Bivalirudin: A Direct Thrombin Inhibitor for Percutaneous Transluminal Coronary Angioplasty

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The treatment of patients with acute coronary syndromes has changed dramatically over the last several years. Most patients now undergo some form of percutaneous coronary intervention (PCI), which includes either stent placement or percutaneous transluminal coronary angioplasty (PTCA). Along with new medical interventions for acute coronary syndromes comes the need for new antithrombotic therapies. Combination therapy with antiplatelet agents (aspirin, adenosine diphosphate inhibitors), glycoprotein (GP) IIb-IIIa receptor inhibitors, and anticoagulants (unfractionated heparin or low-molecular-weight heparins) is administered, depending on the type of intervention and severity of the coronary lesion. Bivalirudin is a direct thrombin inhibitor that recently was approved as an alternative to heparin in patients undergoing PTCA. Compared with unfractionated heparin, bivalirudin reduces the rate of death, myocardial infarction, or revascularization, with a concurrent reduction in bleeding. This agent offers promise as a replacement for unfractionated heparin in PCI and is being studied in comparison with unfractionated heparin plus GP IIb-IIIa receptor inhibitors in patients undergoing intracoronary stent placement.
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OUTLINE

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Coronary artery disease affects more than 7 million Americans and accounts for more than 500,000 deaths/year in the United States.[1, 2] Acute coronary syndromes resulting from narrowing or occlusion of a coronary artery include unstable angina, non–ST segment elevation myocardial infarction, and ST segment elevation myocardial infarction. In 1996, unstable angina and non–ST segment elevation myocardial infarction accounted for 1.43 million hospitalizations and ST segment elevation myocardial infarction for 350,000 hospitalizations

in the United States.[3] Medical costs associated with managing coronary artery disease are approximately $12,000/patient, or $16 billion/year.[4] These amounts include the cost of percutaneous coronary intervention (PCI), a group of procedures aimed at mechanically improving flow in the affected coronary vessel.

More than 500,000 PCI procedures are performed annually in the United States, greater than 70% of which involve the use of intracoronary stents.[5] Administration of antithrombotic therapy in the setting of PCI significantly reduces the likelihood of rethrombosis of the culprit coronary artery and/or myocardial infarction. Effective antithrombotic therapy is essential to ensure successful PCI outcomes. The recommended combination of agents includes an oral antiplatelet agent (aspirin in combination with clopidogrel or ticlopidine), a glycoprotein (GP) IIb-IIIa receptor antagonist (abciximab, tirofiban, or eptifibatide), and a systemic anticoagulant (unfractionated heparin or a low-molecular-weight heparin [LMWH]).[5]

Unfractionated heparin has several noteworthy limitations.[6] In addition to binding to antithrombin to accelerate its action against factors IIa and Xa, unfractionated heparin binds to plasma proteins, macrophages, and endothelial cells. In addition, the effect of unfractionated heparin is reduced by the presence of platelet factor 4 (heparin cofactor), an acute phase reactant released from activated platelets that is elevated in acute coronary syndromes. These limitations alter its bioavailability and result in a nonlinear pharmacokinetic profile. Dose response is variable and inconsistent, requiring frequent laboratory monitoring of the activated partial thromboplastin time (aPTT) to ensure a therapeutic effect. Although unfractionated heparin is monitored routinely with aPTT, in the setting of PCI, the activated clotting time (ACT) typically is used. The ACT is a point-of-care assay that is used to ensure effective heparin therapy. During PCI, unfractionated heparin is administered by intravenous bolus, and administration is repeated as needed to maintain the ACT at an appropriate level. Finally, unfractionated heparin is associated with a 2–5% frequency of type II heparin-induced thrombocytopenia (HIT), an immune-mediated reaction that leads to platelet aggregation and results in high rates of thrombosis, amputation, and death.

The LMWHs have overcome many of the shortcomings of unfractionated heparin.[6] Like unfractionated heparin, LMWHs induce an anticoagulant effect by accelerating the action of antithrombin against factors IIa and Xa. However, the antifactor Xa:antifactor IIa ratio is much larger for LMWHs than for unfractionated heparin. The LMWHs also offer an improved and more consistent dose response and better bioavailability. They can be dosed subcutaneously once/day or twice/day based on total body weight and do not require routine laboratory monitoring to ensure an appropriate antithrombotic effect. Like unfractionated heparin, LMWHs can cause type II HIT, but in a lower percentage of patients (1–2%). However, LMWHs are contraindicated in patients with HIT because of a high rate of cross-reactivity.

Although unfractionated heparin has been the primary systemic anticoagulant in PCI, enoxaparin has been of interest because of its numerous practical advantages. In a recent registry of patients undergoing elective PCI, 88% of whom received intracoronary stents and all of whom were treated with abciximab and enoxaparin, rates of death, myocardial infarction, and revascularization were similar to those rates seen in other randomized trials of abciximab with unfractionated heparin, as were major bleeding rates.[7] In the setting of unstable angina and non–ST segment elevation myocardial infarction, enoxaparin is more effective than unfractionated heparin in preventing death, myocardial infarction, and revascularization, with a similar risk of major hemorrhage.[8, 9]

Bivalirudin (Angiomax; The Medicines Company, Cambridge, MA) is a direct thrombin inhibitor that recently was approved by the U.S. Food and Drug Administration (FDA) as an alternative to unfractionated heparin in patients undergoing percutaneous transluminal coronary angioplasty (PTCA). Compared with unfractionated heparin, bivalirudin reduces the combined frequency of death, myocardial infarction, or revascularization at 90 days and 6 months, with a significantly lower risk of major hemorrhage.[10] Although its role in contemporary coronary intervention is not yet clearly defined, its potential advantages over unfractionated heparin are intriguing.

Pharmacology

Thrombin (factor IIa) is a serine protease formed by proteolytic cleavage of prothrombin (factor II) by factor Xa and plays a central role in maintaining hemostasis and in pathologic clot

formation.[11] The actions of thrombin include cleavage of fibrinogen to fibrin, activation of factor XIII to increase fibrin strand cross-linking, and activation of factors V and VIII to accelerate further thrombin formation. In addition, thrombin is the single most potent stimulant of platelet activation and aggregation and promotes the release of platelet-activating substances.[12]

The thrombin molecule contains three essential binding sites (Figure 1).[13] The catalytic site (active site) is responsible for the enzymatic actions of thrombin, for example the cleavage of substrates. The substrate recognition site (exosite 1) acts as a docking station for these substrates. This is also the binding site for the antithrombin component of the heparin-antithrombin complex. Finally, exosite 2 serves as the site for binding of thrombin to a fibrin clot. Exosite 2 also serves as the binding site for the heparin component of the heparin-antithrombin complex. When thrombin is bound to fibrin, this site is inaccessible to binding by heparin. By this mechanism, heparin and LMWHs are able to inhibit soluble thrombin but not clot-bound thrombin.[14]

Direct thrombin inhibitors exert their anticoagulant effect by blocking the active site of the thrombin molecule and/or by preventing substrates from binding to the substrate recognition site without requiring additional cofactors like antithrombin.[15] As a result of their binding properties, direct thrombin inhibitors can inactivate both soluble and fibrin-bound (clot-bound) thrombin. This action may result in an improved antithrombotic effect in comparison to traditional antithrombotic agents that inhibit only soluble thrombin.

The prototypic direct thrombin inhibitor, hirudin, a 65–amino acid polypeptide, was isolated from the saliva of the medicinal leech, *Hirudo medicinalis*. Hirudin, its recombinant derivatives (lepirudin and desirudin), and polyethylene glycol–coupled hirudin are large molecules that irreversibly bind both the catalytic site and the substrate recognition site of the thrombin molecule. Two smaller molecules, synthetic direct thrombin inhibitors (argatroban and ximelagatran) reversibly bind only to the catalytic site.[16] Both lepirudin and argatroban are approved by the FDA as alternative anticoagulants in patients with type II HIT.

Bivalirudin is a synthetic 20–amino acid polypeptide composed of a peptide that binds reversibly to the active site of the thrombin molecule and is linked covalently to a dodecapeptide analog of hirudin that binds to the substrate recognition site (Figure 1). Once bound, thrombin slowly cleaves the bond between these distinct peptides, resulting in recovery of the active site. The dodecapeptide remains bound to the substrate recognition site.[17]

Inhibition of thrombin by bivalirudin results in a systemic anticoagulant effect characterized by inhibition of cleavage of fibrinogen to fibrin, and

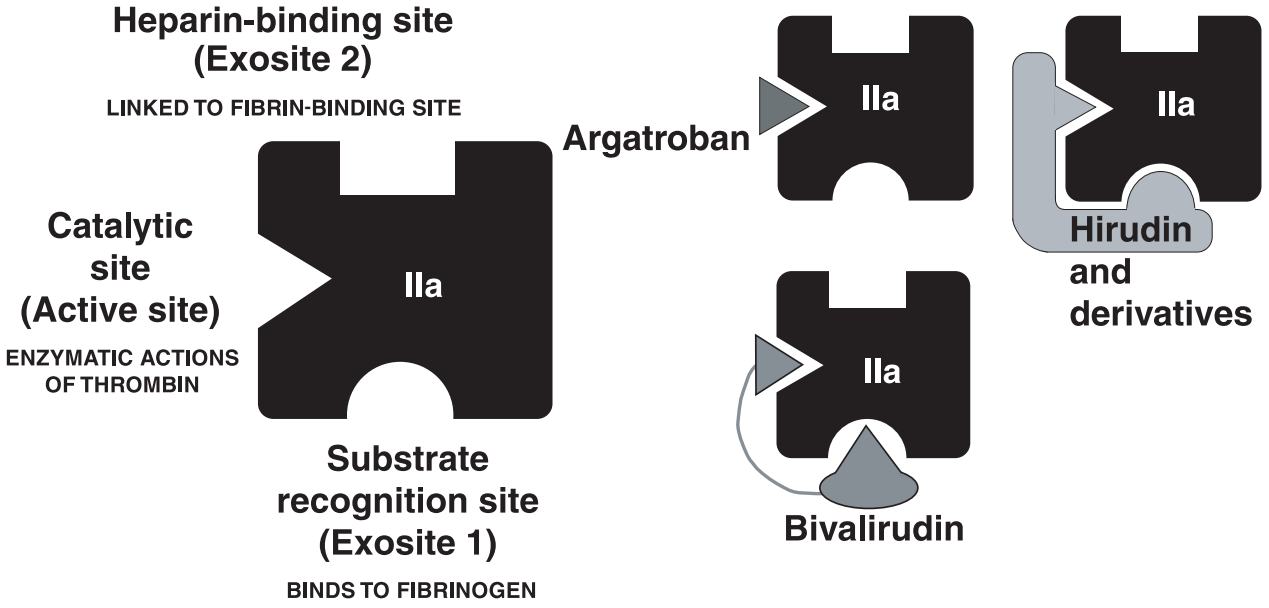

Figure 1. Three essential binding sites of a thrombin molecule and binding properties of some direct thrombin inhibitors.

inhibition of the activation of factors XIII, V, and VIII. In addition, bivalirudin has been shown to inhibit thrombin-mediated platelet activation without affecting adenosine 5′-diphosphate (ADP)– or collagen-mediated platelet activation and, unlike heparin, does not induce platelet aggregation.[18] These combined anticoagulant-antiplatelet effects may be especially useful in the platelet-rich environment of acute coronary syndromes.

Pharmacokinetics

Bivalirudin has a small volume of distribution (0.24 L/kg), suggesting that most drug distribution is limited to the intravascular compartment.[19, 20] Bivalirudin does not bind to plasma proteins, other than thrombin, or to red blood cells.[21]

The elimination of bivalirudin is through rapid plasma clearance by both a renal mechanism and proteolytic cleavage.[22] Metabolism of bivalirudin occurs in the liver or by other sites by means of proteolysis.[23] Bivalirudin exhibits linear pharmacokinetics after intravenous administration in patients with normal renal function (creatinine clearance [Cl_{cr}] > 90 ml/min) and in those with mild renal insufficiency (Cl_{cr} 60–89 ml/min).[22, 24] The dosing regimen for the kinetics studies was 1-mg/kg intravenous bolus followed by a 4-hour infusion at 2.5 mg/kg/hour.

The elimination half-life of bivalirudin is approximately 25 minutes in patients with normal renal function. A mean steady-state plasma concentration of 12.3 ± 1.7 µg/ml is attained after a 1-mg/kg bolus and a 2.5-mg/kg/hour infusion for 4 hours.[21]

The pharmacokinetics of bivalirudin are altered in patients with moderate-to-severe renal insufficiency (Cl_{cr} 10–59 ml/min).[21] The clearance is reduced by approximately 20% in this patient population, with an elimination half-life of 34–57 minutes.

Bivalirudin is removed partially by hemodialysis, with approximately 25% of the drug being cleared.[22] In patients dependent on dialysis, clearance is reduced by approximately 80% and elimination half-life is extended to 3.5 hours.[22]

Pharmacodynamics

After intravenous administration, bivalirudin produces an immediate anticoagulant effect. Bivalirudin has a linear dose-dependent pharmacologic effect, as well as alterations in coagulation parameters. This is evidenced by a corresponding elevation in the ACT, aPTT, thrombin time, and prothrombin time as the bivalirudin dose is increased.[22]

Coagulation parameters return to baseline values approximately 1 hour after cessation of the infusion.[22] The effect on aPTT profiles is similar in patients with normal, mild, or moderately reduced renal function. However, in patients with severe renal dysfunction (Cl_{cr} < 30 ml/min) and in patients requiring hemodialysis, the aPTT is significantly prolonged. Data are limited on administration of bivalirudin in patients with renal impairment. Evaluation of the derived maximal effect in patients with normal renal function compared with those requiring hemodialysis showed an average derived maximal effect of 57 seconds for normal, mild, or moderate renal function; 79.4 seconds for severe renal insufficiency; and 84.4 seconds in patients requiring hemodialysis.[19, 25] However, the number of patients in this evaluation was small (30 patients), making the safe administration of bivalirudin in patients with moderate-to-severe renal impairment a clinical challenge until further information becomes available.[19, 25] Recent data also indicate that the relationship between ACT and bivalirudin does not correlate as well as the relationship between bivalirudin and the ecarin clotting time assay.[26]

Review of Clinical Trials

Bivalirudin versus Unfractionated Heparin in PTCA

Results of three randomized, clinical trials of bivalirudin in PTCA have been published.[22, 27, 28] An initial dose-escalation trial in 291 patients evaluated abrupt coronary artery closure after five different dosages of bivalirudin (a bolus dose of 0.15–0.55 mg/kg followed by a continuous infusion dosage of 0.6–2.2 mg/kg/hour for 4 hours).[27] Abrupt vessel closure was lowest in the patients receiving the two highest dosages of bivalirudin. This study was limited because no control group with unfractionated heparin was included and the number of patients evaluated was small. In addition, application of the findings to contemporary practice is difficult owing to increased application of intracoronary stents and GP IIb-IIIa receptor inhibitors, neither of which were included in the trial. Nonetheless, the results suggest efficacy of bivalirudin in prevention of abrupt closure after PTCA.

The results of two large bivalirudin comparative trials were published in 1995 in a single article.[28]

These parallel clinical trials with identical inclusion and exclusion criteria compared bivalirudin with unfractionated heparin in patients undergoing PTCA. The original manufacturer, Biogen (Cambridge, MA), sponsored the trials with the intention of combining the results, for more than 4000 patients, in preparation for submission to the FDA for approval in PTCA. At 121 medical centers in North America, patients with severe, accelerating or rest angina within the last month who had coronary artery stenoses suitable for PTCA were randomly assigned to double-blind treatment with high-dose unfractionated heparin (2151 patients, 175 U/kg followed by an 18–24-hr infusion of 15 U/kg/hr) or bivalirudin (2161 patients, 1-mg/kg bolus followed by a 4-hr infusion of 2.5 mg/kg/hr followed by a 14–20-hour infusion of 0.2 mg/kg/hr). Both treatments were targeted at achieving an ACT of 350 seconds. The median duration of treatment was 16 hours. All patients were treated with aspirin 300–325 mg before PTCA and then daily thereafter. The primary end point of the study was a composite of in-hospital death, myocardial infarction, abrupt vessel closure or rapid clinical deterioration of cardiac origin requiring bypass surgery, intraaortic balloon counterpulsation, or repeat PTCA.

In the original publication, the unadjudicated results of 4098 of the 4312 patients were reported.[28] These preliminary results indicated no statistically significant difference between bivalirudin and unfractionated heparin with respect to the intent-to-treat primary end point (11.8% vs 12.9%, respectively, p=0.26). However, the frequency of the secondary end point, death or myocardial infarction (2.0% vs 5.1%, p=0.04), as well as major hemorrhage, defined as at least a 3-g/dl decrease in hemoglobin, need for transfusion, intracranial hemorrhage, or retroperitoneal bleed (3.8% vs 9.8%, p<0.001), were significantly reduced. Based on the results of this initial analysis, Biogen abandoned drug development. Subsequently, the development and marketing rights were purchased by The Medicines Company, which reanalyzed the data from the trial, now known as the Bivalirudin Angioplasty Trial (BAT), using contemporary definitions of adjudicated end points such as revascularizations and enzymatic or clinical evidence of myocardial infarction with complete follow-up. These trials formed the basis for the drug's approval by the FDA for use in PTCA in 2001. The results were audited and reanalyzed by statisticians from the FDA before approval.

Final data from the BAT trial were published recently and indicated superiority of bivalirudin compared with unfractionated heparin, with a 22% reduction in death, myocardial infarction, or revascularization at 7 days (6.2% vs 7.9%, p=0.039).[10, 22] These differences were sustained at 3 months (15.7% vs 18.5%, p=0.012) but were not statistically significant at 6 months (23% vs 24.7%, p=0.15).[10] There was a 62% reduction in major bleeding (3.5% vs 9.3%, p<0.001), as well as lower transfusion rates (p<0.001).[10, 22] A prespecified subgroup analysis of 741 patients undergoing PTCA within 2 weeks of myocardial infarction also demonstrated lower rates of procedural failure, defined as acute vessel closure, death, myocardial infarction, or revascularization during hospitalization (5.1% vs 10.8%, p=0.004); death or myocardial infarction (0.5% vs 4.3%, p=0.001); death (0% vs 0.8%, p=0.047); myocardial infarction (0.5% vs 3.8%, p=0.001); and revascularization (3.0% vs 6.5%, p=0.028).[29] Some believe that because the definitions of the study end points changed after the completion of the trial, these results should be viewed only as hypothetical.[30]

Bivalirudin versus GP IIb-IIIa Plus Unfractionated Heparin in PCI

Application of the results of BAT to contemporary practice is difficult because intracoronary stent placement now accounts for greater than 70% of PCI procedures.[5] Typical therapy in such procedures consists of unfractionated heparin or LMWH in combination with a GP IIb-IIIa receptor inhibitor, rather than unfractionated heparin alone. In addition, current practice patterns advocate lower dosages of unfractionated heparin and discontinuance of unfractionated heparin immediately after the procedure.[5] However, bivalirudin is being studied in intracoronary stent placement procedures as an alternative to unfractionated heparin and as a potential replacement for GP IIb-IIIa receptor inhibitors.

Preliminary information is available from two clinical trials, as yet unpublished, that have compared bivalirudin with abciximab (standard dosage of 0.25-mg/kg intravenous bolus followed by a 12-hr 0.125-µg/kg/min, maximum 10-µg/min, infusion) plus low-dose unfractionated heparin (70-U/kg bolus) in patients undergoing PCI. In the Comparison of Abciximab Complications with Hirulog and Back-up

Abciximab Events Trial (CACHET) parts B-C, 208 low-risk patients undergoing elective PCI were randomly assigned to receive either low-dose unfractionated heparin (70-U/kg bolus) plus abciximab (0.25 mg/kg followed by a 12-hr infusion of 0.125 µg/kg/min, maximum 10 µg/min) or two different dosages of bivalirudin (either a 0.5-mg/kg bolus followed by an infusion of 1.75 mg/kg/hr in the first 85 bivalirudin-treated patients or a bolus of 0.75 mg/kg followed by an infusion of 1.75 mg/kg/hr in the next 59 bivalirudin-treated patients) continued until the end of the procedure.[28, 31–33] All patients received aspirin and clopidogrel. Administration of provisional abciximab was permitted in the bivalirudin-treated patients at the clinician's discretion if the PCI results were not adequate as defined by diminished flow, greater than 40% residual stenosis, or dissection. Eighty-eight percent of patients received intracoronary stents, and abciximab was given in 24% of patients randomly assigned to receive bivalirudin. Results indicate that the combined bivalirudin groups experienced a lower combined frequency of death, myocardial infarction, revascularization, or major hemorrhage occurring at 7 days when compared with the group receiving unfractionated heparin plus abciximab (3.1% vs 14.1%, p=0.013).[33] Death, myocardial infarction, or revascularization was lower in the bivalirudin-treated patients (2.8% vs 7.8%, p=0.137), and major hemorrhagic events were reduced (1.4% vs 6.3%, p=0.074).

A second clinical trial, Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE) part 1, compared bivalirudin (0.75-mg/kg bolus followed by a 1.75-mg/kg/hr infusion continued to the end of the procedure) with unfractionated heparin (60–70 U/kg) in 1056 patients undergoing PCI.[34] Eighty-five percent of patients underwent intracoronary stent placement, and 72% received concomitant GP IIb-IIIa receptor inhibitor therapy with either abciximab, tirofiban, or eptifibatide in combination with aspirin and clopidogrel. Preliminary results of REPLACE part 1 indicate a 19% reduction (7.1% vs 8.8%, not statistically significant) in the primary composite end point of death, myocardial infarction, revascularization, or clinically significant bleeding occurring at 48 hours or at hospital discharge, whichever occurred first. The frequency of the triple composite end point of death, myocardial infarction, or revascularization also was reduced by 19% (5.6% vs 6.9%, not statistically significant). Major bleeding, defined as intracranial, retroperitoneal, intraocular, or clinically overt bleeding associated with a decrease in hemoglobin of 3 g/dl or more from baseline, was reduced by 22% (2.1% vs 2.7%, not statistically significant). Major bleeding rates were identical in the subgroups of patients receiving bivalirudin or heparin in combination with a GP IIb-IIIa receptor inhibitor (29%). However, the combination of bivalirudin or unfractionated heparin with GP IIb-IIIa receptor inhibitor therapy showed similar or slightly lower major bleeding rates with unfractionated heparin than with bivalirudin, despite significantly higher ACTs with abciximab plus bivalirudin compared with unfractionated heparin (371 vs 304 sec, p<0.001) at the start of the procedure.[34] This was a pilot study and was not powered to detect statistically significant differences in outcomes between the groups.[34]

In the ongoing REPLACE trial part 2, 6000 patients receiving aspirin and clopidogrel will be randomly assigned to receive either unfractionated heparin with the routine GP IIb-IIIa receptor inhibitor administered at each study site, or bivalirudin (0.75-mg/kg bolus followed by 1.75-mg/kg/hr infusion to the end of the procedure) with provisional abciximab.[32] The primary end point is death, myocardial infarction, revascularization, or major hemorrhage occurring at 30 days. A 1-year pharmacoeconomic analysis also is planned. The expected date of study completion is December 2002.

The decision to use major bleeding as a part of the primary composite end point in REPLACE parts 1 and 2 is unique among PCI trials.[32, 34] Preliminary data suggest that bivalirudin is safer than both unfractionated heparin alone and unfractionated heparin with abciximab, without a loss of efficacy. However, major bleeding rates observed in the GP IIb-IIIa receptor inhibitor arms of both the CACHET and REPLACE trials are higher than those observed in other contemporary clinical trials such as Enhanced Suppression of the Platelet IIb-IIIa Receptor with Integrilin Therapy (ESPRIT, 1%) and the Do Tirofiban and ReoPro Give Similar Efficacy Trial (TARGET, 0.9% and 0.7%) despite similar definitions of bleeding.[35, 36] Furthermore, the use of bleeding end points may introduce bias because they often include transfusion rates.

Two dosages of bivalirudin were tested: 1.0-mg/kg bolus followed by 2.5-mg/kg/hour infusion (21 patients) or a 0.75-mg/kg bolus followed by a 1.75-mg/kg/hour infusion (11

patients) for 4 hours. Unfractionated heparin (11 patients) was dosed to an ACT of greater than 200 seconds. Eptifibatide was dosed as a double bolus of 180 µg/kg separated by 10 minutes and followed by an infusion of 2 µg/kg/minute begun after the first bolus (ESPRIT dosing) and continued for 18–24 hours.[35, 37] The small sample prohibits making any definitive conclusions.[37]

Heparin-Induced Thrombocytopenia

Because bivalirudin has no structural similarity to unfractionated heparin, it may be administered safely to patients with HIT or heparin-induced thrombotic thrombocytopenia syndrome (HITTS) or a history of HIT or HITTS. The efficacy and safety of bivalirudin have been reported in 50 patients with HIT.[38] The first 39 patients received bivalirudin for a variety of indications, but most received treatment in the setting of PCI (17 patients). Of these 39 patients, 17 had acute HIT and 22 had a history of HIT. Mortality in these patients was 10%, and all four deaths were related to complications of HIT. Minor bleeding complications occurred in nine patients.[38]

Preliminary information on 11 of a planned 50 patients with acute HIT or HITTS or a history of HIT or HITTS from an ongoing clinical trial (Bivalirudin to Assist in the Performance of Percutaneous Coronary Intervention in Patients with Heparin-Induced Thrombocytopenia [ATBAT] trial) also has been reported. All patients had Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow during PCI. After PCI, no clinical events or major bleeding occurred, and two patients experienced minor bleeding.[38]

Other Investigations with Bivalirudin

A small, randomized, double-blind pilot trial of bivalirudin versus unfractionated heparin in patients with ST segment elevation myocardial infarction who presented within 12 hours of symptom onset was performed in 45 patients treated with intravenous streptokinase and aspirin.[39] Bivalirudin (0.5 mg/kg/hr for 12 hrs reduced to 0.1 mg/kg/hr) or unfractionated heparin (1000 U/hr titrated to maintain an aPTT of 2–2.5 times control) was administered just before or simultaneously with streptokinase 1,500,000 U administered over 60 minutes. Anticoagulant therapy was continued until the time of angiography, which occurred, on average, at day 4. The TIMI grade 3 flow, indicating complete reperfusion, was present in 77% of patients receiving bivalirudin compared with 40% of patients treated with unfractionated heparin ($p<0.02$).[39] Serious bleeding complications were similar between the two groups (unfractionated heparin 27%, bivalirudin 13%, not statistically significant).

In a second study in streptokinase-treated patients with ST segment elevation myocardial infarction performed by the same group of investigators, 70 patients were randomly assigned to two different dosages of bivalirudin (either 0.5 or 0.1 mg/kg/hr) versus unfractionated heparin (dosed as described above). At 90 minutes, the rate of TIMI grade 3 flow was highest in patients treated with the lower bivalirudin dosage ($p=0.04$).[40] The rate of blood transfusions was lower in the bivalirudin-treated patients (5%) compared with that in patients treated with unfractionated heparin ($p<0.02$).[40]

Another dosing strategy for bivalirudin was evaluated in a larger pilot trial of 412 patients with ST segment elevation myocardial infarction who were undergoing thrombolysis with streptokinase, the Hirulog versus Heparin in Patients Receiving Streptokinase and Aspirin for Acute Myocardial Infarction 1 (HERO-1) trial. The higher dosage of bivalirudin in this trial, a 0.25-mg/kg bolus followed by 0.5 mg/kg/hour for 12 hours followed by 0.25 mg/kg/hour for up to 60 hours, was associated with a higher frequency of TIMI grade 3 flow at 90–120 minutes as compared with unfractionated heparin (48% vs 35%, $p=0.03$). Major bleeding was significantly lower with bivalirudin than with unfractionated heparin (27% vs 19%, $p<0.01$).[41] These TIMI grade 3 flow rates are not as high as those of more fibrin-specific thrombolytics in combination with unfractionated heparin, as reported in the Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO)-1 trial with alteplase (48-60%) and the Reteplase (r-PA) versus Alteplase Patency Investigation during Myocardial Infarction (RAPID)-2 with reteplase (59.9%).[42, 43]

This same dosage of bivalirudin was being administered in the Hirulog/Early Reperfusion Occlusion-2 (HERO-2) study.[44] This study evaluated 17,073 patients with ST segment elevation myocardial infarction from 46 countries. Patients receiving streptokinase were randomly assigned to receive either unfractionated heparin (5000-U bolus followed by a weight-based infusion titrated to an aPTT of 50-

70 sec for 48 hrs) or bivalirudin (0.25-mg/kg bolus followed by 0.5 mg/kg/hr for 12 hrs and 0.25 mg/kg for 36 hrs) administered just before or simultaneously with streptokinase.[28] Both treatment groups received aspirin. The study sample was selected to have an 80% power to detect a 15% difference in 30-day mortality. There was no significant difference in the primary end point, 30-day mortality. Mortality as an independent measure was not significantly reduced (10.5% for bivalirudin vs 10.9% for heparin, p=0.46); however, the combined 30-day rate of death or reinfarction was 12.9% for bivalirudin and 14.2% for unfractionated heparin (p=0.023). The results showed a significant reduction in a secondary end point, nonfatal reinfarction, with bivalirudin at 96 hours compared with unfractionated heparin (2.3% vs 1.6%, p=0.001) and was sustained at 30 days (3.5% vs 4.5%, p<0.001).[45] The frequency of severe bleeding between the two treatment groups was not different. However, the rates of moderate and mild bleeding were increased (bivalirudin 0.7%, unfractionated heparin 0.5%, p=0.07). This trial demonstrates that bivalirudin is at least as effective as unfractionated heparin and not inferior when combined with streptokinase for the treatment of ST segment elevation myocardial infarction. Application of the results of this clinical trial to practices in the United States will be limited, however, since more fibrin-specific thrombolytic agents are preferred and no data on the combination of bivalirudin with thrombolytics other than streptokinase are available.[46]

The TIMI-8 trial was terminated prematurely after 133 of a planned 5320 patients with non–ST segment elevation acute coronary syndromes were enrolled because the original sponsor, Biogen, decided to halt drug development. In TIMI-8, unfractionated heparin, administered as a bolus of 70 U/kg followed by an infusion of 15 U/kg/hour titrated to an aPTT of 55–85 seconds, was compared with bivalirudin administered as a bolus of 0.1 mg/kg followed by an infusion of 0.25 mg/kg/hour for a minimum of 72 hours.[47] The primary efficacy end point, a composite of death or myocardial infarction through hospital discharge or 14 days, whichever came first, was 9.2% in the unfractionated heparin group versus 2.9% in the bivalirudin group (p=0.16). Major bleeding occurred in none of the bivalirudin-treated patients versus three patients (4.6%) in the unfractionated heparin group (p=0.11). Although the results of this study appear promising, it is unclear whether the current study sponsor, The Medicines Company, plans to pursue additional bivalirudin clinical trials in patients with non–ST segment elevation acute coronary syndromes.[47]

Monitoring

Bivalirudin appears to produce a linear and dose-dependent increase in several laboratory parameters, including the ACT, aPTT, prothrombin time, and thrombin time.[21] In PCI procedures, in which immediate laboratory results are necessary, ACT measured by a point-of-care device is the standard assessment of intensity of anticoagulation. Results of ACT obtained by using the Hemochron device (International Technodyne Corporation, Edison, NJ) are consistently 28% higher than those obtained with the Hemotec device (Hemotec Inc., Englewood, CO).[48]

Recommendations suggest that patients undergoing PCI who do not receive GP IIb-IIIa receptor antagonists should receive unfractionated heparin sufficient to prolong the ACT to 250–300 seconds with the Hemotec device and 300–350 seconds with the Hemochron device. When unfractionated heparin is given with a GP IIb-IIIa receptor antagonist, unfractionated heparin dosages should be reduced to reach a target ACT of 200 seconds, regardless of the point-of-care device used.[5] A recent meta-analysis of six randomized controlled trials comparing newer antithrombotic strategies with unfractionated heparin compared ACT results with clinical outcomes in patients randomly assigned to receive unfractionated heparin alone.[49] Ninety-five percent of ACT values were obtained with the Hemochron device. Among 5216 patients in whom ACT results were available, values of 350–375 seconds were associated with the lowest rates of the composite end point of death, myocardial infarction, and urgent revascularization (6.6%), which increased to 8.6% at 300–325 seconds. The lowest frequency of minor or major bleeding was observed at ACTs of 300–325 seconds (8.6%) but increased to 12.4% at 350–375 seconds. Therefore, at the recommended ACT values, the risk of worsened outcomes is balanced by the bleeding risk.

In clinical trials comparing GP IIb-IIIa receptor inhibitors with unfractionated heparin, low-dose unfractionated heparin was administered at 60–100 U/kg, with a target ACT of 300–350

seconds. In comparison, in clinical trials comparing bivalirudin with unfractionated heparin, high-dose unfractionated heparin was administered at 175 U/kg, with a target ACT of 350 seconds or greater. At first glance, it might be expected that the lower bleeding rates observed in patients randomly assigned to receive bivalirudin are simply the result of a comparison to excessive heparin dosing. However, in 4312 patients randomly assigned to receive bivalirudin or high-dose unfractionated heparin, bleeding rates were significantly reduced in bivalirudin-treated patients at all ACT values (Figure 2).[50] Based on available data, dosing of bivalirudin should be adjusted to maintain a target ACT of 350 seconds or greater.

Adverse Effects

Bleeding is the primary adverse effect associated with bivalirudin. In two clinical trials that compared bivalirudin with unfractionated heparin in patients undergoing PTCA for postinfarction angina, bivalirudin was associated with a lower major bleeding rate, as well as a lower frequency of blood transfusions.[10, 28] Major bleeding was defined as intracranial bleeding, retroperitoneal bleeding, any clinically overt bleeding that resulted in a decrease of 3% or greater in hemoglobin concentration, or bleeding that necessitated the transfusion of 2 or more units of blood. Should major bleeding occur with bivalirudin, the drug should be discontinued immediately. Protamine will not reverse the effects of direct thrombin inhibitors as it does the effects of unfractionated heparin. Should reversal become necessary, infusion of fresh-frozen plasma appears to be the only feasible option.

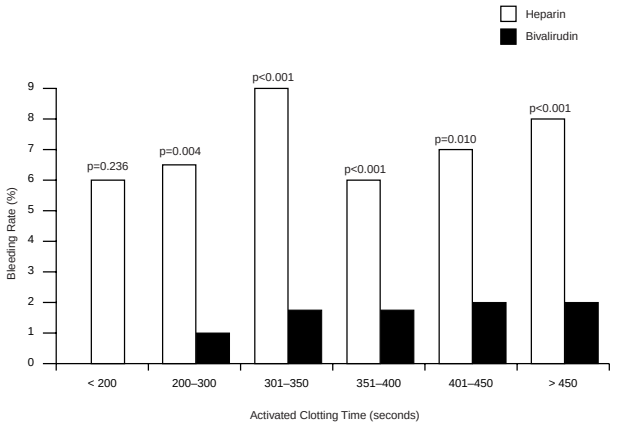

Figure 2. Comparison of activated clotting time with bleeding events for unfractionated heparin and bivalirudin. Bleeding events were defined as overt bleeding requiring transfusion ≥ 2 units, reduction in hemoglobin ≥ 3 g/dl, intracranial hemorrhage, or retroperitoneal hemorrhage. (Adapted from reference 50.)

Nonhemorrhagic adverse events reported most frequently in bivalirudin-treated patients in the two above-mentioned trials were back pain (42%), pain in general (15%), headache (12%), and hypotension (12%).[10, 28] Additional adverse effects that were reported in at least 5% of patients receiving bivalirudin were hypertension, bradycardia, nausea, vomiting, dyspepsia, injection site pain, insomnia, pelvic pain, anxiety, fever, and nervousness. Severe allergic reactions to bivalirudin have not been reported.

Drug Interactions

Drug-drug interaction studies with bivalirudin have been conducted with the ADP antagonist ticlopidine and the GP IIb-IIIa receptor inhibitors abciximab and eptifibatide, as well as with the LMWH dalteparin.[22] Data are limited and do not allow for conclusions regarding efficacy and safety in combination with these agents. However, the results do not suggest pharmacodynamic interactions. In patients treated with dalteparin, the drug was discontinued at least 8 hours before PCI and administration of bivalirudin.[22] In patients receiving eptifibatide, the ACTs were higher in bivalirudin-treated patients than in patients receiving unfractionated heparin. However, the sample was too small to make conclusions regarding risk of bleeding.[37]

In clinical trials of patients undergoing PCI, coadministration of bivalirudin with unfractionated heparin, warfarin, or fibrinolytic therapy was associated with an increased risk of major bleeding events compared with patients not receiving combination therapy.[40, 51, 52]

Dosing

Based on results of the BAT trial, the FDA-approved recommended dosage of bivalirudin for patients undergoing PTCA is an intravenous bolus dose of 1.0 mg/kg followed by a 4-hour infusion of 2.5 mg/kg/hour. Bivalirudin should be started just before PCI. After completing the 4-hour infusion, an additional intravenous infusion (0.2 mg/kg/hr) may be given for up to 18 hours if indicated (e.g., complicated procedures). In patients with renal impairment, the dosage of bivalirudin should be reduced (Table 1).[24]

In the CACHET and REPLACE-1 trials in

Table 1. Suggested Bivalirudin Dosage Adjustments Based on Calculated Creatinine Clearance[22]

Calculated Cl_{cr} (ml/min)	Bivalirudin Half-life (min)	Reduction in Infusion Dosage (%)
> 90	25	0
60–90	22	0
30–59	34	20
10–29	57	60
< 10	210	90

Cl_{cr} = creatinine clearance.

which bivalirudin was given to patients undergoing stent placement, lower dosages of bivalirudin (0.75 mg/kg followed by an infusion of 1.75 mg/kg/hr through the end of the procedure) were administered without any apparent reduction in efficacy.[33, 34] However, bivalirudin is not FDA approved for stent placement nor is this lower dosing regimen FDA approved.

Cost Considerations

To our knowledge, a pharmacoeconomic analysis of bivalirudin has not been published. However, clinical event rates and cost of care were determined as part of the BAT trial.[53] Clinical event rate costs were determined by using a national-representative, 74-hospital claims database of more than 37,000 patients undergoing PCI from October 1995–October 1997. This information, in combination with data from the Evaluation in PTCA to Improve Long-Term Outcome by c7E3 GP IIb-IIIa Receptor Blockade (EPILOG) trial pharmacoeconomic analysis, and a single-center registry, were used to estimate low- and high-end costs for repeat revascularization, myocardial infarction, and bleeding events requiring transfusion. These cost ranges were applied to event rates from the BAT to compare the cost of bivalirudin with that of unfractionated heparin.[53] A per event rate cost for each complication was calculated, and an expected cost of events was determined for each heparin- and bivalirudin-treated patient. When the low-end range of costs was applied, bivalirudin resulted in a $591 cost savings. When the high-end range of costs was applied, bivalirudin resulted in an $843 cost savings (Figure 3). Although these data suggest a cost savings with bivalirudin, prospective cost analyses are needed.

The cost (average wholesale price) of a dosage of bivalirudin (based on a patient weighing 70 kg who received a 1-mg/kg bolus and a 4-hr 2.5-mg/kg/hr infusion) is approximately $1675/patient/procedure (four vials).[54] This compares with a cost of approximately $6.00 for a 4-hour bolus and infusion of unfractionated heparin (70-U/kg bolus, 17-U/kg/hr infusion) for a patient weighing 70 kg. However, the lower dosage (0.75-mg/kg bolus and 1.75-mg/kg/hr infusion that continued only until the end of the procedure) that was administered in the CACHET and REPLACE-1 trials, while not FDA approved, reduces the cost of bivalirudin to approximately $418.75/patient/procedure (the cost of a single 250-mg vial for a 1-hour procedure).

Role in Clinical Practice and Future Implications

Results from published clinical trials indicate bivalirudin is superior to unfractionated heparin in preventing the combination of death, myocardial infarction, and revascularization after PTCA and causes less bleeding. However, the role of bivalirudin in PCI is unclear because intracoronary stent placement combined with a GP IIb-IIIa receptor inhibitor is the standard of care. Several patient populations may be candidates for bivalirudin, including patients at increased risk for bleeding associated with unfractionated heparin, those of advanced age, or patients with reduced renal function, existing thrombocytopenia, or a history of thrombocytopenia associated with unfractionated heparin, LMWH, or GP IIb-IIIa receptor inhibitors. Although bivalirudin is not FDA

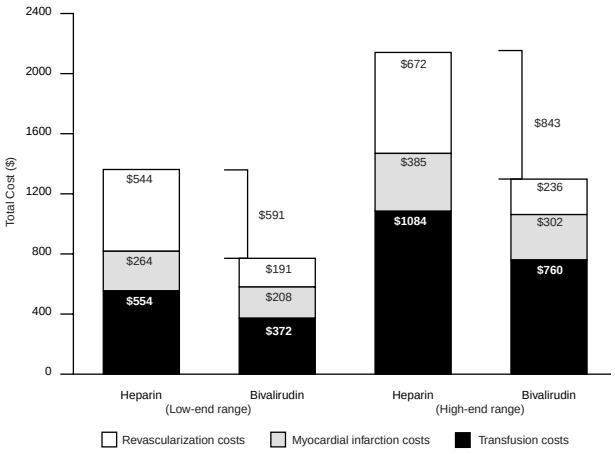

Figure 3. Comparison of costs of clinical events in patients undergoing percutaneous transluminal coronary angioplasty and receiving unfractionated heparin or bivalirudin, based on low-end and high-end range of costs.

approved for patients with HIT or HITTS, it may be an option in this patient population.

Results from REPLACE 2, a direct comparison of bivalirudin with unfractionated heparin combined with a GP IIb-IIIa receptor antagonist in a large number of patients, are eagerly awaited to define the role of bivalirudin in contemporary PCI. Also, since, to our knowledge, no trials comparing bivalirudin with contemporary early medical management of unstable angina or non–ST segment elevation myocardial infarction are planned, additional data are needed to provide guidance on how to transition from these agents to bivalirudin.

Conclusion

Many trials have evaluated various antithrombotic agents in patients undergoing PCI. However, because the results of these trials vary considerably, no definitive summary can be made regarding the role of each agent in the management of acute coronary syndromes. The primary factors to consider are safety, efficacy, and cost. The availability of long-term outcome data certainly will aid in the decision-making process. Little data exist on bivalirudin as a replacement for unfractionated heparin and GP IIb-IIIa receptor inhibitors in patients undergoing coronary stent placement. Therefore, additional trials with bivalirudin in this patient population are warranted. Clinicians may choose to use current guidelines until further information becomes available.

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