Bivalirudin, a bivalent, thrombin specific anticoagulant as an alternative to heparin in interventional procedures

D. P. Chew
Flinders Medical Center, South Australia

Keywords
Bivalirudin, anticoagulant, percutaneous coronary intervention, thrombin inhibitor, unstable angina

Summary
Among the antithrombotic therapies evaluated to date, the synthetic peptide bivalirudin is unique in its ability to reduce both ischemic and bleeding complications associated with percutaneous coronary intervention (PCI). Bivalirudin is a small peptide consisting of 20 amino acid residues that binds thrombin in a direct, reversible, and bivalent fashion. The agent is approved for use in the United States and New Zealand as an anticoagulant in patients with unstable angina undergoing PCI and may also prove beneficial in patients with acute coronary syndromes (ACS), acute myocardial infarction (AMI) and in patients undergoing coronary artery bypass graft (CABG) procedures. This article examines bivalirudin in more detail.

Bivalirudin, ein bivalentes, thrombinspezifisches Antikoagulans als Alternative zu Heparin bei Interventionen

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Heparin is the most widely used anticoagulant in clinical practice, despite of numerous limitations. The recognition of thrombin’s central role in arterial thrombus formation and platelet activation has resulted in the need for more effective and safer anticoagulation. This research led to the development of several new antithrombotic strategies for the treatment of patients with coronary artery diseases. Despite the more recent developments of antiplatelet therapy and low molecular weight heparins (LMWH), the morbidity and mortality associated with coronary artery disease remains high. While progress has been made in reducing ischemic events in clinical trials, this benefit is often offset by an increased risk of bleeding complications. Bivalirudin (Angiomax®, The Medicines Company, Parsippany, NJ, USA) is a thrombin-specific anticoagulant approved for clinical use in the United States and New Zealand as an anti-coagulant in patients with unstable angina undergoing PCI. Bivalirudin is unique among the anticoagulants in its ability to significantly reduce the risk of ischemic complications while being concurrently associated with a low rate of hemorrhagic complications among patients undergoing percutaneous coronary intervention (PCI). Additionally, evidence suggests that bivalirudin may also prove beneficial in other settings where patients require anti-coagulation for thrombotic arterial complications.

Bivalirudin chemistry and mechanism of action

Bivalirudin is a small synthetic peptide with 20 amino acid residues. The drug was specifically designed to achieve high potency and specificity for thrombin inhibition. The molecule consists of three regions:

- the aminoterminal tetrapeptide sequence (D-Phe-Pro-Arg-Pro),
- the highly anionic carboxyterminal dodecapeptide sequence derived from residues 53-64 of hirudin, and
- an intervening segment of 4 glycine residues.

The bivalirudin peptide forms a high-affinity stoichiometric complex that results in neutralization of thrombin action during blood coagulation and thrombin formation (1).

Bivalirudin inhibits thrombin’s cleavage of fibrinogen and its activation of factors V and VIII by binding to thrombin’s active site and to its exosite 1 (Fig. 1) in a bivalent fashion (2). One of the features that distinguishes bivalirudin from hirudin is the reversibility of the bivalirudin:thrombin com-
plex, which is facilitated by thrombin’s slow cleavage of the bivalirudin Arg3-Pro4 bond, and results in recovery of the thrombin active site functions while preserving bivalirudin inhibition of exosite 1.

Bivalirudin demonstrates a dose-dependent inhibition of thrombin-induced platelet activation, and associated granule release, p-selectin expression, and aggregation. Full inhibition of thrombin-induced platelet activation was achieved in vitro at plasma levels approximately 2.2 μg/mL, a level well below the therapeutic level used clinically. Consistent with its mode of action, bivalirudin had no effect on platelet aggregation induced by either ADP or collagen, suggesting that platelet aggregation is still possible, albeit reduced, in the presence of bivalirudin in vivo (3). While heparin activity is neutralized in plasma samples obtained from collagen-activated platelets (possibly related to the increased expression of platelet factor 4), bivalirudin remains a potent inhibitor of thrombin and is unaffected by platelet activation products (3). Like other direct thrombin inhibitors, bivalirudin inhibits both clot-bound and free circulating thrombin (2).

Table 1  Pharmacokinetics and dosage adjustments of bivalirudin in renal impairment

<table>
<thead>
<tr>
<th>renal function</th>
<th>GFR (mL/min)</th>
<th>clearance (mL/min/kg)</th>
<th>half-life (min)</th>
<th>recommended reduction in infusion dose (%)</th>
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<tr>
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<td>2.8</td>
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<td>dependent</td>
<td>off dialysis</td>
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<td>90</td>
</tr>
</tbody>
</table>

Fig. 1  Bivalirudin inhibits thrombin by binding at the active site and exosite 1 on the thrombin molecule. Slow cleavage of the bivalirudin Arg3-Pro4 bond by thrombin results in recovery of the thrombin active site functions while preserving bivalirudin inhibition of exosite 1.

Pharmacology

Pharmacokinetics

Bivalirudin exhibits linear pharmacokinetics following intravenous administration and a half-life of approximately 25 minutes in patients with normal renal function, a volume of distribution of 13.0 ± 0.7 L, and a clearance rate of approximately 419 ± 37 mL/min, or 3.4 mL/min/kg (4, 5). In patients undergoing PCI, a mean steady state concentration of 12.3 μg/mL was achieved following a 1 mg/kg intravenous bolus and a 4-hour 2.5 mg/kg/h infusion (6).

Plasma clearance of bivalirudin is directly proportional to glomerular filtration rate (GFR). Bivalirudin is cleared via a combination of renal mechanisms and proteolytic cleavage. Urinary excretion of the active, unaltered drug substance accounts for approximately 20% of the total dose administered, regardless of route of administration (4). Non-renal proteolysis accounts for the remainder. Pharmacokinetic and pharmacodynamic profiles are similar for patients with normal renal function and those with mild renal impairment (60-89 mL/min). Clearance in patients with moderate and severe renal impairment was reduced approximately 20% and in patients on dialysis by 80% (6) (Table 1). There is no reversal agent for bivalirudin, however, the product is hemodialyzable with approximately 25% of the drug cleared by hemodialysis (6).

Pharmacodynamics

When administered intravenously, bivalirudin exhibited a linear, dose- and concentration-dependent anticoagulant activity as measured by the prolongation of ACT, aPTT, PT, and TT. Bivalirudin doses of either 0.05 mg/kg bolus and 0.2 mg/kg/h infusion or 0.15 mg/kg bolus and 0.6 mg/kg/h infusion both potently suppressed the generation of fibrinopeptide A (7). Upon intravenous administration, bivalirudin showed immediate and rapidly reversible anticoagulant effects, with coagulation times returning to baseline in approximately 60 minutes (4). Bivalirudin does not
bind to red blood cells or to plasma proteins other than thrombin (6).

**Bivalirudin for percutaneous coronary angioplasty**

The consistent level of anticoagulation led to the first trial evaluating the safety and effectiveness of bivalirudin as a replacement for heparin during coronary angioplasty (8). The trial was a non-randomized, open-label, sequential-group dose escalation study using ascending doses of bivalirudin in patients treated with acetylsalicylic acid but not heparin. There were six dosing groups (Table 2) (9).

Both the ACT and the aPTT demonstrated linear dose- and plasma concentration-dependent increases. Procedural ACTs of 300 seconds increased from 12% in the lowest dose group to 100% in the highest dose group (Fig. 2a). In patients receiving adequate anticoagulation (Groups 4-6) 79% had ACT levels >300 seconds. By intention-to-treat analysis, death, myocardial infarction (MI), revascularization and abrupt vessel closure occurred in 12.5% of patients in Groups 1-3 and 3.6% of patients in Groups 4-6 (p = 0.006) (Fig. 2b). Among patients in whom the balloon angioplasty was actually undertaken, the incidence of death, MI, revascularization and abrupt vessel closure was 10.2% in Groups 1-3 and 3.8% in Groups 4-6 (p = 0.038) (9). Only one bleeding event occurred during the course of the trial. Hence there was no observed increase in the risk of bleeding with the higher doses. Results from this trial were the first to suggest that bivalirudin could be used in place of heparin during coronary intervention. This study formed the basis for the larger, definitive double-blind randomized clinical outcome trial as reported by Bittl et al. (10).

In the large double-blind Bivalirudin Angioplasty Trial (BAT), 4312 patients with unstable angina or within two weeks of an MI and requiring PCI were randomized to receive bivalirudin (1 mg/kg bolus; 2.5 mg/kg/h infusion for 4 h then 0.2 mg/kg/h for up to 20 h) or heparin (175 U/kg bolus followed by a 24 h infusion of 15 U/kg/h). Within this study, patients presenting with post-myocardial infarction unstable angina were sub-randomized to ensure equal representation of this high risk group within each study arm. For the composite endpoint death, MI, or revascularization at 7 days there were significantly fewer events with bivalirudin-treated than heparin-treated patients (6.2% versus 7.9%, odds ratio 0.78, 95% CI 0.62, 0.99; p = 0.039) (Fig. 3). This benefit was maintained through 180 days. Among the 741 pre-stratified post MI patients this reduction of ischemic events was even more pronounced in favor of bivalirudin (4.9% vs 9.9%, odds ratio 0.47, 95% CI 0.26, 0.84; p = 0.009). The absolute difference was maintained through 180 days and remained statistically significant (11). Major hemorrhage, defined as overt bleeding which led to a 3 g/dL drop in hemoglobin, transfusion, intracranial hemorrhage, or retroperitoneal bleeding, was significantly reduced in bivalirudin-treated patients (intent to treat population) (3.5% vs 9.3%, odds ratio 0.47, 95% CI 0.26, 0.47; p < 0.001) and in post MI patients (2.4% vs 11.8%, odds ratio 0.16, 95% CI 0.08, 0.36; p < 0.001) (11). In particular, only one intracerebral hemorrhage event occurred among the bivalirudin treated patients.

Based on this trial of more than 4000 patients bivalirudin reduced the relative risk of ischemic complications of the angioplasty procedure by 22% while simultaneously decreasing the risk of bleeding complications by 62% compared with heparin. This was one of the first large-scale trials to demonstrate that reductions in both ischemic and hemorrhagic complications associated with PCI could be obtained. This trial also demonstrated that compared to...
Bivalirudin as an alternative to heparin

Hämostaseologie 3/2002

Bivalirudin provides a more stable, predictable level of anticoagulation among patients undergoing PCI, which appeared to translate into direct clinical benefit.

A small, but more contemporary trial comparing abciximab plus heparin with bivalirudin and provisional abciximab in 144 patients undergoing routine PCI with or without stenting (Comparison of Abciximab Complications with Hirulog (and Back-Up Abciximab) Events Trial (CA-CHEt)) provides evidence of bivalirudin utility in the modern era of stenting and GP IIb/IIIa inhibitors. Stents were placed in 88% of patients and 24% of bivalirudin-treated patients also received abciximab in a provisional manner. Patients treated with bivalirudin had a lower incidence of death, MI and revascularization or major hemorrhage compared to those treated with heparin (3.5% vs 14.1%, p = 0.013) (12). Results of this study continue to demonstrate predictable and stable anticoagulation with reductions in bleeding and ischemic complications and suggest the routine use of bivalirudin may permit a more discretionary use of GP IIb/IIIa inhibition within the modern era of percutaneous coronary intervention.

Further assessment of the role of bivalirudin within contemporary practice has been obtained within another pilot study, REPLACE part 1. Within this study, bivalirudin was directly compared with heparin among patients undergoing PCI. The use of glycoprotein IIb/IIIa inhibitors was left to the discretion of the clinician and was used in over 70% of patients. Also reflecting recent trends, thienopyridine pretreatment was administered in half the patients. Among the 1057 patients referred for percutaneous coronary interventions randomization to bivalirudin demonstrated reductions in both bleeding and ischemic complications compared to heparin therapy despite the high rate of anti-platelet therapy utilization. These findings provide the basis for the larger REPLACE part 2 trial, in which another 6000 patients referred for percutaneous coronary intervention will be treated with bivalirudin and provisional glycoprotein IIb/IIIa inhibitor use, or with heparin plus a glycoprotein IIb/IIIa inhibitor.

Bivalirudin is not immunogenic and thrombocytopenia has not been reported with bivalirudin therapy alone. A ongoing study (ATBAT) is evaluating bivalirudin in heparin-induced thrombocytopenia or heparin-induced thrombocytopenia and thrombosis syndrome patients undergoing percutaneous coronary interventions. Interim results from the trial indicate that bivalirudin provides satisfactory anticoagulation in patients with HIT undergoing PCI. No death, MI, revascularization or major bleeding were reported in the 11 patients evaluated to date (13).

Bivalirudin in acute coronary syndrome patients

Preliminary studies with bivalirudin in acute coronary syndrome patients not undergoing PCI suggest that bivalirudin has the potential to improve results compared to heparin in this patient population. The anticoagulant activities of bivalirudin and heparin were tested in plasma obtained from healthy human volunteers and from patients with stable or unstable angina, and acute myocardial infarction. Heparin showed greater variability than bivalirudin in prolongation of aPTT. No significant differences were observed in the activity of bivalirudin in plasma from volunteers or from patients with coronary artery disease. Heparin activity, however, was reduced significantly in patients with unstable angina and acute MI, consistent with the known non-specific binding of this agent to acute phase reactants (14, 15).

Preliminary dose-finding studies in patients with unstable angina include an open-label pilot study of 20 men with unstable angina. Bivalirudin 0.2 mg/kg/h was administered as a continuous intravenous infusion for 5 days to produce an aPTT of approximately 200% of control. Nineteen patients completed the 5-day infusion period; one patient required coronary bypass surgery because of recurrent angina. No patient developed a transmural MI or died. Major bleeding did not occur; minor bleeding occurred in two patients. APTT increased from a mean of 26.8 seconds before therapy to 61.6 seconds during the infusion and was maintained within a range of 180-220% of control. Acute coronary syndrome patients not undergoing PCI suggest that bivalirudin has the potential to improve results compared to heparin in this patient population. The anticoagulant activities of bivalirudin and heparin were tested in plasma obtained from healthy human volunteers and from patients with stable or unstable angina, and acute myocardial infarction. Heparin showed greater variability than bivalirudin in prolongation of aPTT. No significant differences were observed in the activity of bivalirudin in plasma from volunteers or from patients with coronary artery disease. Heparin activity, however, was reduced significantly in patients with unstable angina and acute MI, consistent with the known non-specific binding of this agent to acute phase reactants (14, 15).

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Two subsequent studies evaluated bivalirudin in open label fashion. Bivalirudin was evaluated in 15 patients with unstable angina. The initial dose was 0.02 mg/kg/h. The bivalirudin infusion rate was increased every 30 minutes to 0.05, 0.1, 0.25, and 0.5 mg/kg/h in these patients for a total infusion period of 150 minutes. Dose-related increases in aPTT were observed, with significant changes compared to baseline at doses of 0.25 mg/kg/h and above (17). In the second study, 45 patients were treated with bivalirudin as a 72-hour continuous intravenous infusion. The initial infusion dose was 0.25 mg/kg/h and was used until two patients failed therapy, after which the dose was increased. Successively higher
doses were then administered until two failures occurred at each dose. Five patients received 0.25 mg/kg/h and 14 received 0.5 mg/kg/h before two failures occurred. Failure occurred in only 1 of 21 patients treated with 1 mg/kg/h. Clinical success (defined as the absence of hemodynamic deterioration, a new MI, or recurrent spontaneous ischemic pain) occurred in 60% of patients (3 of 5) at the low dose, in 86% of patients (12 of 14) at the intermediate dose, and in 95% of patients (20 of 21) at the highest dose. No deaths, MIs, or bleeding complications occurred (17).

In the Thrombin Inhibition in Myocardial Infarction (TIMI I) 7 trial, 410 patients with unstable angina received acetylsalicylic acid 325 mg/d plus bivalirudin as a continuous infusion for 72 hours. Bivalirudin was dosed at 0.02, 0.25, 0.5, or 1 mg/kg/h. The primary endpoint of death, nonfatal MI, rapid clinical deterioration, or recurrent ischemic pain at rest with ECG changes by 72 hours were similar among the therapies (8.1%, 6.2%, 11.4%, and 6.2%, respectively; p: non-significant). The secondary endpoint of death or nonfatal MI through hospital discharge occurred in 10% of patients in the 0.02 mg/kg/h group compared to 3.2% of patients in the other three groups (p = 0.008) again suggesting that this agent has a role in the medical management of acute coronary syndromes (18).

The TIMI I 8 trial had enrolled 133 of a planned 5320 patients with non ST-elevation acute coronary syndromes in a randomized comparison of bivalirudin with heparin when the study was halted for economic reasons. Subsequent review of the data revealed bivalirudin to be associated with a decrease in the combined incidence of death, myocardial infarction or major hemorrhage through 14 days at 13.8% for heparin-treated patients and 2.9% for bivalirudin-treated patients, (p = 0.03). No major hemorrhage was observed in the bivalirudin arm. Within this study, a higher proportion of patients achieved the target aPTT (55-85 sec) within the first 72 hours with 86.5% of patients treated with bivalirudin achieving the therapeutic target in 6-12 hours compared with only 20.4% in the heparin arm. These observations suggest that some of the superior efficacy of this agent may be attributable to a more consistent dose response (19, 20).

Bivalirudin for treatment of ST-segment elevation acute myocardial infarction

In a pilot study, 45 patients with acute myocardial infarction (AMI) received either bivalirudin or heparin as adjunctive therapy to streptokinase. Enrolled patients had onset of chest pain within the previous 6 hours and ST-segment elevation. All patients received acetylsalicylic acid (325 mg). Bivalirudin was administered as 0.5 mg/kg/h for 12 h then 0.1 mg/kg/h. Heparin was administered as 1000 units/h and titrated to maintain aPTT. Infusions were initiated simultaneously with or immediately before streptokinase. A fter 90 minutes, TIMI grade 2 or 3 flow was observed in 77% of the bivalirudin-treated patients compared to 47% of the heparin-treated patients (p <0.05). TIMI grade 3 flow was achieved by 67% and 40% (p = 0.08), respectively. A fter 120 minutes, TIMI grade 2 or 3 flow was observed in 87% and 47% of patients, respectively (p <0.01). TIMI grade 3 flow was achieved by 77% and 40% (p <0.02), respectively. The duration of chest pain was shorter in the bivalirudin group (179 minutes vs 236 minutes, p <0.02). Killip class 3-4 status, stroke, M1 extension, recurrent ischemia, or death occurred more often in the heparin group (47% vs 7%). Bleeding occurred with similar frequency (67%) in the two groups (21).

In a second trial comparing heparin with two different doses of bivalirudin as adjunctive therapy to streptokinase, 68 patients with acute M1 received bivalirudin: 0.5 mg/kg/h for 12 h followed by 0.1 mg/kg/h (low dose), or bivalirudin 1 mg/kg/h for 12 hours followed by placebo (high dose), or heparin 5000 units bolus followed by 1000 U/h titrated to an aPTT 2-2.5 times control after 12 hours. Heparin or bivalirudin administration was initiated a few minutes before streptokinase (1.5 million units) given over 45-60 minutes. All patients received acetylsalicylic acid (325 mg). TIMI flow grade 3 was observed after 4 to 6 days in significantly more patients in the low-dose bivalirudin group, than in the heparin group (Tab. 3). Serious bleeding occurred in 22% of the low-dose group, 18% of the high-dose group, and 31% of the heparin group. No intracranial bleeding or stroke occurred in any group. Transfusions were required in more heparin-treated patients (31% vs 5%, p <0.02) (22).

The subsequent Hirulog and Early Reperfusion/Occlusion (HERO)-1 trial also compared two doses of bivalirudin to heparin in 412 patients presenting within 12 hours of an ST-segment elevation M1 (23). All patients received acetylsalicylic acid and 1.5 million units of streptokinase intravenously prior to randomization in a double-blind manner to receive either heparin (5000 U bolus followed by an infusion of 1000 U/h; 1200 U/h) or bivalirudin at one of two different doses:

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Achievement in TIMI flow in patients treated with bivalirudin versus heparin</th>
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<tr>
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<td>bivalirudin dose (mg/kg/h)</td>
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<tr>
<td>90 minutes</td>
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<tr>
<td>TIMI 2-3 flow</td>
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<td>TIMI 3 flow</td>
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<td>TIMI 2-3 flow</td>
<td>100%</td>
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<td>TIMI 3 flow</td>
<td>92%</td>
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</table>
Bivalirudin as an alternative to heparin

- Low-dose bivalirudin 0.125 mg/kg bolus followed by an infusion of 0.25 mg/kg/h for 12 hours, then 0.125 mg/kg/h;
- High-dose bivalirudin 0.25 mg/kg bolus followed by an infusion of 0.5 mg/kg/h for 12 hours, then 0.25 mg/kg/h.

TIMI 3 flow was observed in 35% of the heparin-treated patients, 46% of the low-dose bivalirudin group, and 48% of the high-dose bivalirudin group. The difference between the high-dose bivalirudin group and the heparin group with regard to early TIMI 3 flow was approximately a 37% relative improvement (p = 0.03). The combined endpoint of death, cardiogenic shock and recurrent MI at 35 days occurred in 18% of the heparin-treated patients, 14% who received low-dose bivalirudin, and 12% who received high-dose bivalirudin (p: non-significant). One hemorrhagic stroke occurred in the high-dose bivalirudin group. There was less major bleeding among the patients receiving bivalirudin compared with those treated with heparin (14% with low dose, 19% with high dose, and 27% with heparin) (23).

These data lead to the HERO-2 trial in which 17,073 patients presenting within 6 hours of acute ST-segment elevation myocardial infarction were treated with acetylsalicylic acid and randomized to receive either intravenous heparin (n = 8557) or bivalirudin (n = 8516) along with streptokinase. This trial gathered substantial information regarding the clinical outcomes of patients throughout the world including a substantial contribution from Eastern Europe and Russia as well as India. Similar to results seen in other contemporary large-scale AMI trials, there was a non-significant reduction in the adjusted mortality rates for bivalirudin-treated patients compared to heparin-treated patients (10.5% vs 10.9%, p = 0.46). However, a significant 30% reduction in the incidence of reinfarction within 96 h was observed in the bivalirudin group (1.6% vs 2.3%, p = 0.001). Despite the high-risk population a low overall rate of intracerebral hemorrhage was seen. Intracranial hemorrhage was not significantly increased among bivalirudin-treated patients compared to heparin-treated patients (0.6% vs 0.4%, p = 0.09) and incidence of severe bleeding was not significantly different between the two groups (0.7% vs 0.5%, p = 0.07) in spite of elevated aPTT levels in bivalirudin-treated patients compared to heparin-treated patients. These data suggest that bivalirudin is a suitable treatment alternative in patients with acute MI treated with streptokinase (24).

Discussion

The relative rapid recovery of normal coagulation after cessation of bivalirudin administration is due in part to its short half-life and the reversible nature of the drug’s binding to thrombin. These properties contribute to the clinical safety of bivalirudin and mitigate the need for antidotal therapy to address exaggerated anticoagulant effects in patients. Bleeding is the primary adverse effect associated with bivalirudin and can occur at any site, although when used in the PCI setting, bleeding primarily occurs at the site of arterial puncture. In a recent meta-analysis, bivalirudin was shown to have lower bleeding risk than either heparin or hirudin (25).

The predictable anti-coagulant effect and short therapeutic half-life of bivalirudin coupled with the demonstrated improved efficacy and safety profile among patients undergoing invasive procedures suggests that this agent may find a particular place within the current era of ever more invasive management. Within this context of coronary intervention, the current data suggest that bivalirudin may be especially suited to specific clinical scenarios. The shorter half-life and lower associated bleeding risk suggests that this agent may be used with advantage among patients at increased risk of post-procedural bleeding complications. Such patient groups include elderly women, patients with moderate to severe renal dysfunction, and such of low body weight. Likewise, patients presenting with high-risk acute coronary syndromes are known to experience a greater rate of bleeding events in addition to the excess ischemic risk and bivalirudin may offer greater efficacy and safety in this setting. Similarly, when glycoprotein IIb/IIIa inhibition is contraindicated due to bleeding risk, bivalirudin presents as an alternative. Within the bivalirudin angioplasty trial, bivalirudin provided more than 60% reduction in the risk of major hemorrhage in all patients examined.

Furthermore, the role of this agent within the early management of patients presenting with ACS requires further evaluation, though early studies remain promising. In particular, the short half-life offers advantages for optimizing clinical treatment among patients presenting with ACS in whom management strategies are determined by invasive testing. The pharmacologic profile of this agent potentially offers anti-coagulation that is easily individualized. These benefits may also extend to the management of ST elevation AMI where support for invasive reperfusion strategies continues to emerge and a reduction in recurrent infarction has been demonstrated with this agent.

Conclusion

Bivalirudin has demonstrated benefit as a replacement for heparin monotherapy in patients undergoing PCI. It appears to be unique in its ability to reduce both ischemic and bleeding complications associated with PCI and while initial data look promising, its role in ACS will be determined by large-scale clinical outcome data. While the role of bivalirudin in the management of AMI is not yet clear, results from the HERO-2 trial suggest that bivalirudin can replace heparin when streptokinase is used as the thrombolytic agent. Trials with newer thrombolytic agents, however, are warranted.

References


16. Correspondence to: Dr. Derek P. Chew
Department of Cardiology
Flinders Medical Center
Flinders Way
Bedford Park, 5042
South Australia
Australia