Bivalirudin in Acute Coronary Syndromes and Percutaneous Coronary Intervention

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The standard of care for patients with acute coronary syndrome is antithrombotic and antiplatelet therapies along with early percutaneous coronary intervention. Because of the limitations of heparin, there has been an interest in direct thrombin inhibitors, such as bivalirudin, which is now the anticoagulant of choice in percutaneous coronary intervention.
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Acute coronary syndromes are caused by an acute or subacute primary reduction of myocardial blood flow (and oxygen supply), provoked by disruption of an atherosclerotic plaque associated with thrombosis, inflammation, vasoconstriction, and microembolization. Depending on the extent and duration of coronary artery obstruction, clinical manifestations range from unstable angina to acute myocardial infarction.[1]

Trauma to the vessel exposes tissue factor in the lipid-rich core of the plaque, which initiates the coagulation process and production of small

quantities of thrombin. Thrombin activates platelets at the site of injury, leading to an inflammatory process and propagation of coagulation.[2] Platelets adhere to the subendothelial proteins exposed at sites of plaque disruption and become activated. Thrombin communicates with platelets and other cell types through activation of protease-activated receptors. Activated platelets provide surfaces for coagulation to amplify the coagulation signal; vasoactive and procoagulant substances released from activated platelets recruit neutrophils and monocytes to the sites of injury and contribute to the inflammatory process. Activated platelets generate more thrombin. The result is an intense production of thrombin—primarily after clot formation.

The standard of care for patients with acute coronary syndrome is antithrombotic and antiplatelet therapies along with early percutaneous coronary intervention (PCI). Because of the limitations of heparin, there has been an interest in direct thrombin inhibitors. We discuss the role of the direct thrombin inhibitor bivalirudin as an alternative to heparin as the anticoagulant of choice in the contemporary PCI setting and its role in acute coronary syndromes.

The Role of Thrombin in Acute Coronary Syndromes

Thrombin plays an important role in acute coronary syndromes because it is the most potent activator of platelets. It is a procoagulant and prothrombotic agent that plays an important role in thrombosis through its actions in the coagulation process and as a platelet activator. By activating platelets, thrombin serves as a key mediator of coagulation, and converts fibrinogen to fibrin, which helps stabilize platelet-rich thrombi formed at the site of plaque rupture, and promotes inflammation. Thrombin also elicits multiple responses in platelets, endothelial cells, and other cells, and promotes vascular healing after arterial injury. Further, thrombin plays a significant role as a hormone-like effector and provides signals to various cell types—such as platelets and endothelial cells—which affect responses in hemostasis and inflammation. Thrombin elicits a host of responses in the vascular endothelium, including shape and permeability changes, mobilization of adhesive molecules to the endothelial surface, and stimulation of autocoid (small-molecule mediators, such as prostaglandins and platelet-activating factor) and cytokine production. Thrombin is chemotactic for monocytes and mitogenic for lymphocytes and mesenchymal cells, and is thus a major player in the inflammatory response. Because of the importance of inhibiting thrombin, it represents an interesting target for drugs that would prevent the formation of fibrin- and platelet-rich thrombi induced by thrombin.

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Current Anticoagulants

Heparin

The most widely used antithrombotic therapy used in acute coronary syndrome and PCI has been heparin, which is an indirect thrombin inhibitor that requires antithrombin to inactivate thrombin.[3] However, it has several limitations and exhibits nonspecific binding to plasma proteins and cells, which leads to a nonlinear dose response and a variable anticoagulant effect that necessitates frequent monitoring. Heparin is not effective against clot-bound thrombin, which remains active in the coagulation process after blood clot formation.[4] In addition, it activates platelets via the glycoprotein (GP) IIb/IIIa receptors that play a pivotal role in the pathogenesis of thrombus formation after plaque rupture, which is responsible for acute coronary syndromes.[5]

Heparin is neutralized by platelet factor 4 (PF4), a chemokine released from platelet alpha-granules upon platelet activation. The concentration of PF4 is likely to be elevated in thrombotic situations, further limiting heparin's effectiveness in high-risk patients (eg, prior myocardial infarction).[6] The heparin:PF4 complex can elicit an immune response and the production of antibodies. In 2% to 3% of patients exposed to heparin, this reaction results in a life-threatening condition called heparin-induced thrombocytopenia/thrombosis syndrome (HITTS).[6] Although the incidence of HITTS is low, antibodies develop in almost half of patients exposed to heparin. The occurrence of HITTS is unpredictable

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in these patients. The limitations of heparin have led to the development of more effective thrombin inhibitors.

Bivalirudin

Bivalirudin is a synthetic 20 amino acid peptide analogue of hirudin that is cleared from plasma predominantly by hydrolysis from endogenous peptidases and is largely independent of organ function. Approximately 20% of bivalirudin is excreted unchanged in the urine.[7] Bivalirudin inhibits thrombin directly with high affinity and specificity and does not require the cofactor antithrombin.[8] After binding to thrombin, bivalirudin is slowly cleaved by thrombin allowing a return of thrombin's activity, which may be responsible for bivalirudin's safety profile. Bivalirudin is an attractive alternative to heparin as an anticoagulant because, as opposed to heparin, it effectively inhibits clot-bound and circulating thrombin. It also inhibits thrombin-mediated platelet activation and significantly decreases platelet reactivity compared to heparin.[9]

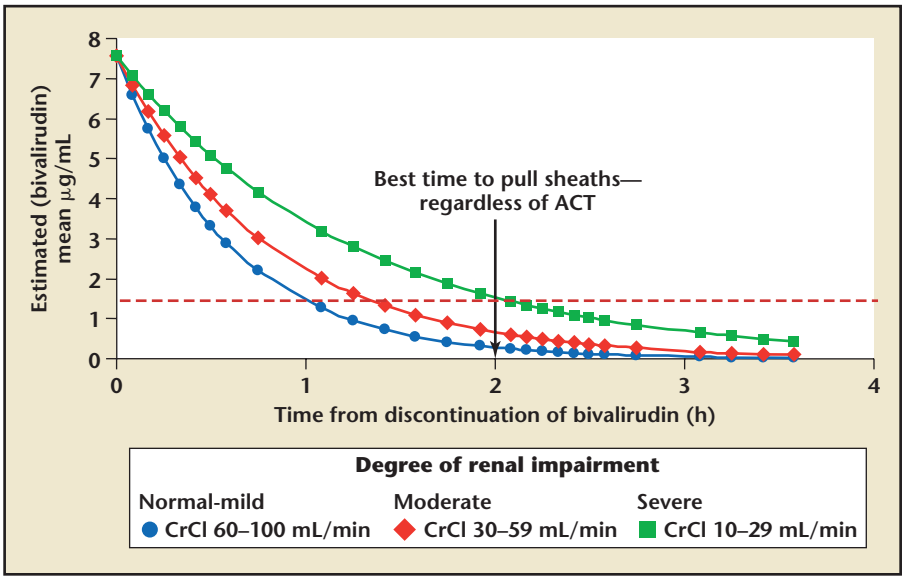
Bivalirudin inhibits thrombin directly with high affinity and specificity and does not require the cofactor antithrombin.

Bivalirudin serum concentrations at steady state are directly proportional to the dose administered, following a linear pharmacokinetic model (Figure 1).[10] Because bivalirudin does not bind to plasma proteins other than thrombin and is not neutralized by PF4, it remains fully active near the thrombus. There is no risk of heparin-induced thrombocytopenia thrombosis syndrome or any of the other thrombotic events associated with heparin/PF4 antibodies.[8]

There is currently no antidote for reversing the effect of bivalirudin. The half-life is 25 minutes.[11] Because of the predictable anticoagulation activity, there is no need for routine monitoring of bivalirudin levels. The levels of bivalirudin fall from therapeutic levels to below 2 mcg/mL within approximately 1 to 2 hours for all patients, except in those patients on dialysis. The predictable clearance of bivalirudin allows the use of time from bivalirudin discontinuation rather than activating clotting time for sheath removal.[12] Arterial sheaths can be removed 2 hours after bivalirudin is discontinued in most patients.[13]

Because of the potential advantages of direct thrombin inhibitors, several randomized clinical studies with bivalirudin have been conducted to assess its efficacy in PCI and acute coronary syndromes.

Figure 1. *Drug clearance and renal function. This graph estimates plasma levels after discontinuation of bivalirudin infusion. The plasma levels of bivalirudin, which has a half-life of 25 minutes, fall from therapeutic levels to below 2 mcg/mL within approximately 1 to 2 hours for all patients, except dialysis patients. This predictable clearance allows the use of time from bivalirudin discontinuation rather than ACT for sheath removal. ACT, activated clotting time; CrCl, creatinine clearance. Adapted with permission from Mehta S et al.[10]*



Bivalirudin in Percutaneous Coronary Intervention

The Bivalirudin Angioplasty Trial (BAT) was a randomized, double-blind trial of 4312 patients undergoing percutaneous transluminal coronary angioplasty (PTCA) comparing bivalirudin versus heparin in patients undergoing PTCA for unstable or postinfarction angina.[14] Angiographic and procedural outcomes were similar for heparin and bivalirudin-treated patients. The combined endpoint of death, myocardial infarction, or repeat revascularization at 7 days (OR 0.78, 95% CI: 0.62-0.99, P = .04) and at 90 days (OR 0.82, 95% CI: 0.70-0.96, P = .01) was significantly reduced in patients treated with bivalirudin. In addition, major bleeding events were significantly reduced

with bivalirudin compared with heparin at 7 days (3.5% and 9.3%, respectively; $P < .001$).

The Comparison of Abciximab Complications with Hirulog for Ischemic Events Trial (CACHET) was a small pilot trial of 268 patients undergoing PCI who were randomized to bivalirudin and preprocedural oral platelet inhibition with planned (group A, n = 30) or provisional (groups B and C, n = 144) abciximab or low-dose heparin plus planned abciximab (n = 94).[15] At 7 days, the rates of the composite endpoint of death, myocardial infarction, target lesion revascularization, or major bleeding were 3.4% for patients treated with bivalirudin and 10.6% for patients treated with heparin and abciximab ($P = .018$). Provisional use of abciximab was 24% in the group B and C combined bivalirudin arms.

The Randomized Evaluation in Percutaneous Coronary Intervention Linking Angiomax to Reduced Clinical Events (REPLACE)-1[16] study was a pilot trial of 1056 patients conducted to assess the outcomes of a lower dose of bivalirudin and to estimate its complication rate in the era of contemporary PCI. GP IIb/IIIa antagonists were used per institutional practice. There was no significant difference in the composite endpoint of death, myocardial infarction, or repeat revascularization before hospital discharge or within 48 hours in patients treated with bivalirudin compared with patients treated with heparin (5.6% vs 6.9%, $P = .40$). There was also no difference in major bleeding in patients randomized to bivalirudin compared with patients randomized to heparin (2.1% vs 2.7%, $P = .52$). There was a high usage of GP IIb/IIIa antagonists (72%), which provided a large amount of safety and efficacy data with the antithrombotic combination of bivalirudin and GP IIb/IIIa antagonists.

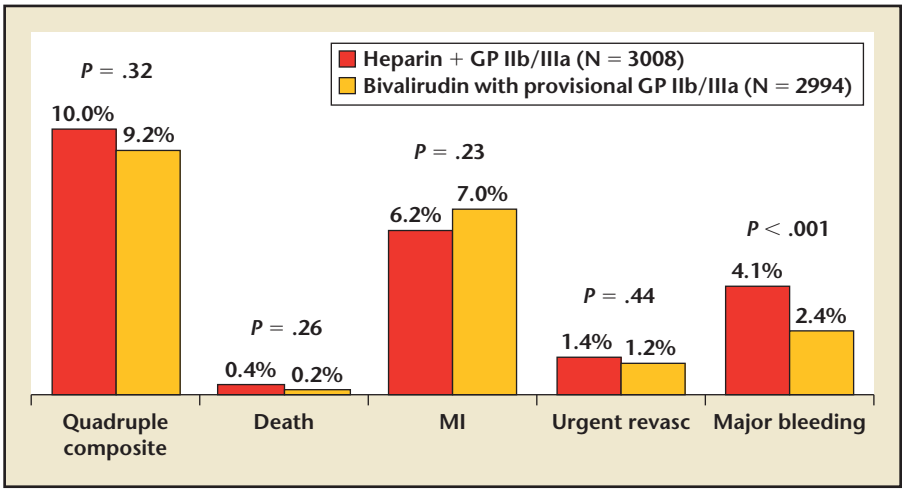
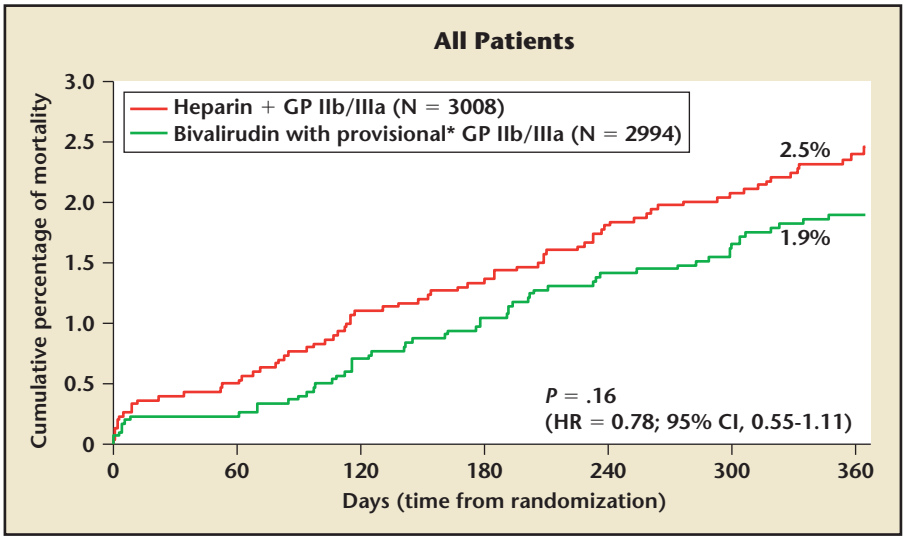


Figure 2. *The 30-day REPLACE-2 data demonstrated a statistically significant reduction in protocol-defined major bleeding (2.4% vs 4.1%, P < .001). There were no statistically significant differences in any of the other 30-day endpoints, including death, MI, or urgent revasc. GP, glycoprotein; MI, myocardial infarction; revasc, revascularization. Adapted from Lincoff AM et al.*[17]

In the REPLACE-2 trial[17] patients undergoing urgent or elective PCI were randomized to receive bivalirudin and provisional use of GP IIb/IIIa antagonists if complications occurred during PCI or heparin and GP IIb/IIIa antagonists. GP IIb/IIIa antagonists were used provisionally in the following circumstances: decreased TIMI flow (0-2) or slow reflow, dissection with decreased flow, new or suspected thrombus, persistent residual stenosis, distal embolization, unplanned stent, suboptimal stenting, side branch closure, abrupt closure, clinical instability, and prolonged ischemia. The protocol-specified statistical

Figure 3. *Kaplan-Meier curve demonstrates a trend (nonsignificant) toward a lower risk of death for bivalirudin with provisional glycoprotein (GP) IIb/IIIa compared with heparin plus GP IIb/IIIa at 1 year. P value is based on the log-rank test. *7.2% of bivalirudin patients received provisional GP IIb/IIIa. Adapted from Lincoff AM et al.*[19]



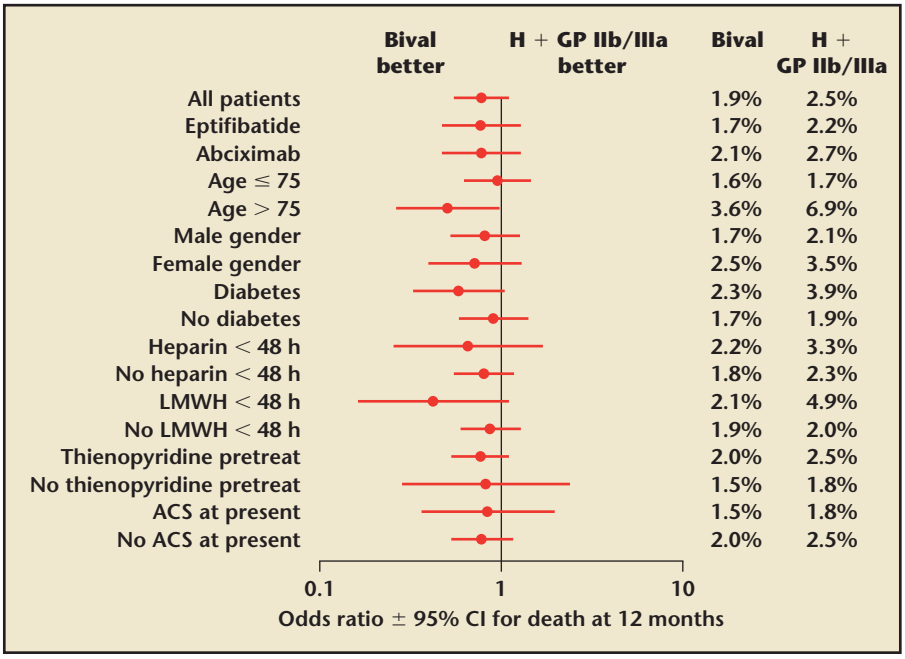


Figure 4. *Rates of 1-year mortality trended lower in the bival group in all prespecified subgroups. Bival, bivalirudin; H, heparin; GP, glycoprotein; LMWH, low-molecular-weight heparin; ACS, acute coronary syndrome; CI, confidence interval. Adapted from Lincoff AM et al.*[19]

criteria for noninferiority were met, as the composite endpoint of death, myocardial infarction, or urgent repeat revascularization by 30 days occurred in 7.6% and 7.1% in those treated with bivalirudin versus heparin and GP IIb/IIIa antagonists, respectively (Figure 2). However, the 30-day data demonstrated a statistically significant reduction in protocol-defined major in-hospital bleeding rates with bivalirudin (2.4% vs 4.1%, $P < .001$). There was a small nonsignificant increase in periprocedural non-Q-wave myocardial infarctions in patients treated with bivalirudin at 30 days.[17] However, by 6 months, there were no significant differences in the rates of death, myocardial infarction, or repeat revascularization between the 2 treatment groups.[18,19] There were statistically significant reductions in hemorrhagic endpoints in the bivalirudin with provisional GP IIb/IIIa group. The 0.2% absolute difference in mortality observed at 30 days trended in favor of bivalirudin (0.2% bivalirudin with provisional GP IIb/IIIa vs 0.4% heparin plus GP IIb/IIIa, $P = .26$) and was maintained at 1 year (0.6%) (1.9% bivalirudin with provisional GP IIb/IIIa vs 2.5% heparin plus GP IIb/IIIa, $P = .16$) (Figure 3). A multivariable analysis was performed to identify higher risk patients by integrating the variety of baseline factors that independently contribute to decreased long-term survival. Multivariate modeling identified 8 baseline variables that were predictive of 1-year mortality (Figure 4). Using this proportional hazards model, patients were categorized into tertiles of risk. Among low- or medium-risk patients, death rates were similar in the bivalirudin versus the heparin plus GP IIb/IIIa inhibitor groups (Figure 5). Regression analysis demonstrated that the largest difference in mortality at 1 year was seen in the highest risk patients and was significantly lower with bivalirudin compared with heparin plus GP IIb/IIIa antagonists. Similar efficacy and safety were seen in patients with renal insufficiency treated with bivalirudin.[20] Anticoagulation cost savings were $402 per patient for the bivalirudin with provisional GP IIb/IIIa group compared with the heparin plus GP IIb/IIIa group ($P < .001$) (Figure 6).[21] In the 1615 patients enrolled with diabetes, the 30-day composite endpoint of death, myocardial infarction, urgent revascularization, and in-hospital major bleeding was similar between bivalirudin and heparin plus GP IIb/IIIa antagonist, and 1-year

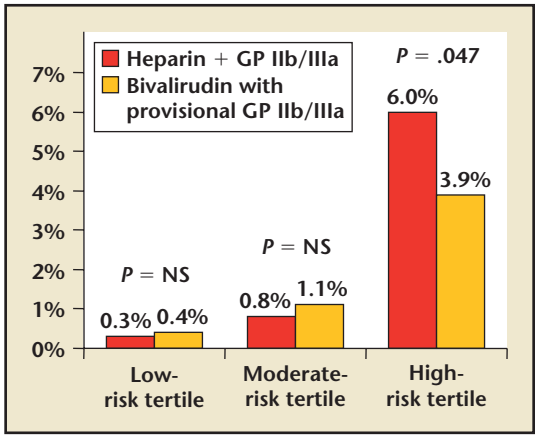


Figure 5. *Among low- or medium-risk patients, death rates were similar in the bivalirudin with provisional GP IIb/IIIa vs the heparin plus GP IIb/IIIa groups. Among high-risk patients, however, death occurred significantly less frequently in the bivalirudin with provisional GP IIb/IIIa group than in the heparin plus GP IIb/IIIa group (3.9% vs 6.0%, P = .047). Adapted from Lincoff AM et al.*[19]

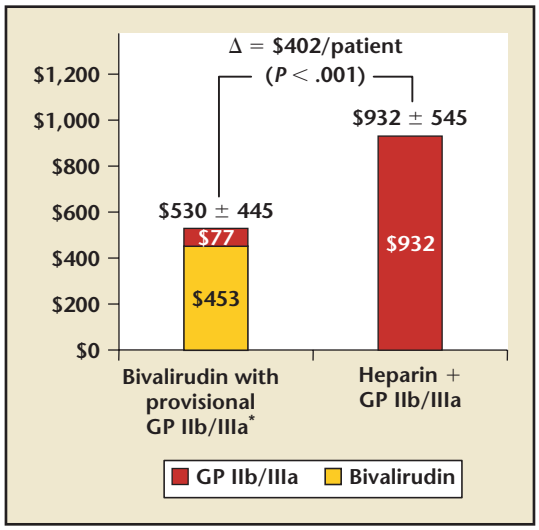


Figure 6. *Significant anticoagulant cost savings per patient. The total anticoagulant cost savings is $402/patient in the bivalirudin with provisional glycoprotein (GP) IIb/IIIa group. The cost for bivalirudin was $453/patient on average with $77 added for provisional GP IIb/IIIa. The cost for GP IIb/IIIa was $932/patient on average. *7.7% of bivalirudin patients received provisional GP IIb/IIIa. Adapted from Cohen DJ et al.*[21]

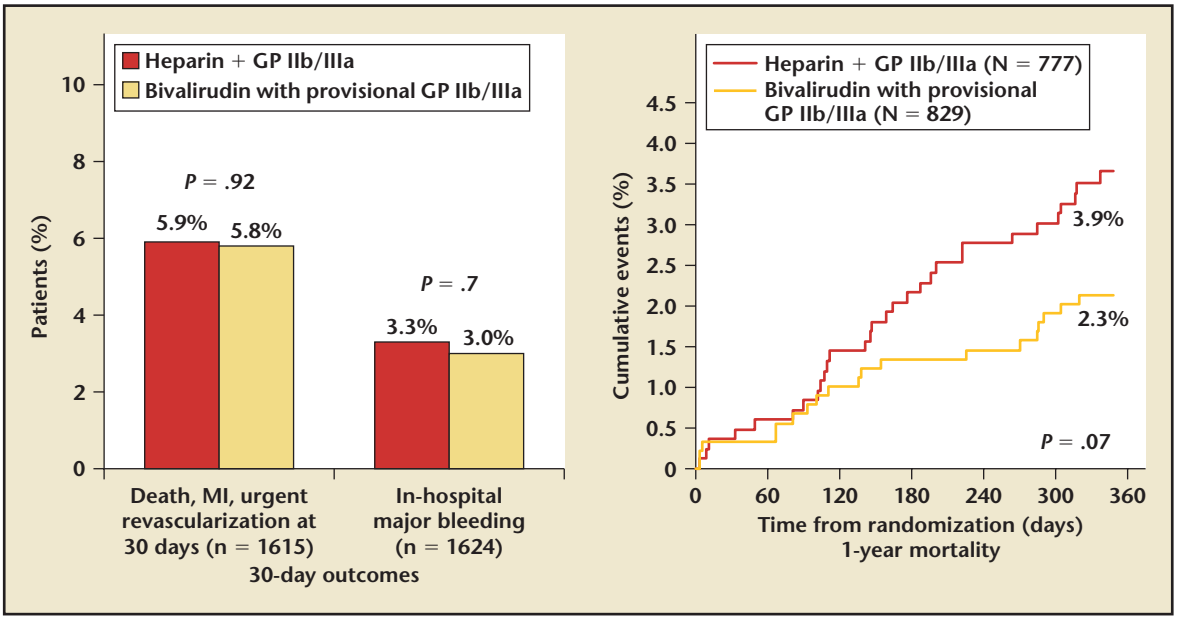
mortality data for this high-risk population showed a trend toward lowered mortality favoring bivalirudin (Figure 7). At 30 days, the mortality rate for patients who experienced a major bleed was 5.2% compared with a 0.2% mortality rate in patients who did not experience major bleeding. At 1-year follow-up, the mortality rate for patients who experienced an in-hospital major bleed was 8.8% compared with a 2.0% mortality rate in patients who did not experience major bleeding. The results of REPLACE-2 were confirmed by a large registry at a single center of almost 7000 patients undergoing "real-world" PCI.[22]

Bivalirudin in Acute Coronary Syndrome Treated with Percutaneous Coronary Intervention

The Acute Catheterization and Urgent Intervention Triage strategY (ACUITY) trial is a large clinical study (n = 13,800) that assessed the role of bivalirudin in moderate- to high-risk patients with acute coronary syndromes undergoing early (< 72 hours) invasive strategy.[23] ACUITY also attempted to address the need for and timing of GP IIb/IIIa antagonists.

The Harmonizing Outcomes with Revascularization and Stents (HORIZONS) trial will assess the role of bivalirudin in ST-segment elevation myocardial infarction treated with primary PCI. In this study, bivalirudin plus bailout GP IIb/IIIa inhibitor will be compared with heparin plus GP IIb/IIIa antagonists.

Figure 7. *Clinical endpoints in diabetic patients. Side-by-side presentation of 30-day composite of death, myocardial infarction (MI), or urgent revascularization, in-hospital major bleeding, and 1-year mortality data for the high-risk diabetes subgroup. The data show a trend toward lowered mortality in this high-risk subgroup in the bivalirudin with provisional glycoprotein (GP) IIb/IIIa. Event is defined as the first-time occurrence within the period. P value is based on log-rank test. Adapted from Lincoff AM et al*[17] *and Lincoff AM et al.*[19]



Bivalirudin in Renal Insufficiency

Patients with renal insufficiency are at higher risk for bleeding complications. The half-life of bivalirudin is prolonged from 25 minutes in normal renal function to 57 minutes in patients with severe renal impairment (CrCl < 30 mL/min) and 3.5 hours in dialysis patients. Consequently, in patients with renal insufficiency, no reduction in the bolus of bivalirudin is necessary, but in patients with severe renal insufficiency (CrCL < 30 mL/min), a reduction in the infusion rate to 1.0 mg/kg per hour should be considered. The infusion in patients on hemodialysis should be reduced to 0.25 mg/kg per hour. Furthermore, anticoagulation should be monitored in patients with renal impairment.

Conclusions

Clinical trials demonstrate that bivalirudin significantly reduces ischemic and bleeding complications in PTCA compared to heparin with significant reductions in costs. Bivalirudin with provisional use of GP IIb/IIIa antagonists is effective compared with heparin and GP IIb/IIIa in ischemic outcomes with significantly less major bleeding in PCI. Efficacy of bivalirudin with provisional use of GP IIb/IIIa antagonists was also observed in prespecified subgroups at higher risk for cardiovascular events. The recent American College of Cardiology/American Heart Association guidelines recommend bivalirudin as an alternative to heparin during PCI in patients with stable coronary artery disease.[24] Patients with heparin-induced thrombocytopenia (HITS)/HITTS or patients who cannot tolerate heparin and who undergo PCI can also be considered for treatment with bivalirudin.[25] The recently completed ACUITY trial and the ongoing HORIZONS trial will help define the role of bivalirudin in the treatment of acute coronary syndrome. ■

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Main Points

- Thrombin represents an interesting target for drugs that would prevent the formation of fibrin- and platelet-rich thrombi induced by thrombin.
- Bivalirudin is an attractive alternative to heparin as an anticoagulant because, as opposed to heparin, it effectively inhibits clot-bound and circulating thrombin.
- Bivalirudin significantly decreases platelet reactivity compared to heparin.
- Bivalirudin with provisional use of glycoprotein IIb/IIIa antagonists is effective compared with heparin and glycoprotein IIb/IIIa in ischemic outcomes, with significantly less major bleeding in percutaneous coronary intervention.

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