = Unfractionated Heparin; OR = odds ratio.

Figure 3: Funnel plot of all studies included in the meta-analysis. The standard error (SE) of the ln odds ratio was plotted against the odds ratio (OR) for mortality. No skewed distribution was observed suggesting no publication bias.
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din as compared to UFH (6.9% vs 5.9%, OR [95% CI] = 1.10 [0.99 – 1.21], p = 0.07, p het = 0.65 [fixed effect]; OR [95% CI] = 1.10 [0.99 – 1.21], p = 0.07, p het = 0.56 [random effect]) (Figure 5).

Safety endpoint
A total of 693 patients experienced a major bleeding complication. The rate was significantly lower with bivalirudin (1.7% vs 3.4%, OR [95% CI] = 0.51 [0.44, 0.60], p < 0.0001, p het = 0.05 [fixed effect]; OR [95% CI] = 0.52 [0.44, 0.60], p < 0.0001, p het = 0.1 [random effect]) as compared to UFH (Figure 6). No significant relationship (r = –0.61, p = 0.16) was observed between the risk of bleeding complications and the benefits in terms of major bleeding complications with bivalirudin (Figure 7). No difference was observed in terms of intracranial hemorrhage between bivalirudin and UFH (0.04% vs 0.07%, OR [95% CI] = 0.59 [0.18–1.90], p = 0.37, p het = 0.97 [fixed effect]; OR [95% CI] = 0.59 [0.17–1.87], p = 0.37, p het = 0.98 [random effect]) (Figure 8).

Discussion
This is the first meta-analysis on bivalirudin as adjunctive antithrombotic therapy among patients undergoing percutaneous coronary angioplasty. The results of our meta-analysis of nine RCTs (7, 16–21, 23–24), including 28,759 patients, showed that

Figure 4: Regression line showing no significant relationship between the benefits from bivalirudin in terms of death vs patient’s risk profile (expressed as odds of UFH group). Each trial is represented by a circle, whose size is proportional to the sample size of each trial. UFH = Unfractionated Heparin.

Figure 5: Myocardial infarction at follow-up, with odds ratios and 95% confidence intervals (CI). The size of the data markers (squares) is approximately proportional to the statistical weight of each trial. *reinfarction; UFH = Unfractionated Heparin; OR = odds ratio.
bivalirudin is associated with a significant reduction in major bleeding complications without any benefit in death or myocardial infarction.

Due to its costs, intravenous UFH is still a pivotal antithrombotic therapy among patients undergoing coronary angioplasty. Despite the significant reduction in dosage (from 140 to 60–70 U/Kg) observed in the last years, major bleeding complications are still disappointingly high and associated with higher mortality (25–27).

Due to its more favourable properties compared to UFH (9), such as more stable activity, short half life and clearance only partially (20%) mediated by the kidney, large interests have been focused on bivalirudin, with several randomised trials being conducted in the last years in patients undergoing coronary angioplasty.

The BAS trial (16) is the first randomised trial, including 4098 patients with unstable or postinfarction angina undergoing angioplasty. Despite some benefits in terms of major bleeding complication, no benefits were observed in terms of death and myocardial infarction. Similar results have been observed in the large REPLACE-2 (19). In the ISAR-REACT-3 (21), including elective patients or unstable patients with negative troponin despite the large amount of heparin (140 IU/Kg), there was no difference in terms of TIMI major bleeding complications but only in major bleedings according to the definition proposed in the REPLACE-2 (19), without any difference in death and myocardial infarction. The ACUITY trial was dedicated to patients with acute coronary syndromes undergoing coronary angioplasty.
Among patients undergoing angioplasty (those included in the meta-analysis) (20), despite the significant reduction in major bleeding complications with bivalirudin, no difference was observed in death and myocardial infarction. The HORIZONS trial (7), including patients undergoing primary angioplasty, was the only trial showing significant benefits in terms of mortality, in addition to the reduction in bleeding complications, despite a significantly higher rate of acute stent thrombosis.

Despite the already shown benefits with bivalirudin in terms of bleeding complications in several randomised trials (7, 16–24), the benefits in terms of mortality and reinfarction are still controversial. In our meta-analysis, we observed a significant reduction in major bleeding complications (1.7% vs 3.4%). However, no difference was observed in terms of mortality with even a trend in higher risk of myocardial infarction with bivalirudin as compared to UFH.

These findings may be explained by the fact that bleedings may not be by themselves the determinant of mortality, but the association with mortality may be mediated by a higher risk profile for thrombotic complications of patients at risk for bleedings (25–26), by blood transfusion (26, 31–33), and disparities in medical therapies (34).

It must be recognised that a larger use of radial approach (35–36), use of 5F sheath when femoral approach is preferred or needed (37–38), in addition to lower dosage of heparin and early sheath removal (37) with protamine administration (39), may probably suffice to reduce the risk of bleeding complications, preserving optimal antithrombotic therapies. In fact, it must be considered that excessive fear of bleeding complications might carry a higher risk of thrombotic complications due to undertreatment of patients that commonly are at higher risk of thrombotic complications. Large randomised trials are certainly needed to investigate if the benefits in major bleeding complications and mortality with bivalirudin observed in the Horizons trials among patients undergoing primary angioplasty may persist, especially in high-risk patients, even with these preventive measures aiming at minimising the risk of bleeding complications.

Limitations
This meta-analysis was not performed on individual patient's data, that would have certainly improved the results, particularly by performing subgroup analyses. No uniform definition was adopted across trials in terms of major bleeding complications. However, TIMI major bleeding definition was preferred, when available. Extensive caution should be exercised in the interpretation of the results, due to clinical and observed statistical heterogeneity among included trials, especially due to the routine use of Gp IIb-IIIa inhibitors as adjunct to UFH in many trials (7, 17–20, 23) (with potential high-risk of bleeding complications), use of protamine in the ARNO trial (24), and use of high-dose of UFH in the BAS (16) and ISAR-REACT-3 (21) trial. Finally, it must be remarked the extreme variability across trials in the duration of follow-up, that ranged from two to 180 days.

**Figure 8. Intracranial haemorrhage, with odds ratios and 95% confidence intervals (CI).** The size of the data markers (squares) is approximately proportional to the statistical weight of each trial. UFH = Unfractionated Heparin; OR = odds ratio.
Conclusions
This meta-analysis shows that among patients undergoing coro-

References

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