Research Review
PRODUCT REVIEW

Angiomax® (bivalirudin)

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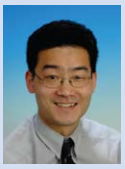

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Research Review publications are intended for New Zealand medical professionals.

This review discusses the evidence in support of the use of Angiomax® (bivalirudin), a thrombin-specific anticoagulant that is indicated for use as an anticoagulant in the treatment of patients with moderate to high risk acute coronary syndromes (ACS) (unstable angina, non-ST-elevation myocardial infarction [NSTEMI], or ST-elevation myocardial infarction [STEMI]) who are undergoing early invasive management, and in patients undergoing percutaneous coronary intervention (PCI).

Acute coronary syndromes in New Zealand

Acute coronary syndrome diagnoses cover a wide variation in risk, require complex and time urgent risk stratification and represent a large social and economic burden.[1]

While the mortality rate for coronary heart disease has been steadily decreasing since 1970 in New Zealand, it remains the second leading cause of mortality after cancer.[2] In 2002/2003, more than twice as many New Zealanders suffered acute MIs than in 1989 and there were 9,000 more admissions for ACS than in 1989.[3]

It is well recognised that acute STEMI is associated with a high mortality rate,[4-6] which can be significantly reduced with timely and appropriate reperfusion via thrombolysis or PCI.[7-9]

PCI vital for re-establishing coronary blood flow

Most acute coronary ischaemic events (sudden death, MI, myocardial ischaemia) occur when an atherosclerotic plaque ruptures or erodes, leading to thrombus formation within a coronary artery.[10] The immediate goals of treatment are to re-establish coronary flow, reduce clot burden and prevent recurrent thrombus formation. Most patients with acute coronary syndromes undergo some form of PCI, which includes either stent placement or percutaneous transluminal coronary angioplasty (PTCA). Treatment goals for unstable angina and ACS are to maintain myocardial perfusion by inhibiting platelet aggregation and fibrin deposition at sites of plaque rupture, thereby preventing ongoing or new myocardial ischaemia and cardiac death.[10]

Routine management has comprised aspirin for its platelet inhibitory effects and heparin for its inhibition of thrombin generation and activity.[10] However, such therapy is associated with unacceptably high numbers of patients who develop an MI, and in particular, the well-known limitations of heparin have prompted the development of new agents for use in combination with, or instead of, heparin.

Management of PCI has thus expanded to include more potent inhibitors of platelet aggregation – the adenosine diphosphate (ADP) inhibitors (ticlopidine and clopidogrel) and glycoprotein (GP) IIb/IIIa receptor inhibitors (e.g. tirofiban, eptifibatide, abciximab), while low-molecular-weight heparins (LMWHs) and direct thrombin inhibitors (e.g. bivaliruin) were developed to overcome the limitations of unfractionated heparin. LMWHs provide a more stable pharmacodynamic response and are more convenient to use than unfractionated heparin. Direct thrombin inhibitors show promise for inhibiting thrombin-mediated platelet aggregation and fibrin deposition. These agents play an important role in limiting clot formation and propagation, particularly during the PCI procedure itself, and reduction of PCI-related procedural bleeding complications.[11,12]

Anticoagulation essential during PCI

The need for adequate anticoagulation during PCI is well known.[13-16] Plaque rupture, or arterial injury after the direct introduction of thrombogenic wire and catheter equipment into the diseased coronary artery, as well as inflation of an intracoronary balloon, expose thrombogenic components to intraluminal blood; this process triggers thrombosis through platelet adhesion and activation, and activates other components of the coagulation cascade.[17] Anticoagulation is therefore essential in PCI.[18]

Thrombin plays a critical role

Thrombin plays a critical and central role in thrombogenesis:

- By activating platelets, thrombin contributes to the formation of a platelet-rich thrombus[10]
- By converting fibrinogen to fibrin, thrombin activates factor XIII, which stabilises the fibrin clot[10]
- By activating factors V and VIII, which promote further thrombin generation.[10]

Inhibiting thrombin generation or its action is therefore a key treatment strategy for ACS. The two basic types of thrombin inhibitors include direct thrombin inhibitors, such as bivalirudin, and indirect thrombin inhibitors, such as heparin and LMWHs.[16]

Limitations of current treatments

GP IIb/IIIa receptor inhibitors have shown benefit in unstable angina and ACS. These agents inhibit fibrinogen binding to GPIIb/IIIa, blocking the final common pathway of platelet aggregation, but fail to block coagulation factor assembly that occurs on the surface of activated platelets and that results in thrombin generation.[10] Consequently, GPIIb/IIIa antagonists may need to be used in combination with agents that block thrombin generation or activity.

Ticlopidine and clopidogrel irreversibly inhibit the ADP receptor on platelets and thereby block ADP-dependent platelet activation, but like aspirin, these agents inhibit only one mechanism of platelet aggregation.[10,19]

The indirect thrombin inhibitors unfractionated heparin and LMWHs do not inhibit clot-bound thrombin; both agents depend on antithrombin for inactivation of thrombin activity.

Heparin is widely considered to be a cornerstone in anticoagulation therapy. However, major limitations of unfractionated heparin include the following:

- an unpredictable anticoagulant response, making careful laboratory monitoring necessary to achieve an adequate anticoagulant effect.[10]
- Heparin is neutralised by platelet factor 4, large quantities of which are released from platelets activated at sites of plaque rupture.[20]
- Inability to inactivate platelet-bound factor Xa.[10]
- Bound factor Xa activates prothrombin, and the resultant thrombin then binds to fibrin, where it also is protected from inactivation by heparin.[10]
- Fibrin-bound thrombin remains enzymatically active[21] and causes thrombus growth by locally activating platelets[22] and amplifying coagulation.
- Limited efficacy in the treatment of ACS, especially in established coronary thrombosis, such as residual thrombus after MI.
- Providing continued anticoagulation for thrombosis associated with heparin-induced thrombocytopenia (HIT) or heparin-induced thrombocytopenia-thrombosis syndrome (HITTS) is clinically challenging.[23]

Clinical trial evidence suggests that LMWH anticoagulant activity is at least as effective as unfractionated heparin in patients with unstable angina.[10] Advantages over heparin include the fact that LMWHs have greater ability to inhibit factor Xa and that an LMWH can be given subcutaneously without laboratory monitoring.[10] However, as with heparin, LMWHs can potentially produce an immune response,[24] have a slow onset of action, and it is not possible to use activated clotting time (ACT) or activated partial thromboplastin time (aPTT) to measure anticoagulant activity.[25]

Direct thrombin inhibitors

The direct thrombin inhibitors, such as bivalirudin, offer several advantages over indirect thrombin inhibitors:

- The ability to inhibit clot-bound and free-circulating thrombin[26]
- Independence of binding cofactors such as antithrombin[26]
- Do not bind to plasma proteins[26]
- A more predictable anticoagulant response[26]
- No cross-reactivity with HIT antibodies.[23]

Bivalirudin

Bivalirudin is a direct thrombin inhibitor that was approved in December 2000 as an alternative to heparin for use in patients with unstable angina undergoing PTCA.[27] In June 2005, an additional indication was added for the use of bivalirudin alongside provisional GP IIb/IIIa receptor inhibitor therapy for patients undergoing PCI. The added indication was largely based on the REPLACE-2 trial,[28-30] which showed that compared with heparin plus GP IIb/IIIa receptor inhibitors, bivalirudin with provisional GP IIb/IIIa receptor inhibitor therapy was non-inferior with respect to outcomes including bleeds, repeat revascularisation, and death, and additionally lowered the risk of major bleeds. Thus, bivalirudin has become a common treatment for patients undergoing PCI.[31,32] Additional clinical data subsequently confirmed the non-inferiority result from REPLACE-2,[33-35] and demonstrated that bivalirudin monotherapy may significantly reduce the risk of major bleeds[33-35] as well as the short-term risk of death.[34]

- Bivalirudin is as effective as heparin with GP IIb/IIIa inhibitors[28,29,33,34,36]
- Significantly fewer bleeding complications and less thrombocytopenia than heparin plus GP IIb/IIIa inhibitors[28,37]
- Provides predictable and easily managed anticoagulation.*[37]
- Exhibits linear pharmacokinetics and a short half-life.[17,37]

* For patients with renal insufficiency undergoing PCI, the dose of bivalirudin may need to be reduced, and the anticoagulation status (ACT levels) monitored.

Bivalirudin is a synthetic 20-amino acid polypeptide and is an analogue of the anticoagulant hirudin.[38] Bivalirudin is a direct and specific inhibitor that binds both to the catalytic site and the anion-binding exosite of circulating and clot-bound thrombin.[37] Once bivalirudin is bound, thrombin slowly cleaves the bivalirudin-Arginine-Proline bond, resulting in the recovery of the thrombin active site functions.[37] Because bivalirudin produces only transient inhibition of the active site of thrombin, other substances (such as fibrinogen) can compete with, and displace, bivalirudin.[10] In contrast to heparin, direct thrombin inhibitors can inactivate fibrin-bound thrombin as well as free thrombin.[10] *In vitro*, bivalirudin dose-dependently prolongs thrombin time (TT), aPTT and prothrombin time (PT) of normal human plasma.[37] Bivalirudin does not bind to plasma proteins (other than thrombin) or to red blood cells.[37]

Pharmacokinetic profile

The pharmacokinetics of bivalirudin are linear in patients undergoing PCI and in patients with ACS.[37] In patients with normal renal function undergoing PCI, bivalirudin is characterised by a rapid plasma clearance. Bivalirudin is rapidly distributed between plasma and extracellular fluid, with a volume of distribution of 0.1 L/kg.[37] The elimination half-life is about 30 minutes in patients with normal renal function.[37]

The plasma clearance of bivalirudin is affected by the glomerular filtration rate (GFR).[39] The total plasma clearance is similar for patients with normal renal function (GFR ≥90 mL/min) and for those with mild renal impairment (GFR 60–89 mL/min), whereas clearance is reduced by approximately 20% ($t_{½}$ of 34–57 minutes) in patients with moderate renal insufficiency (GFR 30–59 mL/min) and similarly reduced in patients with severe renal impairment (GFR 10–29 mL/min). Plasma clearance is reduced by approximately 80% in dialysis-dependent patients ($t_{½}$ of 3.5 hours).[37] The bivalirudin dosage may need to be adjusted in patients with renal impairment.

Dosage and administration in PCI
Bolus and infusion rates calculated by patient weight

	Using a 5 mg/mL Concentration		
	Bolus (all patients)	Standard Infusion for the Duration of the PCI Procedure*	Hemodialysis-Dependent Infusion*
Patient Weight	*0.75 mg/kg*	*1.75 mg/kg/hour*	*0.25 mg/kg/hour*
kg	**mL**	**mL/hour**	**mL/hour**
43-47	7	16	2.3
48-52	7.5	17.5	2.5
53-57	8	19	2.8
58-62	9	21	3
63-67	10	23	3.3
68-72	10.5	24.5	3.5
73-77	11	26	3.8
78-82	12	28	4
83-87	13	30	4.3
88-92	13.5	31.5	4.5
93-97	14	33	4.8
98-102	15	35	5
103-107	16	37	5.3
108-112	16.5	38.5	5.5
113-117	17	40	5.8
118-122	18	42	6
123-127	19	44	6.3
128-132	19.5	45.5	6.5
133-137	20	47	6.8
138-142	21	49	7
143-147	22	51	7.3
148-152	22.5	52.5	7.5
153-157	23	54	7.8
158-162	24	56	8
163-167	25	58	8.3
168-172	25.5	59.5	8.5
173-177	26	61	8.8
178-182	27	63	9
183-187	28	65	9.3
188-192	28.5	66.5	9.5
193-197	29	68	9.8
198-202	30	70	10

* Continuation of the infusion for up to 4 hours postprocedure is optional, at the discretion of the treating physician

Specialist commentary on current treatments

Bivalirudin as an adjunct during PCI has major advantages, particularly from the point of view of reducing haemorrhagic complications, facilitating efficient post-procedural management/vascular sheath removal. It has been added to the Dunedin Hospital formulary after institutional review for use during primary percutaneous coronary intervention for acute ST-elevation myocardial infarction. Review of outcomes since the move to bivalirudin monotherapy with clopidogrel preloading has indicated excellent outcomes in this subset of patients undergoing PCI: equivalence from the point of view of ischaemic complications with an important reduction of haemorrhagic complications. Use of alternative and more expensive older regimens has reduced to vanishing point. Depending on cost-efficacy considerations, we may expand use of bivalirudin to other patient subsets in our institutional guidelines.

Clinical efficacy of bivalirudin in patients requiring PCI

In clinical trials, bivalirudin has demonstrated efficacy as an anticoagulant in patients undergoing PCI for a broad spectrum of indications:

- Stable disease undergoing urgent or elective PCI[28,29]
- Moderate to high risk ACS NSTEMI patients[33,36]
- Acute MI STEMI patients.[34]

REPLACE-2[28,29]

Summary: The large-scale REPLACE-2 (Randomised Evaluation in PCI Linking ANGIOMAX to reduced Clinical Events part 2) study randomised patients undergoing PCI to receive either bivalirudin with "provisional" GP IIb/IIIa or heparin plus planned GP IIb/IIIa inhibitors. All pre-specified clinical objectives of the trial were met. Bivalirudin was shown to be non-inferior to heparin plus GP IIb/IIIa inhibitors and superior to a heparin historical control arm, for the primary endpoint of death, MI, urgent revascularisation or major bleeding at 30 days. In addition, bivalirudin was associated with a significant reduction in in-hospital major bleeding, as well as a non-significant trend towards better survival at 1 year.

Method/Results: The multinational REPLACE-2 enrolled 6002 patients undergoing urgent or elective PCI, and was designed to determine if bivalirudin with provisional GP IIb/IIIa inhibitors administered during PCI could provide protection from ischaemic and bleeding complications of PCI comparable with low-dose heparin plus routine GP IIb/IIIa inhibitors. At 30 days, bivalirudin met all pre-specified clinical objectives of the trial and significantly reduced the risk of bleeding and thrombocytopenia compared to heparin plus GP IIb/IIIa inhibitors.

At 6 months, no significant between-group differences were observed for the accumulation of events. At 1 year, the efficacy of bivalirudin in suppressing ischaemic complications remained comparable with that of heparin plus GP IIb/IIIa inhibitors; there was a non-significant trend towards reduced mortality among bivalirudin recipients. In a multivariate analysis using the intention-to-treat population at 12 months, mortality was significantly reduced among patients in the high risk tertile group who were treated with bivalirudin compared with those given heparin plus GP IIb/IIIa inhibitors.

Comment: This study established efficacy and safety for bivalirudin use during elective PCI. The advantage compared to cheaper regimens, typically unfractionated heparin, is reduced haemorrhagic complications with more efficient post-procedural care. An economic analysis has suggested cost efficacy and clinical practice has evolved in some settings to incorporate sole use of bivalirudin for all PCIs or particularly in subgroups at increased risk of bleeding due to patient or clinical characteristics such as age, body mass index, renal dysfunction, pre-existing anaemia, etc.

ACUITY[33,36]

Summary: Outcomes for the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial in moderate- to high-risk unstable angina or NSTEMI ACS were consistent with REPLACE-2 findings. Bivalirudin monotherapy was associated with ischaemic rates that were non-inferior to those associated with the use of heparin (either unfractionated or enoxaparin) plus a GP IIb/IIIa inhibitor, but was associated with a significantly reduced incidence of major bleeding. Bivalirudin in combination with a GP IIb/IIIa inhibitor was associated with rates of ischaemic and haemorrhagic complications that were non-inferior to those associated with heparin plus a GP IIb/IIIa inhibitor. Bivalirudin showed an overall net benefit in clinical outcome.

Method/Results: The ACUITY trial randomly assigned 13,819 patients to one of three treatment options: heparin (either unfractionated or enoxaparin) plus a GP IIb/IIIa inhibitor (n=4603); bivalirudin plus GP IIb/IIIa inhibitor (n=4604); or bivalirudin alone (n=4612). Patients were then triaged to PCI, CABG or medical management at the discretion of the physician.

At 30 days, net clinical outcomes (composite ischaemia or major bleeding) were similar between patients treated with bivalirudin plus a GP IIb/IIIa inhibitor and for those given heparin plus a GP IIb/IIIa inhibitor. While the rates for composite ischaemia were similar between the bivalirudin monotherapy group and the heparin plus a GP IIb/IIIa inhibitor group, bivalirudin monotherapy was associated with a significantly lower risk of major and minor bleeding complications, resulting in a non-significant trend towards better 30-day net clinical outcomes.

At 1 year, bivalirudin with or without a GP IIb/IIIa inhibitor maintained the ischaemic and mortality benefit.

Comment: This study expanded the indications for use of bivalirudin to higher risk patients with acute coronary syndrome, typically those with positive biomarkers of cardiac troponin undergoing PCI. The study led to US Food and Drug Administration approval for use of bivalirudin in ACS but interpretation of the study has been contentious according to some experts. There may be a signal of some increased ischaemic complications, particularly acute stent thrombosis after PCI and the interpretation of non-inferiority here has been disputed. There is, however, again a demonstrated important significant reduction in bleeding. Depending on how the results are aggregated, bivalirudin may be seen as a major advantage, with net clinical benefit, particularly from the point of view of significant reductions in noncardiac death. Certainly, bivalirudin is likely to be more cost-effective than blanket use of GP IIb/IIIa inhibitors in all such patients.

HORIZONS-AMI[34]

Summary: The HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial enrolled patients with acute STEMI undergoing PCI and compared standard care (unfractionated heparin plus routinely administered GP IIb/IIIa inhibitors) with bivalirudin monotherapy (with GP IIb/IIIa inhibitors on an as-needed basis for suboptimal PCI outcomes). The bivalirudin treatment arm was associated with significant reductions in the 30-day primary endpoints of net adverse clinical events and major bleeding, as well as a significant reduction in cardiac-related mortality at 30 days.

Method/Results: The HORIZONS-AMI trial was designed to evaluate the clinical value of bivalirudin in patients with STEMI undergoing a primary PCI management strategy. The trial enrolled 3602 such patients and randomly assigned them to one of two treatment arms: unfractionated heparin plus a GP IIb/IIIa inhibitor (n=1802), or bivalirudin alone with or without provisional GP IIb/IIIa inhibitors (n=1800).

Compared with heparin plus the routine use of GP IIb/IIIa inhibitors, bivalirudin monotherapy was associated with: a significant 24% relative reduction in the 30-day primary endpoint of net adverse clinical events; a significant 40% relative reduction in the 30-day primary endpoint of major bleeding; and a significant reduction in cardiac-related mortality at 30 days.

There was no between-group difference for major adverse cardiovascular events. Acute stent thrombosis (occurring within 24 hours of PCI) tended to be higher in the bivalirudin group versus the heparin plus GP IIb/IIIa inhibitor group (1.3% vs 0.3%), but this did not result in increased rates of reinfarction or mortality at 30 days.

Comment: This study established use of bivalirudin to cover the final indication for PCI, acute STEMI. This study emphasises the prognostic importance of minimising haemorrhagic complications and how this probably translates into better longer term outcomes, including significantly reduced mortality for such patients. Such issues can be a cause of excess morbidity and mortality in this high risk subgroup of patients. Despite being of higher risk for ischaemic complications, there has been less reason for concern about stent thrombosis rates in the bivalirudin randomised patients. Subsequent analyses of this prospective randomised controlled trial show how very optimal outcomes can be obtained with bivalirudin, pre-treatment with oral clopidogrel 600 mg, and an unfractionated heparin bolus in the emergency department or ambulance before going urgently to the cath lab. This trial has led to changes in professional body guidelines and practice in our institution.

Safety and effectiveness of bivalirudin in routine care of patients undergoing percutaneous coronary intervention[40]

Summary: In the context of routine care of PCI patients treated throughout the USA, this nonrandomised study showed that bivalirudin is protective compared to heparin plus GP IIb/IIIa inhibitor with regard to the risk of blood transfusions, and may even exceed estimates in randomised trials for protection against death.

Method/Results: Data were obtained from a representative inpatient administrative database covering approximately one-sixth of all hospitalisations in the USA. A total of 127,185 patients were identified who underwent inpatient PCI between June 2003 and December 2006 and were administered either bivalirudin plus provisional GP IIb/IIIa inhibitors or the comparator, heparin plus a GP IIb/IIIa inhibitor. For the primary outcome of blood transfusions, the multivariate analysis indicated a 33% risk reduction (HR 0.67) when patients were treated with bivalirudin compared with heparin plus a GP IIb/IIIa inhibitor; a post-hoc instrumental variable analysis showed a weaker protective effect (HR 0.72). Bivalirudin was also protective against in-hospital death, with a 49% risk reduction in the multivariate analysis (HR 0.51).

Comment: ACS and particularly STEMI care has evolved significantly from double digit or even 20% 1-year mortality rates seen a decade or two ago to the less than 5% 1-year mortality seen currently. These outcomes have been built on gradual improvements/innovations and what are sometimes interpreted as modest marginal benefits accrued in randomised controlled trial (RCT) settings. The advances in outcomes achieved in real world registries such as this one sometimes indicate a multiplicative effect, even greater than what was observed or could be extrapolated from RCTs. Real world experience and assessment of outcomes/cost efficacy will determine whether such treatments become embedded or abandoned/superseded. Formal assessments of real world trends against or in favour of either GP IIb/IIIa vs bivalirudin use measured against outcomes will likely continue.

Use of bivalirudin during primary PCI for acute STEMI[41]

Summary: This retrospective analysis of patients who presented to Dunedin Public Hospital with an acute presentation (<12 hours) of a STEMI and received PCI at Dunedin Hospital during the period of January 2007 through November 2009 compared clinical outcomes and direct costs of bivalirudin treatment with those relating to the previous regimen of heparin +/- abciximab. Outcomes slightly favoured the heparin +/- abciximab group for being alive at discharge, at 30 days and at 1 year, compared to the bivalirudin group. However, the risk of PCI bleeding complications, repeat MI and repeat hospitalisation due to cardiovascular disease was lower for the bivalirudin group. Bivalirudin was also associated with lower direct costs (as assessed by resource utilisation system cost and length of stay in hospital), compared with the previous regimen.

Comment: This was a retrospective analysis of outcomes after institutional change of practice to using bivalirudin as sole adjunct during acute STEMI PCI. As far as we are aware, Dunedin is the only institution in New Zealand to make the policy switch to bivalirudin for this PCI indication, thus replacing traditional regimens of unfractionated heparin +/- GP IIb/IIIa inhibitor. Adding bivalirudin to the hospital formulary required institutional and pharmacy department review and this audit was stipulated as part of the approval process. Although other changes were notable in the period analysed (increasing use of acute catheter reperfusion, thrombus aspiration, and predominant transradial approach, including for STEMI), there are measurable trends of reduced bleeding mirroring the HORIZONS-AMI results with no increase in ischaemic complications or MACCE (major adverse cardiac and clinical endpoints). From the pharmacoeconomic point of view, the average difference in cath lab costs (equipment and drugs) was NZ$3925 vs NZ$3070 in favour of a bivalirudin strategy, which likely translates into substantial savings compared to the expense of traditional PCI adjuncts for STEMI.

CONCLUSION

Bivalirudin has fulfilled the promise suggested by its basic science and pharmacology with good clinical data now available demonstrating efficacy, safety, and significant reductions in haemorrhagic complications. This is in a range of patients undergoing PCI for stable, unstable coronary syndromes, and during acute STEMI. Cost considerations and competing regimens in public institutions mean its use is restricted to the highest risk cases, which traditionally received abciximab or other GP IIb/IIIa inhibitors. Our institutional data, however, suggest at least equivalent outcomes with bivalirudin now, probably significant reductions in bleeding, and likely superior cost efficacy.

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Please consult the full bivalirudin data sheet at www.medsafe.govt.nz before prescribing.
Treatment decisions based on these data are the full responsibility of the prescribing physician.