Bivalirudin: role in current percutaneous coronary intervention practice

Bivalirudin is the only thrombin-specific anticoagulant currently licensed in the UK for use as an anticoagulant during percutaneous coronary intervention. This review examines the rationale for, and data supporting, its use in contemporary percutaneous coronary intervention practice.

Since the introduction of balloon angioplasty for coronary stenoses in the late 1970s (Gruntzig et al, 1979), percutaneously-delivered strategies for the investigation and treatment of coronary disease have evolved apace. The major issues of patient safety – procedure conversion to urgent coronary artery bypass graft surgery (CABG) – and of target lesion restenosis have been drastically reduced by routine uptake of coronary artery stent deployment, adjunctive use of improved antiplatelet and anticoagulant therapies, and the development of drug coatings for stents that inhibit restenosis.

Concurrent with such refinements of percutaneous coronary intervention (PCI) practice, the delivery of revascularization therapies for coronary artery disease has undergone a paradigm shift: rates of CABG worldwide, for so long the mainstay of treatment of coronary disease, have been outstripped severalfold by the growth in number of PCI procedures. With improved safety and high rates of technical success, many patients find a minimally invasive procedure more attractive than open-heart surgery; in turn, interventional cardiologists have pushed back the boundaries of previously accepted PCI practice, tackling increasingly complex lesion subsets, including multivessel and left mainstem disease, in high-risk groups such as diabetics and patients with renal dysfunction.

PCI practice in the UK

The National Service Framework for Coronary Heart Disease (Department of Health, 2000) established new targets for revascularization in the UK, sparking growth in numbers of centres performing PCI and PCI numbers in established centres. With the decreased complication rates associated with contemporary PCI, many secondary care district general hospitals have developed 'off-site' PCI services (as cardiothoracic surgical cover is off-site) to deliver revascularization for their catchment populations. For such services to be viable, safety is vital and limiting ischaemic complications of PCI is a primary aim; administration of adjunctive pharmacotherapies, e.g. glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors (abciximab, eptifibatide, tirofiban) which potently inhibit platelet aggregation, are proven to reduce major adverse cardiac events when used during PCI with coronary stenting (EPISTENT Investigators, 1998; ESPRIT Investigators, 2000). However, they may increase the risk of bleeding complications, especially in acute coronary syndrome (ACS) patients who may also have received extensive antiplatelet, anticoagulant and fibrinolytic therapy.

Bivalirudin: mechanism of action

Bivalirudin (Angiox, Nycomed, Oxford), a recombinant hirudin analogue, binds to thrombin and thereby inhibits its procoagulant actions (De Nisio et al, 2005). Thrombin is generated as a downstream consequence of the interaction between tissue factor, exposed on damaged vascular endothelium, and factor VII; it is responsible for the conversion of fibrinogen to fibrin, the stimulation of circulating platelets and the activation of clotting factors, and is therefore central to arterial thrombogenesis. In contrast to heparin, which requires soluble thrombin and circulating antithrombin to achieve anticoagulation, bivalirudin can inhibit fibrin/clot-bound thrombin in situ and may therefore offer advantages in procedures such as PCI, where thrombus may already be present within target vessels or may form following iatrogenic vascular injury. Bivalirudin is removed from the circulation by renal excretion and hepatic metabolism, and has a short plasma half-life of only 20–25 minutes, potentially offering advantages in terms of restriction of haemorrhagic complications, but also for arterial access site haemostasis following PCI.

Bivalirudin in PCI

Initial comparisons of bivalirudin with heparin in patients undergoing balloon angioplasty following presentation with ACS suggested a reduction in adverse cardiac events, driven principally by a reduced need for early repeat revascularizations (Bittl et al, 2001). There was also a reduction in serious bleeding complications with bivalirudin compared with unfractionated heparin, which was reproduced in the subgroup of patients undergoing PCI in a large-scale meta-analysis of patients with ACS receiving direct thrombin inhibitors. However, there appeared to be no efficacy benefit in terms of major adverse cardiac events (Direct Thrombin Inhibitor Trialists' Collaborative Group, 2002).

Dr Nick West *is Consultant Cardiologist, Gloucestershire Hospitals NHS Foundation Trust, Gloucester GL1 3NN and Honorary Consultant Cardiologist, John Radcliffe Hospital, Oxford*

The REPLACE-2 trial randomized patients undergoing elective or urgent PCI to receive periprocedural anticoagulation with either unfractionated heparin plus GPIIb/IIIa inhibitor therapy or bivalirudin with provisional use of GPIIb/IIIa inhibitors (Lincoff et al, 2003; 2004). A composite outcome including death, major adverse cardiac events and serious bleeding was no different between the groups, despite only the minority of the bivalirudin arm receiving GPIIb/IIIa inhibitors. Serious bleeding complications were significantly less likely in bivalirudin-treated patients. Since this study, further subgroup analyses of the data have been carried out, and mortality data extended to 1 year; these data are summarized in *Figure 1* and confirm bivalirudin's non-inferiority to the hitherto optimal antithrombotic PCI strategy of heparin plus GPIIb/IIIa inhibitor (Saw et al, 2004; Chew et al, 2005; Gurm et al, 2005). Since REPLACE-2, it has become evident that routine GPIIb/IIIa inhibitor use may not be necessary in all PCI patients; for some elective procedures, GPIIb/IIIa therapy may offer no advantage over adequate preloading with clopidogrel (Kastrati et al, 2004).

Studies from Australasia and the USA (where over 300 000 patients had received bivalirudin to late 2004) have demonstrated substantial cost savings, reduced hospital stay and early ambulation after PCI with bivalirudin (Ormiston et al, 2002; Cohen et al, 2004; Schussler et al, 2004), as well as a lack of negative interaction with novel technologies including drug-eluting stents and distal protection or 'filter' devices used during PCI in saphenous vein graft lesions (Rha et al, 2004; 2005).

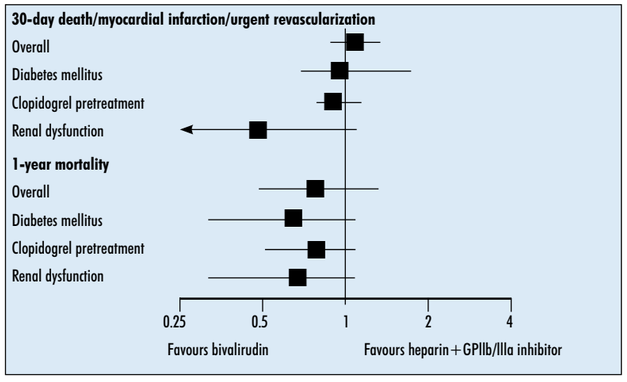
When should we use bivalirudin?

The recently-published European Society of Cardiology guidelines for PCI practice (Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology, 2005) have recommended the use of bivalirudin during PCI as an alternative to unfractionated heparin or low molecular-weight heparin with or without GPIIb/IIIa inhibitor use, whenever bleeding complications are a consideration. (It is also recommended for use in PCI in the uncommon occurrence of heparin-induced thrombocytopaenia.)

Bleeding complications may be an issue in patients undergoing urgent PCI following ACS; troponin-positive ACS patients, by NICE guidance (National Institute for Clinical Excellence, 2002), should receive GPIIb/IIIa therapy, but many UK interventional cardiologists are loath to expose these patients routinely to the potential haemorrhagic risks associated with GPIIb/IIIa use, mainly as many of these patients may also have either what is felt to be a technically straightforward lesion for PCI or have recently received extensive anticoagulant and/or thrombolytic therapy which may further aggravate bleeding risk.

GPIIb/IIIa treatment may still be the optimal therapy in some patients: insulin-treated diabetics may be at particular advantage in terms of freedom from reintervention (Marso et al, 1999) and patients undergoing primary PCI for acute ST-segment elevation myocardial infarction (for whom there are currently no data on bivalirudin use). Ongoing trials may help clarify bivalirudin's role in these cases.

Figure 1. Outcomes of patient groups in the REPLACE-2 study (n=6010 patients) comparing bivalirudin plus provisional glycoprotein IIb/IIIa (GPIIb/IIIa) use during percutaneous coronary intervention with heparin plus routine GPIIb/IIIa use; squares indicate odds ratio and bars 95% confidence intervals. Bars crossing the midline (odds ratio=1.0) indicate no difference between therapies. (Data derived from Lincoff et al, 2003, 2004; Saw et al, 2004; Chew et al, 2005; Gurm et al, 2005.)



Bivalirudin: a single-centre experience

Since being licensed for use in the UK in late 2004, 20 PCI centres have used bivalirudin, with over 2000 patient prescriptions.

GPIIb/IIIa inhibitor use during PCI in ACS was audited at the author's centre, according to NICE guidance: over a 12-month period, in 131 consecutive patients (troponin-positive and -negative), only 56% received periprocedural GPIIb/IIIa inhibitor therapy (West NEJ, Khan ZI, Chamberlain-Webber R, unpublished observations, 2005). Similar experiences are reported at other UK centres, according to audit data from the British Cardiovascular Intervention Society.

Since commencing use of bivalirudin in troponin-positive ACS patients, PCI has been performed in a further 75 patients presenting acutely over 3 months; bivalirudin has been used in 47 (63%) cases (82% of those presenting troponin-positive), with two cases also receiving GPIIb/IIIa therapy. Overall, 78% of patients (98% troponin-positive) received either bivalirudin or GPIIb/IIIa therapy, improving optimization of peri-PCI anticoagulation at a substantial cost saving. To date, there has been only one bleeding complication (a femoral access site haematoma >5 cm diameter) and no periprocedural ischaemic complications (*Figure 2*).

Conclusions

Bivalirudin appears to offer patients undergoing PCI equivalent efficacy to the established combination of unfractionated heparin plus GPIIb/IIIa inhibitor treatment, based on current data from the mixed, predominantly low-risk population in REPLACE-2. The upcoming ACUITY trial (due to report at the American College of Cardiology meeting, 2006) may shed further light on its role relative to heparin with or without GPIIb/IIIa inhibitor therapy in higher-risk patients presenting with acute coronary syndromes. The place of clopidogrel preloading in such populations will be further addressed in the ISAR REACT-2 study, also due to report next year. Such considerations aside, bivalirudin's short half-life has clearly been shown to allow early femoral arterial sheath removal and consequent ambulation, with potential relative cost savings in terms of bed use and inpatient stay, as well as absolute savings in terms of drug costs. Its use is endorsed in the European Society of Cardiology PCI guidelines (Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology, 2005) and uptake has been extensive in Europe, the USA and Australasia. **BJHM**

Conflict of interest: Dr West has received sponsorship for travel to national and international meetings from Boston Scientific, Cordis (coronary stent manufacturers), Nycomed (UK distributors of Angiox (bivalirudin)) and Lilly (manufacturers of Reopro (abciximab)).

Bittl JA, Chaitman BR, Feit F, Kimball W, Topol EJ (2001) Bivalirudin versus heparin during coronary angioplasty for unstable or postinfarction angina: final report reanalysis of the bivalirudin angioplasty study. *Am Heart J* **142:** 952–9

Chew DP, Lincoff AM, Gurm H et al (2005) Bivalirudin versus heparin and glycoprotein IIb/IIa inhibition among patients with renal impairment undergoing percutaneous coronary intervention (a subanalysis of the REPLACE-2 trial). *Am J Cardiol* **95:** 581–5

Cohen DJ, Lincoff AM, Lavelle TA et al (2004) Economic evaluation of Bivalirudin with provisional glycoprotein IIb/IIIa inhibition versus heparin with routine glycoprotein IIb/IIIa inhibition for percutaneous coronary intervention: results from the REPLACE-2 trial. *J Am Coll Cardiol* **44:** 1792–800

De Nisio M, Middeldorp S, Buller HR (2005) Direct thrombin inhibitors. *N Engl J Med* **353:** 1028–40

Department of Health (2000) *National Service Framework for Coronary Heart Disease.* Department of Health, London

Direct Thrombin Inhibitor Trialists' Collaborative Group (2002) Direct thrombin inhibitors in acute coronary syndromes: principal results of a meta-analysis based on individual patients' data. *Lancet* **359:** 294–302

EPISTENT Investigators (1998) Randomized placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with the use of platelet glycoprotein-IIb/IIIa blockade. *Lancet* **352:** 87–92

ESPRIT Investigators (2000) Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomized, placebo-controlled trial. *Lancet* **356:** 2037–44

Gruntzig AR, Senning A, Siegenthaler WE (1979) Nonoperative dilatation of coronary-artery stenosis: percutaneous transluminal coronary angioplasty. *N Engl J Med* **301:** 61–8

Gurm HS, Sarembock IJ, Kereiakes DJ et al (2005) Use of bivalirudin during percutaneous coronary intervention in patients with diabetes mellitus: an analysis from the randomized evaluation linking angiomax to reduced clinical events (REPLACE)-2 trial. *J Am Coll Cardiol* **45:** 1932–8

Kastrati A, Mehilli J, Schulen H et al (2004) A clinical trial of abciximab in elective percutaneous coronary intervention after pretreatment with clopidogrel. *N Engl J Med* **350:** 232–8

Lincoff AM, Bittl JA, Kleiman NS et al (2003) Bivalirudin and provisional glycoprotein IIb/IIIa blockade vs heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary revascularization: the REPLACE-2 randomized trial. *JAMA* **289:** 853–63

Lincoff AM, Kleiman NS, Kereiakes DJ et al (2004) Long-term efficacy of bivalirudin and provisional glycoprotein IIb/IIIa blockade vs heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary revascularization (REPLACE-2 randomized trial). *JAMA* **292:** 696–703

Marso SP, Lincoff AM, Ellis SG et al (1999) Optimizing the percutaneous interventional outcomes for patients with diabetes mellitus: results of the EPISTENT (Evaluation of Platelet IIb/IIIa Inhibitor for Stenting Trial) diabetic substudy. *Circulation* **100:** 2477–84

National Institute for Clinical Excellence (2002) *Guidance on the use of Glycoprotein IIb/IIIa inhibitors in the Treatment of Acute Coronary Syndromes.* Technology appraisal no.47. National Institute for Clinical Excellence, London

Ormiston JA, Shaw BL, Panther MJ et al (2002) Percutaneous coronary intervention with bivalirudin anticoagulation, immediate sheath removal and early ambulation: a feasibility study with implications for day-stay procedures. *Cathet Cardiovasc Interv* **55:** 289–93

Rha S, Kuchulakanti PK, Pakala R et al (2004) Bivalirudin versus heparin as an anthithrombotic agent in patients treated with a sirolimus-eluting stent. *Am J Cardiol* **94:** 1047–50

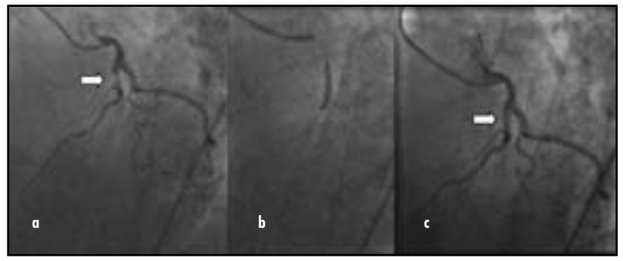
Rha S, Kuchulakanti PK, Pakala R et al (2005) Bivalirudin versus heparin as an antithrombotic agent in patients who undergo percutaneous saphenous vein graft intervention with a distal protection device. *Am J Cardiol* **96:** 67–70

Saw J, Lincoff AM, DeSmet W et al (2004) Lack of pre-treatment effect on the relative efficacy of Bivalirudin with provisional glycoprotein IIb/IIIa blockade compared to heparin with routine glycoprotein IIb/IIIa blockade: a REPLACE-2 substudy. *J Am Coll Cardiol* **44:** 1194–9

Schussler JM, Cameron CS, Anwar A, Donsky MS, Johnson KB, Vallabhan RC, Wischmeyer JB (2004) Effect of bivalirudin on length of stay in the recovery area after percutaneous coronary intervention compared with heparin alone, heparin + abciximab, or heparin + eptifibatide. *Am J Cardiol* **94:** 1417–19

Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology (2005) Guidelines for percutaneous coronary interventions. *Eur Heart J* **26:** 804–7

Figure 2. Coronary angiographic images during percutaneous coronary intervention (PCI) with bivalirudin: this 75-year-old woman woman presented with ventricular fibrillation and subsequent troponin rise during a routine carotid endarterectomy. Her electrocardiogram demonstrated changes compatible with an inferolateral non-ST elevation myocardial infarction. a. Diagnostic coronary angiography 10 days post-carotid surgery revealed significant lesions in the left anterior descending artery (LAD, lesion indicated by arrow) and the right coronary artery (not shown). PCI was undertaken with bivalirudin anticoagulation to limit bleeding complications in the context of recent surgery. b. Following balloon predilatation, a 3.0 mm x 23 mm stent was deployed in the proximal LAD (stent balloon inflated between marker dots) with (c) an excellent angiographic result. The right coronary lesion was also stented. The patient made an uneventful recovery and was well at 2-month follow up.



KEY POINTS

- Bivalirudin is a thrombin-specific anticoagulant licensed in the UK for anticoagulation during percutaneous coronary intervention (PCI).
- Bivalirudin offers equivalent efficacy to heparin plus glycoproteinIIb/IIIa inhibitor usage during PCI, with less bleeding complications and added cost savings.
- Bivalirudin's use during PCI has been endorsed by the recent European Society of Cardiology guidelines for PCI practice.