Bivalirudin in percutaneous coronary intervention

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Abstract

Bivalirudin is a direct thrombin inhibitor that will be available in the UK in November 2004 as adjunctive anticoagulant therapy during percutaneous coronary intervention (PCI). Its mechanism of action offers potential advantages over heparin in terms of both efficacy and bleeding. Bivalirudin is convenient – ACT monitoring is unnecessary, infusion is only for the duration of the procedure, and half-life is short so that early sheath removal and ambulation are possible. Finally, bivalirudin may offer major cost savings over glycoprotein (GP) IIb/IIIa inhibitors. The REPLACE-2 trial demonstrated equivalent efficacy and reduced bleeding with bivalirudin alone versus heparin-plus-GP IIb/IIIa inhibition in 6,010 patients undergoing elective or urgent PCI (30-day MACE 7.6% *vs.* 7.1%, major bleeding 2.4% *vs.* 4.1%). Further trials are underway to evaluate the efficacy of bivalirudin during PCI for high-risk acute coronary syndromes (ACS) and acute myocardial infarction (AMI).

This paper considers when bivalirudin should be used in contemporary PCI. The ISAR-REACT study provides firm evidence that heparin alone is safe and effective for elective PCI in low-to-moderate risk patients (30 day MACE 4% heparin-alone *vs.* 4% abciximab). Patients with AMI or unstable ACS were not included in the REPLACE-2 trial and should continue to receive GP IIb/IIIa inhibitors until further data are available. Bivalirudin could be considered in patients at intermediate risk in whom GP IIb/IIIa inhibitors are currently widely used, including during complex elective PCI, elective PCI in diabetics, and in patients with stabilised or low-risk ACS. Bivalirudin will also have a specific role in patients at increased risk of bleeding and with heparin-induced thrombocytopaenia. Further data are required before more widespread adoption of bivalirudin can be recommended.

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Introduction

In 1995 the Bivalirudin Angioplasty Study demonstrated equivalent efficacy and reduced bleeding using bivalirudin compared with heparin in over 4,000 patients undergoing coronary angioplasty for unstable or post-infarction angina.[1] Following an unfavourable cost comparison with heparin, however, development of bivalirudin was suspended. More recently, a new, less expensive, manufacturing process has been developed, and further data have emerged supporting the efficacy and safety of this anticoagulant in contemporary percutaneous coronary intervention (PCI). Bivalirudin will be available in the UK in November 2004.

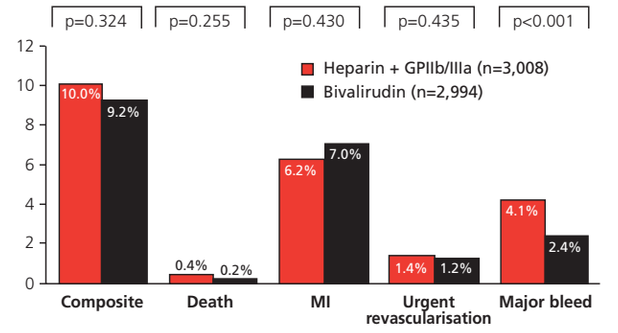
Bivalirudin is a potent direct thrombin inhibitor which can reduce thrombus burden during PCI both by blocking formation of fibrin and by suppressing platelet aggregation, since thrombin is a potent stimulus for platelet activation.[2] Bivalirudin has a number of theoretical advantages over heparin: it is able to inhibit both fluid-phase and clot-bound thrombin, it does not bind to plasma proteins, it is not neutralised by platelet factors and, unlike heparin, it does not increase platelet activation during PCI. Its binding to thrombin is non-competitive and reversible, so that haemostatic capacity is more readily restored, and hence bleeding, as well as ischaemic complications, may be reduced.[3] Finally, bivalirudin is convenient. Monitoring of ACT/APTT is unnecessary, infusion is required only for the duration of the procedure, and its short half-life enables earlier sheath removal and ambulation.

Evidence for bivalirudin in contemporary PCI

Re-analysis of the original angioplasty trial using contemporary end points and intention-to-treat analysis revealed a 22% reduction in major adverse cardiac events (MACE) (i.e. death, myocardial infarction or revascularisation) and a 62% reduction in bleeding with bivalirudin at seven days.[4] However, this trial predated coronary stents, thienopyridines and glycoprotein (GP) IIb/IIIa inhibitors. A small pilot study subsequently suggested that bivalirudin with planned or provisional abciximab may be at least as safe and effective as heparin plus abciximab during contemporary PCI, paving the way for a pivotal randomised controlled trial.[5]

The REPLACE-2 trial randomised 6,010 patients undergoing

Figure 1. Primary end points in the REPLACE-2 study showing no significant differences between any parameter except major bleeding



Key: MI = myocardial infarction

Adapted from Lincoff AM *et al.*[6]

elective or urgent PCI to receive bivalirudin with provisional GP IIb/IIIa inhibition (abciximab or eptifibatide), or heparin and planned GP IIb/IIIa inhibition.[6] Several points are important to note when interpreting the findings of this study. The trial was conceived in North America, where GP IIb/IIIa inhibitor use is routine in both elective and urgent PCI, and the investigators argued that it would be unethical to have a heparin-only control group. Instead, an imputed comparison to heparin was developed. The investigators performed a meta-analysis of two historical trials of abciximab and eptifibatide versus heparin-only during PCI to derive an assumed odds ratio for MACE with heparin-plus-GP IIb/IIIa inhibitor versus heparin-only of 0.68. Although patients undergoing urgent PCI were eligible for REPLACE-2, patients with acute myocardial infarction (AMI) or unstable acute coronary syndromes (ACS) requiring empiric GP IIb/IIIa inhibition were not included. Pre-treatment with clopidogrel was given to 86% of patients overall, although in 26% it was administered in less than two hours pre-procedure.

Thirty-day MACE occurred in 7.6% of patients in the bivalirudin *vs.* 7.1% of patients in the heparin-plus-GP IIb/IIIa inhibitor group (p=ns). Major bleeding was reduced from 4.1% with heparin-plus-GP IIb/IIIa inhibitor to 2.4% with bivalirudin (p<0.001) (figure 1). Bivalirudin was associated with a significant reduction in MACE versus the imputed heparin-only group (OR 0.62). One-year follow-up demonstrated a trend to a reduction in mortality with bivalirudin versus heparin-plus-GP IIb/IIIa inhibitor (1.9% *vs.* 2.5%, p=0.16).[7] Subgroup analysis found a significant mortality benefit in the elderly (> 75 years), and in patients with unstable angina (> 48 hours pre-procedure), as well as a strong trend to a reduction in mortality in diabetics and in patients with renal insufficiency.

In summary, REPLACE-2 demonstrated that bivalirudin has at least equivalent efficacy to heparin-plus-GP IIb/IIIa inhibitor in low-to-moderate risk patients undergoing elective or urgent PCI, with significantly reduced bleeding. Efficacy in unstable ACS patients remains unknown, while the reported superiority over heparin alone should be interpreted with caution.

The REPLACE-1 trial (published after REPLACE-2) randomised 1,056 patients to heparin versus bivalirudin, with GP IIb/IIIa inhibition in 72% of patients in each group.[8] There was no difference in MACE at 48 hours between the bivalirudin and heparin groups (5.6% *vs.* 6.9%, p=0.4), and no difference in major bleeding (2.1% *vs.* 2.7%, p=0.52). These findings suggest that concomitant administration of a GP IIb/IIIa inhibitor with bivalirudin removes the beneficial reduction in bleeding complications seen with bivalirudin alone, without any apparent gain in efficacy. Cost savings from avoiding GP IIb/IIIa inhibitor use are also lost.

Heparin only for elective PCI

With high-pressure stent deployment and thienopyridine antiplatelet therapy, elective PCI in stable patients is low-risk. Is heparin alone an adequate anticoagulant in this group? The ISAR-REACT study randomised 2,159 patients undergoing elective PCI to abciximab or placebo.[9] All patients were pre-treated with clopidogrel 600 mg ≥ 2 hours pre-procedure. High-dose heparin was given: 70 units/kg in the abciximab group and 140 units/kg in the placebo group. The incidence of MACE at 30 days was 4% in the abciximab group and 4% in the placebo group. While they represent a somewhat lower risk group, these results supersede REPLACE-2 with regards to the efficacy of heparin-only in elective PCI. The claimed superiority of bivalirudin over heparin in REPLACE-2 was based on an assumption from historical data that outcome with heparin-only is significantly worse than heparin-plus-GP IIb/IIIa inhibitor. ISAR-REACT indicates that, in elective PCI with high-dose clopidogrel pre-treatment and high-dose heparin, this assumption is incorrect.

Cost assessment of bivalirudin

In North America, where GP IIb/IIIa inhibitor use was routine in all PCI, bivalirudin has been widely adopted because of the cost savings offered. The average price of bivalirudin in the United States is US$395, compared to US$615 for eptifibatide and US$1,300 for abciximab. In the UK, no price had been issued for bivalirudin at the time of this article, but similar savings compared to GP IIb/IIIa inhibitors are likely, particularly since abciximab, at an average cost of £1,054, accounted for 95% of all GP IIb/IIIa inhibitor prescriptions during PCI in the UK in 2002.[10] However, GP IIb/IIIa inhibitors were only used at all in 44%, primarily in ACS patients, with heparin-only in the remainder. Bivalirudin may offer significant cost savings in those patients undergoing PCI who currently receive abciximab. But it is uncertain in how many of these patients bivalirudin can be considered to have equivalent efficacy to abciximab.

When might we use bivalirudin?

Elective PCI

In low-to-moderate risk patients undergoing elective PCI, heparin-only is effective and should be the strategy of choice. There is no good evidence to demonstrate superiority of

bivalirudin in this patient group and the cost implications of replacing heparin with bivalirudin would be considerable. However, effective thienopyridine pre-treatment with clopidogrel 300 mg > 6 hours pre-procedure, or 600 mg > 2 hours pre-procedure, is essential, perhaps with higher-dose heparin. In higher-risk patients undergoing complex and/or multivessel elective PCI, bivalirudin is a reasonable, and economical, alternative to GP IIb/IIIa inhibitors. Bivalirudin may also have a role in diabetics undergoing elective PCI, in whom GP IIb/IIIa inhibitors are currently considered the standard of care. Both the EPISTENT and ESPRIT trials demonstrated a greater reduction in long-term mortality with GP IIb/IIIa inhibitor therapy in diabetics than in non-diabetics.[11,12] National Institute for Clinical Excellence (NICE) guidelines support GP IIb/IIIa inhibitor use during PCI in all patients with diabetes.[13] Subgroup analysis of REPLACE-2 revealed at least equivalent efficacy of bivalirudin to heparin-plus-GP IIb/IIIa inhibition in patients with diabetes, with a trend to a reduction in one-year mortality.

Urgent PCI

The ability of bivalirudin to inhibit clot-bound thrombin may be of particular benefit during PCI in patients with ACS although patients with AMI or unstable ACS were not included in the REPLACE-2 trial. These patients should continue to receive GP IIb/IIIa inhibitors, which have proven efficacy in this setting.[14] More stable ACS patients were included in REPLACE-2 and, in this group, bivalirudin was at least as effective as heparin-plus-GP IIb/IIIa inhibition. It might be appropriate to use bivalirudin in ACS patients without markers of high-risk or in whom unstable symptoms have settled.

Specific patient subgroups

1. Increased bleeding risk

Bivalirudin markedly reduces bleeding complications compared to GP IIb/IIIa inhibitors, and in historical studies was associated with less bleeding than high-dose heparin alone.[4] Bivalirudin could be used in preference to GP IIb/IIIa inhibitors in ACS patients at high risk of bleeding. In elective patients the benefit of bivalirudin over heparin is less certain, and probably does not justify the extra cost.

2. Heparin-induced thrombocytopaenia

Up to 5% of patients given heparin develop heparin-induced thrombocytopaenia (HIT). Bivalirudin was found to be safe and effective in a single-centre registry of 52 patients with HIT, and should represent standard therapy in this small but significant patient group.[15]

3. Day-case PCI

Given its shorter half-life and the reduction in bleeding and access site complications, bivalirudin permits earlier ambulation after transfemoral PCI. Ormiston and colleagues performed transfemoral PCI with bivalirudin in 100 consecutive patients, with immediate sheath removal and ambulation after two hours.[16] One patient developed a groin haematoma and two had

Key messages

- Bivalirudin is a potent direct thrombin inhibitor that will be available in the UK in November 2004 for use as adjunctive anticoagulant therapy during PCI
- Bivalirudin offers potential advantages over heparin in terms of both efficacy and reduced incidence of bleeding
- Bivalirudin is convenient – monitoring of ACT/APTT is unnecessary, infusion is required only for the duration of the procedure, and its half-life is short, so that earlier sheath removal and ambulation are possible
- Bivalirudin is likely to offer considerable cost-savings compared to glycoprotein (GP) IIb/IIIa inhibitors
- The REPLACE-2 trial demonstrated equivalent efficacy and reduced bleeding with bivalirudin alone versus heparin-plus-GP IIb/IIIa inhibition in 6,010 patients undergoing elective or urgent PCI
- On current evidence, bivalirudin could be used in patients undergoing high-risk elective PCI, with stabilised or low-risk acute coronary syndromes, at increased risk of bleeding, and with heparin-induced thrombocytopaenia

MACE. While both transfemoral and transradial day-case PCI have been shown to be possible with heparin,[17,18] use of bivalirudin may facilitate its development.

Future developments

The efficacy of bivalirudin relative to GP IIb/IIIa inhibitors in unstable ACS and AMI remains uncertain. This issue is of particular relevance in the UK, where GP IIb/IIIa inhibitor use is predominantly in these settings. The ACUITY trial is a 13,800 patient trial of ACS patients randomised to bivalirudin or GP IIb/IIIa inhibitors, while the HORIZONS-AMI trial will compare bivalirudin and heparin-plus-GP IIb/IIIa inhibition during infarct angioplasty. These studies are underway and should determine the role of bivalirudin in these high-risk groups.

Conclusions

Bivalirudin has re-emerged as an anticoagulant therapy which offers a highly attractive combination of efficacy, safety, and convenience. At present, however, evidence to determine its place in contemporary PCI remains limited. We believe heparin alone, with effective clopidogrel pre-treatment, remains the therapy of choice in low-to-moderate-risk elective PCI. GP IIb/IIIa inhibitors are the only proven therapy in unstable ACS and AMI. However, bivalirudin may have a role in patients at intermediate risk in whom GP IIb/IIa inhibitors are currently widely used, including during complex elective PCI, elective PCI in diabetics, and in patients with stabilised ACS. Bivalirudin will also have a specific

role in patients at increased risk of bleeding and with heparin-induced thrombocytopaenia, and may facilitate the spread of day-case PCI.

Conflict of interests

APB has acted as a consultant for Nycomed, UK distributors of bivalirudin.

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