Cardiovascular Drug Reviews
Vol. 23, No. 4, pp. 345–360
© 2005 Neva Press, Branford, Connecticut

Bivalirudin: Pharmacology and Clinical Applications

Nicolas W. Shammas

Midwest Cardiovascular Research Foundation, Davenport, Iowa, USA

Keywords: Acute coronary syndrome — Anticoagulants — Bivalirudin — PCI — Percutaneous coronary intervention — Thrombin inhibitors.

ABSTRACT

Bivalirudin (Hirulog®, Angiomax®) is a specific, reversible and direct thrombin inhibitor with a predictable anticoagulant effect. It is cleared by both proteolytic cleavage and renal mechanisms, predominantly glomerular filtration. Bivalirudin inhibits both circulating thrombin and fibrin bound thrombin directly by binding to thrombin catalytic site and anion-binding exosite I in a concentration-dependent manner. Bivalirudin prolongs activated partial thromboplastin time, prothrombin time, thrombin time and activated clotting time (ACT). ACT levels with bivalirudin do not correlate with its clinical efficacy. Bivalirudin with a provisional GpIIb/IIIa inhibitor is indicated in elective contemporary percutaneous coronary intervention (PCI). In respect to combined ischemic and hemorrhagic endpoints of death, myocardial infarction, unplanned urgent revascularization and major bleeding during PCI (including subgroups of patients with renal impairment and diabetes) bivalirudin is not inferior to unfractioned heparin or planned GpIIb/IIIa inhibitors. In addition, bivalirudin has been consistently shown to have significantly less in-hospital major bleeding than heparin alone or heparin in combination with-a GpIIb/IIIa inhibitor. Bivalirudin appears to be also safe and effective during PCI in patients with heparin-induced thrombocytopenia. Finally, data from PCI studies support the safety and efficacy of bivalirudin, although its direct randomized comparison with unfractionated heparin is lacking.

Address correspondence and reprint re quests to: Nicolas W. Shammas, MS, MD, FACC, Research Director, Midwest Cardiovascular Research Foundation, Cardiovascular Medicine, PC, 1236 E. Rusholme, Suite 300, Davenport, IO 52803, USA.
Tel.: +1 (563) 324-2992; Fax: +1 (563) 324-449-8446. E-mail: shammas@mchsi.com

INTRODUCTION

Bivalirudin, a synthetic peptide analogue of hirudin, was invented and developed at Biogen. In December 2002, following its acquisition by The Medicines Company, bivalirudin was approved by the Food and Drug Administration (FDA) for use as an anticoagulant during coronary angioplasty in unstable angina patients.

Bivalirudin was developed as an alternative to unfractionated heparin for use during percutaneous interventions. Heparin is an indirect thrombin inhibitor and requires antithrombin to inhibit the effects of thrombin. In addition, it binds to serum proteases, endothelial cells and macrophages and, therefore, exhibits non-linear pharmacokinetic and pharmacodynamic characteristics with an unpredictable anticoagulant response. Heparin can also induce thrombocytopenia and subsequent thrombotic complications. In contrast, bivalirudin has a more predictable anticoagulant effect, it does not activate platelets and binds to the circulating as well as to the fibrin-bound thrombin. This review covers pharmacology and clinical use of bivalirudin.

CHEMISTRY

Bivalirudin (Hirulog®, Angiomax®) is a direct thrombin inhibitor with specific and reversible actions. It is a synthetic, 20-amino acid peptide ($C_{98}H_{138}N_{24}O_{33}$) with a molecular weight of 2180.19 Da (anhydrous free base peptide). Its chemical name is D-phenylalanyl-L-prolyl-L-arginyl-L-prolyl-glycyl-glycyl-glycyl-glycyl-L-asparagyl-glycyl-L-aspartyl-L-phenylalanyl-L-glutamyl-L-glutamyl-L-isoleucyl-L-prolyl-L-glutamyl-L-glutamyl-L-tyrosyl-L-leucine trifluoroacetate (salt) hydrate (4,40) (Fig. 1).

Bivalirudin is administered intravenously. It is supplied as a sterile white lyophilized cake (250 mg per vial) and when reconstituted with water yields an acidic (pH 5.0–6.0), clear to opalescent, colorless to slightly yellow solution. Once reconstituted, bivalirudin can be utilized up to 24 h and should be stored at 2–8°C. The recommended dosage of bivalirudin is an intravenous (i.v.) bolus dose of 1.0 mg/kg followed by a 4-h-long i.v. infusion at a rate of 2.5 mg/kg/h. If clinically warranted, it can be followed by an i.v. infusion at a rate of 0.2 mg/kg/h for up to 20 h (4). In animal models, plasma level of bivalirudin peaked at 2 minutes of i.v. administration of the drug and returned to baseline within 2 h. Subcutaneous administration of bivalirudin is not an approved method of administration. Plasma bivalirudin levels peak at 30–180 min after subcutaneous administration and return to baseline within 24 h (20,40,44). Its pharmacokinetics, pharmacodynamics and toxicology have been described in numerous publications (20,21,36,40,41,46, 57) and are summarized below. The details are also available at the Center for Drug Evaluation and Research website as a part of an NDA (Number 20-873) submitted by The Medicines Company (40).

Bivalirudin inhibits both circulating and bound thrombin directly by binding to thrombin catalytic site and anion-binding exosite. Bivalirudin contains 3 structural domains: 1) the NH_2 terminal sequence (D-Phe-Pro-Arg-Pro) that binds the thrombin active site, 2) the COOH-terminal sequence that binds the anion-binding exosite, and 3) the tetraglycyl spacer that links the NH_2 and COOH-terminal sequences. The binding to thrombin is

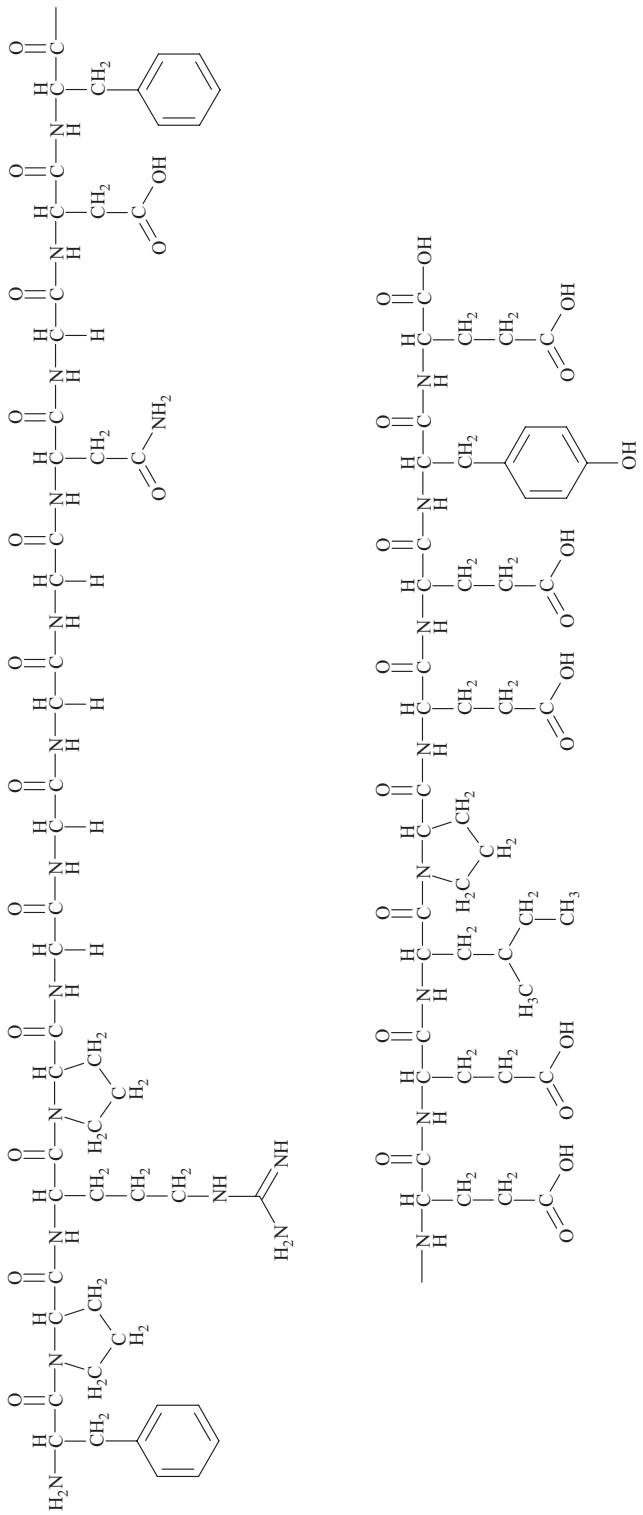

FIG. 1. Chemical structure of bivalirudin.

reversible as the affinity of bivalirudin to thrombin is 1000-fold lower than that of hirudin. Thrombin cleaves Arg3-Pro4 bond of bivalirudin resulting in recovery of the active site.

In vitro studies have shown that bivalirudin (100 nM to 125 mM) inhibits a-thrombin in a concentration-dependent manner. The formation of the bivalirudin-thrombin complex is postulated to involve 4 steps: 1) the COOH-terminal binds to the anion-binding exocite to form enzyme-inhibitor complex1 (EI^1) with a dissociation constant of 0.75 mM, 2) intramolecular conformational change is induced by step 1 to form EI^2, 3) P1 arginine of bivalirudin interacts with the primary specificity pocket to form EI^3, 4) a second intramolecular confirmation change occurs to form EI^4 with a rate constant of 30 S^{-1}. The formation of EI^3 and EI^4 results in a stable bivalirudin-thrombin complex. In humans, the K_i of bivalirudin was determined to be 2.3 nM.

ANIMAL PHARMACOLOGY

Bivalirudin has been shown to prolong activated partial thromboplastin time (APTT), prothrombin time (PT) and thrombin time (TT) in several species. In humans bivalirudin, at 0.2 μg/mL, prolonged APTT by 196%. At a concentration range of 0.2 to 1 μg/mL, species specificity for APTT prolongation was as follows: mouse > rat > human > monkey > bovine > porcine > canine > rabbit. Bivalirudin does not bind significantly to plasma proteins and only minimally to red blood cells (7%). The binding to red blood cells plays little if any role in its thrombin inhibitory activity. In a baboon (*Papio anubis*) arteriovenous (AV) shunt model, bivalirudin, was studied at a dose range of 0.12 to 12.0 mg/kg/h i.v. Its effects on bleeding time and platelet-dependent thrombus time were evaluated using various thrombogenic surfaces including an endarterectomized baboon aorta and a collagen coated Gortex and a Dacron vascular grafts. Bivalirudin prolonged APTT in a dose-dependent manner but at ≤0.3 mg/kg/h had no effect on bleeding time (at higher doses it prolonged bleeding time). At ≤0.6 mg/kg/h, bivalirudin interrupted platelet and fibrin deposition on the endarterectomized aorta, and at a dose of 12 mg/kg/h it had the same effect in the vascular grafts.

Bivalirudin does not activate platelets and is not inhibited by platelet products. *In vitro*, bivalirudin displays a concentration-dependent inhibition of thrombin-induced platelet aggregation. At 0.02 and 0.034 mg/mL, bivalirudin inhibited thrombin-induced platelet aggregation by 96.9 and 100%, respectively. The inhibition of thrombin-induced platelet aggregation and alpha granule secretion by bivalirudin is dose-dependent with an IC_{50} of 81.1 ng/mL. At concentrations up to 217.8 μg/mL bivalirudin has no effect on collagen- or ADP-induced platelet aggregation. In a bovine thrombin-induced intracranial platelet accumulation model, bivalirudin, by intracarotid injection at 90 mU/kg, reduced platelet accumulation in a dose-dependent manner; platelet aggregation declined to 62.9, 19.8, and 2.0% at the drug concentration of 0.05, 0.1, and 0.2 mg/kg, respectively. Bivalirudin had no effect on the kinetics and fibrinolytic potential of tissue-type plasminogen activator (t-PA), on Human Factors VIIa, Xa, XIIa, or plasmin. In a rat thrombolysis model, bivalirudin increased vessel patency and reduced reperfusion as well as reocclusion time. It was more effective than unfractionated heparin or recombinant hirudin

In the clinic bivalirudin is administered with aspirin. Its combination with aspirin (20) or t-PA bivalirudin does not cause any unexpected toxic effects but its expected biological effects are exaggerated. Addition of warfarin does not alter pharmacokinetics of bivalirudin (T_{max}, C_{max}, and AUC) and does not prolong APTT and PT time beyond values achieved with bivalirudin alone.

Bivalirudin does not have any significant effects on neurologic, gastrointestinal, renal or clinical chemistry parameters. In rat and dog models, bivalirudin increased blood pressure. In rats, at 1 mg/kg i.v., bivalirudin increased blood pressure to 99/64 from 88/53 mm Hg and at 5 mg/kg to 133/93 from 98/67 mm Hg. In dogs infusion of 5 mg/kg bivalirudin over 15 min increased systolic blood pressure by 28 to 51% with an increase in the left ventricular end-diastolic pressure by 26–74% over the baseline. After cessation of the infusion the hemodynamic changes returned to baseline. This effect was not seen in baboons or cynomolgus monkeys.

PHARMACOKINETICS

The pharmacokinetics of bivalirudin was examined in various animal models, including rats, rabbits, baboons and cynomolgus monkeys. The volume of distribution of bivalirudin, by either i.v. or s.c. administration, exceeded that of blood volume indicating substantial tissue distribution of the drug. The distribution and metabolism of bivalirudin were studied using either [^{3}H] or [^{14}C]bivalirudin. [^{3}H] was located on proline in position 2 (part of the NH_2 terminal sequence), while [^{14}C] was located on glycine in positions 5, 6, 7, 8 (part of the tetraglycyl sequence) and/or in position 10 (part of the COOH terminal sequence). Clearance of [^{14}C] was negligible and [^{14}C] was widely distributed into several tissues. Less than 25% of [^{14}C] radiolabel was excreted in urine and feces indicating that with the exception of the first two aminoacids (phenylalanine and proline) in the bivalirudin sequence, the remaining 18 aminoacids are degraded and utilized for new protein synthesis. [^{3}H] activity disappeared between 1 and 4 h after administration of [^{3}H]bivalirudin. Its clearance exceeded hepatic or renal blood flow suggesting metabolic clearance. At 24 h after i.v. administration of [^{3}H]bivalirudin, radioactivity was confined mostly to the kidneys indicating that the first two aminoacids (phenylalanine and [^{3}H]proline) were cleaved by thrombin and were excreted by the kidneys.

Bivalirudin is cleared partly by a renal mechanism (glomerular filtration) and, therefore, its dose needs to be adjusted in patients with renal impairment (43,44). The half-life of the drug is 25 minutes in patients with normal renal function. In patients undergoing coronary angioplasty mild renal impairment did not affect total body clearance of bivalirudin (60–89 mL/min). Clearance was reduced by approximately 20% in patients with moderate and severe renal impairment (30–59 mL/min), by 60% in patients with severe renal impairment (10–29 mL/min), and by approximately 80% in dialysis-dependent patients. In patients with renal impairment the initial bolus dose of bivalirudin is usually not reduced, while the infusion dose is reduced by 20 to 60% (in patients with moderate or severe renal impairment, respectively). In patients on dialysis the infusion rate of bivalirudin is reduced by 90%. The anticoagulant effect of bivalirudin is not antagonized by any known drug. However,25% of the drug can be cleared by hemodilalysis.

In contrast to unfractionated heparin (UFH), bivalirudin binds thrombin directly and reversibly in a mixed competitive/non-competitive manner and irrespective of whether thrombin is free or fibrin-bound. Bivalirudin-induced inhibition of either free or clot-bound thrombin is concentration-dependent. UFH inhibits thrombin indirectly via binding anthithrombin III. The products of platelet activation, such as platelet factor IV, reduce its activity. In contrast to hirudin, bivalirudin binds thrombin reversibly and is not immunogenic.

TOXICOLOGY

The acute toxicity of bivalirudin was evaluated in rats (22), mice and cynomolgus monkeys. In mice and at doses up to 200 mg/kg i.v. bivalirudin did not increase mortality and there were no signs of any toxicity. In rats, and at doses of ≥50 mg/kg i.v. bivalirudin caused pulmonary distress, followed by death. In the cynomolgus monkeys, at a dose of 100 mg/kg i.v. bivalirudin produced no signs of toxicity.

By repeated infusion to rats bivalirudin, at doses up to 36 mg/kg/day for 14 days, produced no clinical signs of toxicity. Biliary hyperplasia was, however, detected by pathological evaluation. In a 28-day long study, bivalirudin was administered at doses of 25, 75, and 250 mg/kg/day i.v. At 25 mg/kg/day there was no clinical toxicity. At 250 mg/kg/day mortality occurred. Organ studies showed pancreatitis and sinusoidal histiocytosis as well as centrilobular and midzonal necrosis in the liver. Also, phlebitis at infusion site was seen, particularly at high doses. With the exception of the latter, no treatment-related changes were seen at the end of 14 days-long recovery period. Similar toxicological studies were conducted in cynomolgus monkeys. In a 28-days-long study, the maximal tolerated dose of bivalirudin was 36 mg/kg/day i.v. with no target organ toxicity seen at this dose. At 150 mg/kg/day, skeletal muscle degeneration and/or necrosis were seen.

Mating and general reproductive performance was unaffected in rats at doses ≤150 m/kg/day for 2 weeks s.c. At 500 mg/kg/day s.c., testicular toxicity was not evident in rats and monkeys, but overall mortality and impairment of body weight gain were seen for male and female animals. Also, litter sizes and live fetuses in rats were reduced. Fetal skeletal variations were also noted. Some of these changes could be attributed to maternal toxicity observed at high dosing. Finally, bivalirudin was found to have no genotoxic potential.

CLINICAL APPLICATIONS

Percutaneous Coronary Interventions

Bivalirudin is currently approved by the FDA as an anticoagulant to be used with aspirin in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA) in elective non-emergent PCI. Bivalirudin does not alter restenosis

rate post PCI (9). A review of the clinical trials of bivalirudin in PCI and PPI is presented below (Table 1).

Bivalirudin angioplasty trial (BAT)

In the first BAT trial (6) 4312 patients with unstable angina and undergoing percutaneous transluminal angioplasty were randomized to bivalirudin versus high dose heparin. In this multicenter, double-blind trial, patients treated with bivalirudin ($n = 2161$) had a 22% reduction in the 7-day composite endpoint of death, myocardial infarction, and repeat revascularization as compared to the heparin-treated patients ($n = 2151$) (6.2 vs. 7.9%, $p = 0.0386$). The composite endpoint difference was sustained at 90 days ($p = 0.012$) and 180 days ($p = 0.153$). Major bleeding was significantly reduced by 62% with bivalirudin compared to heparin (9.3 vs. 3.5%, *p*vs.0.001). Based on this study, the Food and Drug Administration approved the use of bivalirudin in patients undergoing percutaneous coronary angioplasty. The BAT trial, however, was done prior to the era of stents and GPIIb/IIIa inhibitors use and therefore, its conclusions do not apply to today's interventional practice.

Comparison of abciximab complications with hirulog for ischemic events trial (CACHET)

The CACHET trial (35) was the first to test bivalirudin safety and effectiveness when compared to UFH and GPIIb/IIIa inhibition in patients undergoing stenting. In this pilot trial of 268 patients, patients were randomized in 3 sequential phases to 1) bivalirudin (1.0 mg/kg bolus, infusion of 2.5 mg/kg/h for 4 h) and abciximab, 2) bivalirudin (0.5 mg/kg bolus, infusion of 1.75 mg/kg/h for the duration of the procedure) plus provisional abciximab, or 3) bivalirudin (0.75 mg/kg bolus, infusion of 1.75 mg/kg/h for the duration of the procedure) plus provisional abciximab versus the control arm of UFH and

TABLE 1. Clinical trials with bivalirudin

Trials	Reference No.
Bivalirudin Angioplasty Trial (BAT)	7
Comparison of Abciximab Complications with Hirulog for Ischemic Events Trial (CACHET)	35
Randomized Evaluation of PCI Linking Angiomax to reduced Clinical Events (REPLACE)-1 trial	8
The Randomized Evaluation in PCI Linking Angiomax to reduced Clinical Events (REPLACE)-2 trial	9–13
Hirulog and Early Reperfusion/Occlusion (HERO)-1 trial	60
Hirulog and Early Reperfusion or Occlusion (HERO-2) trial	62
Thrombolysis In Myocardial Infarction-8 (TIMI-8) trial	5
Acute Catheterization and Urgent Intervention Triage strategY (ACUITY) trial	17
The Anticoagulant Therapy with Bivalirudin to Assist in the performance of PCI in patients with HIT (ATBAT)	18
The Angiomax Peripheral Procedure Registry Of Vascular Events trial (APPROVE)	19

abciximab. A composite clinical endpoint of death, myocardial infarction, repeat revascularization, or major bleeding by 7 days occurred in 3.3, 5.9, 0, and 10.6% of these 4 groups, respectively ($P = 0.018$ for the pooled bivalirudin groups versus the heparin group). In this study, bivalirudin with planned or provisional abciximab was at least as safe and effective as low-dose heparin plus abciximab during PCI.

Randomized evaluation of PCI linking angiomax to reduced clinical events [REPLACE]-1 trial

In the REPLACE-1 trial (33), 1056 patients at 77 sites in the USA undergoing contemporary coronary interventions were randomized in a large-scale pilot study to unfractionated heparin (70 U/kg initial bolus) versus bivalirudin (0.75 mg/kg bolus, 1.75 mg/kg/h infusion during the procedure). In contrast to the BAT trial, stents and GPIIb/IIIa inhibitors were used in 85 and 72% of patients respectively. Furthermore, 56% of patients were pretreated with clopidogrel. The composite incidence of death, myocardial infarction, or urgent revascularization (before hospital discharge or within 48 h) in the heparin group ($n = 524$) was 6.9% compared to 5.6% in the bivalirudin group ($n = 532$) ($p = 0.4$). Bivalirudin showed less major bleeding compared to heparin (2.1 vs. 2.7% respectively, $p = 0.52$). This trial confirmed the safety of the combined approach of bivalirudin with GPIIb/IIIa inhibition and demonstrated that bivalirudin can be effective in contemporary PCI. This study was not designed to address bivalirudin as a replacement to the combined therapy of heparin and GpIIb/IIIa inhibition during angioplasty.

The randomized evaluation in PCI linking angiomax to reduced clinical events (REPLACE)-2 trial

In the REPALCE-2 trial (32,34), 6010 patients undergoing elective or urgent PCI at 233 sites in the US, Canada, Europe, and Israel were randomized in a double-blind, active-controlled trial of bivalirudin monotherapy (0.75 mg/kg bolus plus 1.75 mg/kg/h for the duration of the PCI) with provisional GPIIb/IIIa inhibition ($n = 2999$) vs. unfractionated heparin (65 U/kg bolus) with planned GPIIb/IIIa inhibition (eptifibatide or abciximab) ($n = 3011$). The primary 30-day composite endpoint of death, myocardial infarction, urgent repeat revascularization and in-hospital major bleeding was 9.2% in the bivalirudin arm vs. 10% in the heparin-GpIIb/IIIa arm ($p = 0.32$). The secondary 30-day composite endpoint of death, myocardial infarction and urgent revascularization in the bivalirudin group met the prespecified statistical criteria for non-inferiority to the heparin-GPIIb/IIIa group. Provisional GpIIb/IIIa inhibitors were administered to 7.2% of bivalirudin patients. Also, bivalirudin led to significantly less in-hospital major bleeding when compared to heparin-GpIIb/IIIa inhibitor combination (2.4 vs. 4.1%, $p < 0.001$).

The recent one-year mortality (34) follow-up data of REPLACE-2 showed that death occurred in 1.89% of patients randomized to bivalirudin versus 2.46% in the heparin-GpIIb/IIIa group ($p = 0.16$). This non-significant trend toward lower 1-year mortality with bivalirudin was present among all subgroups and was greatest in the high-risk patients.

In the REPLACE-2 trial, clopidogrel pretreatment (85.8% in the bivalirudin arm versus 84.6% in the heparin arm), and irrespective of the pretreatment duration, did not affect the relative efficacy of bivalirudin when compared to heparin-GpIIb/IIIa inhibition (45).

However, among the bivalirudin group, patients pretreated with 300 mg clopidogrel loading and 75 mg/day maintenance dose had a lower primary endpoint than patients who did not receive pretreatment (8.7 vs. 12.9%, $p = 0.007$). A similar non-significant trend was seen with the heparin-GpIIb/IIIa arm (9.7 vs. 11.7%, $p = 0.2$). This illustrates the importance of pretreatment of patients with clopidogrel prior to percutaneous intervention.

The overall data from REPLACE-2 also continued to be consistent with 2 subgroup analyses that focused primarily on patients with renal impairment and in diabetics. In the renal impairment subgroup (12), patients experienced higher ischemic and bleeding events and excess 12-month mortality. Bivalirudin provided, however, equivalent suppression of ischemic events comparable to heparin and GpIIb/IIIa inhibition and fewer bleeding events irrespective of the degree of renal dysfunction.

The REPLACE-2 trial enrolled 1624 diabetics and 4368 non-diabetic patients (25). Compared with the non-diabetic, diabetic patients had a higher mortality at 1 year (3.06 vs. 1.85%, $p < 0.001$). However, diabetics randomized to the bivalirudin arm had no difference in long- and short-term ischemic events compared to those who received heparin and GpIIb/IIIa inhibition. Also, bivalirudin patients had lesser minor bleeding (12.6 vs. 24.4%, $p < 0.001$) with similar major bleeding rate (3 vs. 3.3%, $p = 0.69$) and a trend toward lower mortality at one year (2.3 vs. 3.9%) when compared to the heparin and GpIIb/IIIa arm.

The above findings from randomized trials have been substantiated in a recent large "real-world" analysis showing that bivalirudin is associated with fewer bleeding complications with no evident increase in ischemic complications in patients undergoing percutaneous coronary intervention. Furthermore, a meta-analysis by Yusuf et al. (16) has also shown that bivalirudin has a significant advantage over unfractionated heparin in reducing major bleeding during percutaneous interventional procedures.

Recently, drug-eluting stents (DES) have been introduced as a powerful tool to reduce restenosis, the Achilles' tendon of angioplasty. The REPLACE-2 trial was done prior to the introduction of DES. At this time, there is no published large randomized data with the use of bivalirudin vs. heparin and GPIIb/IIIa inhibitors in patients receiving DES. However, recently published "real world" experience (15) suggests that the use of bivalirudin in patients with sirolimus-eluting stents ($n = 1182$) results in low rates of major adverse cardiac events (0.3% mortality,4.4% myocardial infarction, 1.7% target vessel revascularization), stent thrombosis (0.6%) and major bleeding (0.8%). In this prospective registry, clopidogrel was administered before PCI in 79% of patients and only 5.3% received adjunctive GpIIb/IIIa inhibitors.

Given the favorable data with the use of bivalirudin during PCI, the American Heart Association (AHA), American College of Cardiology and Society for Cardiovascular Angiography and Interventions jointly released their updated guidelines on the use of bivalirudin in PCI granting it a Class IIa recommendation (weight of evidence in favor of usefulness) as an alternative to unfractionated heparin and GpIIb/IIIa inhibitors in non-high risk patients undergoing elective PCI.

Acute Coronary Syndromes

Acute coronary syndromes (ACS) are mediated by plaque rupture and subsequent thrombus formation. Bivalirudin inhibits clot-bound as well as circulating thrombin and

therefore, might be effective in the setting of ACS (5,7,10,18,19,60). The Direct Thrombin Inhibitor Trialists' Collaboration meta-analysis has shown that bivalirudin is superior to UFH in reducing myocardial infarction with sustained benefit at 30 days after drug cessation in patients with ACS. Data from the Hirulog and Early Reperfusion/Occlusion (HERO)-1 trial ($n = 412$) (60) indicate that bivalirudin is more effective than UFH in improving early patency in patients receiving streptokinase. Furthermore, data from the Hirulog and Early Reperfusion or Occlusion (HERO-2) trial ($n = 17,073$) (62) have shown that in patients receiving fibrinolytic therapy bivalirudin is superior to UFH in reducing adjudicated 96-h myocardial reinfarction by 30%. There was no advantage of bivalirudin in reducing mortality at 30 days over UFH in this study. The differences in the severe bleeding and intracranial hemorrhage rates were not statistically significantly different in the bivalirudin and UFH groups (1.32 [1.00–1.74], $p = 0.05$). In patients with moderate and minor bleeding the difference between two treatments was significant in favor of bilirudin group (1.47 [1.34–1.62], $p < 0.0001$). A trend toward lower rate of death and myocardial infarction was also seen in the Thrombolysis in Myocardial Infarction-8 (TIMI-8) trial (5) without increased risk of bleeding in patients with unstable angina and ST segment myocardial infarction. Although the data seem favorable for bivalirudin in patients with ACS, bivalirudin alone in the setting of PCI might not be superior to UFH in a subgroup of patients with visible intracoronary thrombus. In an observational analysis of the Hirulog Angioplasty Study ($n = 4098$) in which unstable or postinfarction angina patients were randomized to receive either bivalirudin or heparin during coronary angioplasty, 567 patients had thrombus-containing lesions on angiography (47). The primary endpoint of death, myocardial infarction, emergency coronary artery bypass graft surgery or abrupt vessel closure before hospital discharge was not different between the bivalirudin- and heparin-treated groups. More studies are needed to determine the best combination of drugs and/or mechanical devices to treat these high-risk lesions.

The currently ongoing Acute Catheterization and Urgent Intervention Triage StrategY (ACUITY) trial (55) is prospectively randomizing 13,800 patients with moderate to high risk unstable angina and non-ST segment elevation myocardial infarction to three different anticoagulation strategies including bivalirudin with provisional GpIIb/IIIa inhibition, and enoxaparin or unfractionated heparin with planned GpIIb/IIIa inhibition. All patients undergo angiography and PCI if needed within 72 h of randomization. The primary endpoint will be the composite endpoint of death, myocardial infarction, urgent repeat revascularization and major bleeding at 30 days with clinical follow up at one year. Data from ACUITY is expected to be presented at the American College of Cardiology annual meeting in March of 2006.

Heparin-Induced Thrombocytopenia (HIT)

The advantage of bivalirudin over heparin is also apparent in patients with a history of heparin-induced thrombocytopenia (HIT) (17,37,42). In the multicenter, prospective, open-label The Anticoagulant Therapy with Bivalirudin to Assist in the performance of PCI in patients with HIT (ATBAT) study (37), the safety and efficacy of bivalirudin in patients with HIT or HIT with thrombotic syndrome (HITTS) undergoing coronary intervention was evaluated. The primary endpoint of the study was major bleeding 48 h after discontinuation or until discharge, whichever occurred first. Fifty-two patients were en-

rolled in this study. No patient had significant thrombocytopenia following the treatment with bivalirudin. The clinical success (absence of death, emergency bypass surgery or Q wave myocardial infarction) was achieved in 96%. In patients with a history of HIT, bivalirudin appeared safe and effective. Although not yet approved by the FDA for HIT, the AHA/ACC updated guidelines granted bivalirudin a Class I recommendation (general agreement that it is useful and effective) in patients with HIT and undergoing elective PCI.

Vascular Brachytherapy

The safety and effectiveness of bivalirudin in brachytherapy has not been established in large studies. Vascular brachytherapy is highly thrombogenic and is associated with significant platelet activation (26), probably as a result of the indwelling catheter inside the coronaries. Smaller studies indicate that bivalirudin is safe with the use of beta emitters as their dwelling time tends to be short, a matter of minutes. Brachytherapy with gamma radiation has been associated with higher in-hospital intracoronary thrombosis and is not recommended in this setting (25 vs. 0.7%, $p < 0.01$ for γ- vs. β-radiation, respectively) (30). When bivalirudin was compared to UFH and GPIIb/IIIa inhibitors in patients undergoing brachytherapy, a non randomized study suggested that bivalirudin as a single agent is associated with lower postprocedural CPK-MB elevation, minor bleeding complications, 30-day non-Q-wave MI rates, and a trend toward lower major bleeding and in-hospital adverse events when compared with UFH and eptifibatide (31).

Cost-Effectiveness Studies

Several studies have looked at the cost-effectiveness of bivalirudin in the setting of coronary interventions (13,14,54). Bivalirudin has been shown to offset its cost by reducing ischemic and hemorrhagic complications. Resource utilization data were collected prospectively through 30-day follow-up on all U. S. patients in the REPALCE-2 trial. Compared with routine GP IIb/IIIa, in-hospital and 30-day costs were reduced by $405 (95% confidence interval [CI] $37 to $773) and $374 (95% CI $61 to $688) per patient with bivalirudin ($p < 0.001$ for both) and this reduction was related to cost of drugs and reductions in major bleeding (cost savings = $107/patient), minor bleeding ($52/patient), and thrombocytopenia ($47/patient) (13). Reduced bleeding with bivalirudin appeared to reduce cost in single center experiences but also yielded better staff and patient satisfaction and improved throughput (39).

Percutaneous Peripheral Interventions (PPI)

The use of bivalirudin in PPI is presently off-label. Currently no randomized studies exist with bivalirudin vs. unfractionated heparin in the periphery. Bivalirudin however, was shown to offer very predictable anticoagulation in percutaneous interventions including PPI in contrast to unfractionated heparin (1,2,48). Thrombin activation is expected to be significant in PPI because of the extent of atherosclerotic burden and large vessel size dilated with balloon angioplasty. During PPI low dose heparin with a GpIIb/IIIa inhibitors or high dose heparin alone continue to be more popular during PPI than thrombin

inhibitors (51). Direct thrombin inhibition with bivalirudin, therefore, might offer some advantages over heparin in PPI by providing a more effective thrombin inhibition. Finally, the short half-life of bivalirudin might also allow early sheath removal, less bleeding complications, and a more reliable anticoagulation than heparin with no need for frequent ACT measurements during long procedures (3). Furthermore, in patients undergoing PCI with frequent stent and use of potent platelet inhibitors, ACT values do not correlate with ischemic complications and have only a modest association with bleeding complications, driven mainly by minor bleeding. Lower values do not appear to compromise efficacy while increasing safety (8,11).

Numerous reports on the use of bivalirudin in the periphery have been recently published or presented at the scientific meetings (1–3,23,28,48,53). The data appear favorable showing lower major bleeding rate and adverse events compared to historic data with unfractionated heparin. None of these studies, however, are randomized and double-blind. The Angiomax Peripheral Procedure Registry of Vascular Events Trial (APPROVE) is the largest published multicenter, prospective registry in the periphery (1,50). In APPROVE, 503 patients underwent renal, iliac and infrainguinal interventions with bivalirudin as a primary anticoagulant. The REPLACE-2 dose was utilized and consisted of 0.75 mg/kg i.v. bolus followed by 1.75 mg/kg/h infusion during the length of the procedure. In this registry, ischemic events (death, amputation, unplanned urgent revascularization at the treated site, myocardial infarction) were low (1.4%) and similar between vessel types. Protocol-defined major hemorrhage and TIMI major hemorrhage rates were 2.2 and 0.4%, respectively. The strongest predictor of major bleeding alone at discharge ($p = 0.0041$) and at 30 days ($p = 0.0016$) was the number of exchanges to larger sheath size. Also, female gender ($p = 0.08$) and low weight (stratified by gender with <80 kg vs. >92 kg for males and <62 kg vs. >77 kg for females) ($p = 0.096$) showed a trend toward predicting major bleeding at 30 days.

Recently, Allie et al. (2) presented data on the use of bivalirudin and GpIIb/IIIa inhibitors in PPI in patients with chronic limb ischemia as compared to a historic control with heparin alone. In this non-randomized study, there was a trend toward lower 6-month secondary re-intervention and limb salvage rates (10.7 vs. 18.8%, $p = 0.0501$, and 93.9 vs. 88.5%, $p = 0.053$) in the bivalirudin-GP IIb/IIIa inhibitor group compared to the unfractionated heparin group, respectively. Angiographically relevant distal embolization occurred less in the bivalirudin-GpIIb/IIIa inhibitor group (1.3 vs. 5.4%).

Randomized trials are needed in the set up of contemporary PPI. The role of GPIIb/IIIa inhibitors in PPI is still poorly defined but its role along with bivalirudin in chronic limb ischemia is promising.

Cardiopulmonary Bypass

Bivalirudin has been used in cardiac surgical patients with heparin-induced thrombocytopenia (HIT) or suspected HIT (4,17,29,38,56,58). Cardiopulmonary bypass leads to the development of heparin-dependent antibodies in about 25–50% of patients, particularly with continued UFH postoperatively (49). Re-exposure to UFH can lead to a prothrombotic disorder called heparin-induced thrombocytopenia (HIT). HIT, generally associated with a high incidence of deep vein thrombosis, pulmonary emboli and arterial thrombosis occurs in approximately 3.8% of patients who have undergone cardiac surgery and are

placed postoperatively on high-dose intravenous UFH (49). In antibody positive patients the use of bivalirudin might offer a safer alternative to UFH to reduce the incidence of HIT. Recently, the FDA approved the use of bivalirudin in patients with or at risk of HIT/HITTS — heparin-induced thrombocytopenia and thrombosis syndrome (HITTS) — undergoing percutaneous coronary intervention (56,58). Safety and efficacy studies are currently ongoing to evaluate the role of bivalirudin in cardiopulmonary bypass surgery as an alternative to UFH.

CONCLUSIONS

Bivalirudin is a very promising direct thrombin inhibitor with favorable pharmacokinetics and pharmacodynamics. It has been shown to be superior to UFH in the setting of PCI and could be used as a substitute for heparin and GpIIb/IIIa inhibitors in non-emergent interventions and in patients with HIT. Also, bivalirudin is safe and effective in PPI, but randomized trials are lacking. The use of bivalirudin in high-risk interventions such as emergent acute coronary syndromes or chronic limb ischemia appears promising but more data are needed to demonstrate its safety and cost-effectiveness.

Acknowledgment. Supported by the Midwest Cardiovascular Research Foundation, Iowa, USA

REFERENCES

1. Allie DE, Hall P, Shammas NW, et al. The Angiomax Peripheral Procedure Registry of Vascular Events Trial (APPROVE): In-hospital and 30-day results. *J Invasive Cardiol* 2004;16:651–656.
2. Allie DE, Hebert CJ, Lirtzman MD, et al. A safety and feasibility report of combined direct thrombin and GP IIb/IIIa inhibition with bivalirudin and tirofiban in peripheral vascular disease intervention: Treating critical limb ischemia like acute coronary syndrome. *J Invasive Cardiol* 2005;17:427–432.
3. Allie DE, Lirtzman MD, Wyatt CH, et al. Bivalirudin as a foundation anticoagulant in peripheral vascular disease: A safe and feasible alternative for renal and iliac interventions. *J Invasive Cardiol* 2003;15: 334–342.
4. Angiomax Prescribing Information, The Medicines Company, 2002.
5. Antman EM, McCabe CH, Braunwald E. Bivalirudin as a replacement for unfractionated heparin in unstable angina/non-ST-elevation myocardial infarction: Observations from the TIMI 8 trial. The Thrombolysis in Myocardial Infarction. *Am Heart J* 2002;143:229–234.
6. Bittl JA, Chaitman BR, Feit F, Kimball W, Topol EJ. Bivalirudin vs. heparin during coronary angioplasty for unstable or post infarction angina: Final report reanalysis of the Bivalirudin Angioplasty Study. *Am Heart J* 2001;142:952–959.
7. Bittl JA, Feit F. A randomized comparison of bivalirudin and heparin in patients undergoing coronary angioplasty for postinfarction angina. Hirulog Angioplasty Study Investigators. *Am J Cardiol* 1998;82:43P–49P.
8. Brener SJ, Moliterno DJ, Lincoff AM, Steinhubl SR, Wolski KE, Topol EJ. Relationship between activated clotting time and ischemic or hemorrhagic complications: Analysis of 4 recent randomized clinical trials of percutaneous coronary intervention. *Circulation* 2004;110:994–998.
9. Burchenal JE, Marks DS, Tift Mann J, et al. Effect of direct thrombin inhibition with Bivalirudin (Hirulog) on restenosis after coronary angioplasty. *Am J Cardiol* 1998;82:511–515.
10. Carswell CI, Plosker GL. Bivalirudin: A review of its potential place in the management of acute coronary syndromes. *Drugs* 2002;62:841–870.

11. Cheneau E, Canos D, Kuchulakanti PK, et al. Value of monitoring activated clotting time when bivalirudin is used as the sole anticoagulation agent for percutaneous coronary intervention. *Am J Cardiol* 2004;94: 789–792
12. Chew DP, Lincoff AM, Gurm H, et al. Bivalirudin vs. heparin and glycoprotein IIb/IIIa inhibition among patients with renal impairment undergoing percutaneous coronary intervention (a subanalysis of the REPALCE-2 trial). *Am J Cardiol* 2005;95:581–585
13. Cohen DJ, Lincoff AM, Lavelle TA, et al. Economic evaluation of bivalirudin with provisional glycoprotein IIB/IIIA inhibition vs. heparin with routine glycoprotein IIB/IIIA inhibition for percutaneous coronary intervention: Results from the REPLACE-2 trial. *J Am Coll Cardiol* 2004;44:1792–1800.
14. Compton A. A practical cost analysis of bivalirudin. *Pharmacotherapy* 2002;22(6, Pt 2):119S–127S.
15. Dangas G, Lasic Z, Mehran R, et al. Effectiveness of the concomitant use of bivalirudin and drug eluting stents (from the prospective multicenter BivAlirudin and Drug-Eluting STents [ADEST] study. *Am J Cardiol* 2005;96:659–663.
16. Direct Thrombin Inhibitor Trialists' Collaborative Group. Direct thrombin inhibitors in acute coronary syndromes: Principal results of a meta-analysis based on individual patients' data. *Lancet* 2002;359:294–302
17. Dyke CM, Koster A, Veale JJ, Maier GW, McNiff T, Levy JH. Preemptive use of bivalirudin for urgent on-pump coronary artery bypass grafting in patients with potential heparin-induced thrombocytopenia. *Ann Thorac Surg* 2005;80:299–303.
18. Eikelboom JW, French J. Management of patients with acute coronary syndromes: What is the clinical role of direct thrombin inhibitors? *Drugs* 2002;62:1839–1852.
19. Eikelboom J, White H, Yusuf S. The evolving role of direct thrombin inhibitors in acute coronary syndromes. *J Am Coll Cardiol* 2003;41(4, Suppl S):70S–78S.
20. Fox I, Dawson A, Loynds P, et al. Anticoagulant activity of Hirulog, a direct thrombin inhibitor, in humans. *Thromb Haemost* 1993;69:157–163.
21. Gladwell TD. Bivalirudin: A direct thrombin inhibitor. *Clin Ther* 2002;24:38–58.
22. Gleason TG, Chengelis CP, Jackson CB, Lindstrom P. A 24-h continuous infusion study of bivalirudin in the rat. *Int J Toxicol* 2003;22:195–206.
23. Grubbs G. Single center experience with bivalirudin anticoagulation in peripheral vascular interventions: Possible benefits over unfractionated heparin. Poster presented at Cardiovascular Revascularization Therapy conference; January 26–29, 2003, Washington, D.C.
24. Gurm HS, Rajagopal V, Fathi R, et al. Effectiveness and safety of bivalirudin during percutaneous coronary intervention in a single medical center. *Am J Cardiol* 2005;95:716–721.
25. Gurm HS, Sarembock IJ, Kereiakes DJ, et al. Use of bivalirudin during percutaneous coronary intervention in patients with diabetes mellitus: An analysis from the randomized evaluation in percutaneous coronary intervention linking angiomax to reduced clinical events (REPLACE)-2 trial. *J Am Coll Cardiol* 2005;45: 1932–1938.
26. Jaster M, Fuster V, Rosenthal P, et al. Catheter based intracoronary brachytherapy leads to increased platelet activation. *Am Heart J* 2005;150:832–837.
27. Katzen BT, Ardid MI, MacLean AA, et al. Bivalirudin as an anticoagulation agent: Safety and efficacy in peripheral interventions. *J Vasc Interv Radiol* 2005;16:1183–1187.
28. Knopf W. Joseph's Hospital experience: Direct thrombin inhibitors in ACS and PCI: The case for bivalirudin replacing unfractionated heparin in PCI. Paper presented at Transcatheter Cardiovascular Therapeutics 14th Annual Scientific Symposium; September 24–28, 2002; Washington D.C.
29. Koster A, Spiess B, Chew DP, et al. Effectiveness of bivalirudin as a replacement for heparin during cardiopulmonary bypass in patients undergoing coronary artery bypass grafting. *Am J Cardiol* 2004;93:356–359
30. Kuchulakanti P, Wolfram R, Torguson R, et al. Brachytherapy and bivalirudin evaluation study. *Am Heart J* 2005;150:832–837.
31. Kuchulakanti P, Wolfram R, Torguson R, et al. Bivalirudin compared with IIb/IIIa inhibitors in patients with in-stent restenosis undergoing intracoronary brachytherapy. *Cardiovasc Revasc Med* 2005;6:154–159.
32. Lincoff AM, Bittl JA, Harrington RA, et al. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa during percutaneous coronary intervention; the REPLACE-2 randomized trial. *JAMA* 2003;289:853–863
33. Lincoff AM, Bittl JA, Kleiman NS, et al. Comparison of bivalirudin vs. heparin during percutaneous coronary intervention (the Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events [REPLACE]-1 trial. *Am J Cardiol* 2004;93:1092–1096

34. Lincoff AM, Kleiman NS, Kereiakes DJ, et al. Long-term efficacy of bivalirudin and provisional glycoprotein IIb/IIIa blockade vs heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary revascularization: REPLACE-2 randomized trial. *JAMA* 2004;292:696–703
35. Lincoff AM, Kleiman NS, Kottke-Marchant K, et al. Bivalirudin with planned or provisional abciximab versus low-dose heparin and abciximab during percutaneous coronary revascularization: Results of the Comparison of Abciximab Complications with Hirulog for Ischemic Events Trial (CACHET). *Am Heart J* 2002;143: 847–853
36. Lui HK. Dosage, pharmacological effects and clinical outcomes for bivalirudin in percutaneous coronary intervention. *J Invasive Cardiol* 2000;12(Suppl F):41F–52F.
37. Mahaffey KW, Lewis BE, Wildermann NM, et al. The anticoagulant therapy with bivalirudin to assist in the performance of percutaneous coronary intervention in patients with heparin-induced thrombocytopenia (ATBAT) study: Main results. *J Invasive Cardiol* 2003;15:611–616.
38. Merry AF. Bivalirudin, blood loss, and graft patency in coronary artery bypass surgery. *Semin Thromb Hemost* 2004;30:337–346
39. Ormiston JA, Shaw BL, Panther MJ, et al. Percutaneous coronary intervention with bivalirudin anticoagulation, immediate sheath removal, and early ambulation: A feasibility study with implications for day-stay procedures. *Catheter Cardiovasc Interv* 2002;55:289–293.
40. Pharmacology Review. Hirulog. Center For Drug Evaluation and Research. http://www.fda.gov/cder/foi/nda/2000/20873 Angiomax.htm. Application Number 20-873.
41. Reed MD, Bell D. Clinical pharmacology of bivalirudin. *Pharmacotherapy* 2002;22(6, Pt 2):105S–111S.
42. Riess FC. Anticoagulation management and cardiac surgery in patients with heparin-induced thrombocytopenia. *Semin Thorac Cardiovasc Surg* 2005;17:85–96.
43. Robson R. The use of bivalirudin in patients with renal impairment. *J Invasive Cardiol* 2000;12(Suppl F): 33F–36F.
44. Robson R, White H, Aylward P, Frampton C. Bivalirudin pharmacokinetics and pharmacodynamics: Effect of renal function, dose, and gender. *Clin Pharmacol Ther* 2002;71:433–439.
45. Saw J, Lincoff AM, DeSmet W, et al. Lack of clopidogrel pretreatment effect on the relative efficacy of bivalirudin with provisional glycoprotein IIb/IIIa blockade compared to heparin with routine glycoprotein IIb/IIIa blockade: A REPLACE-2 substudy. *J Am Coll Cardiol* 2004;44:1194–1199.
46. Sciulli TM, Mauro VF. Pharmacology and clinical use of bivalirudin. *Ann Pharmacother* 2002;36: 1028–1041.
47. Shah PB, Ahmed WH, Ganz P, Bittl JA. Bivalirudin compared with heparin during coronary angioplasty for thrombus-containing lesions. *J Am Coll Cardiol* 1997;30:1264–1269.
48. Shammas NW. Complications in peripheral vascular interventions: Emerging role of direct thrombin inhibitors. *J Vasc Interv Radiol* 2005;16(2, Pt 1):165–171.
49. Shammas NW. Pulmonary embolus after coronary artery bypass surgery: A review of the literature. *Clin Cardiol* 2000;23:637–644.
50. Shammas NW, Allie D, Hall P, et al.; APPROVE Investigators. Predictors of in-hospital and 30-day complications of peripheral vascular interventions using bivalirudin as the primary anticoagulant: Results from the APPROVE Registry. *J Invasive Cardiol* 2005;17:356–359.
51. Shammas NW, Dippel EJ, Lemke JH, et al. Eptifibatide Does not Reduce Inflammatory Markers in Patients Undergoing Peripheral Vascular Interventions: Results of the INFLAME trial. *J Invasive Cardiol* 2006;18: 6–12.
52. Shammas NW, Lemke JH, Dippel EJ, et al. In-hospital complications of peripheral vascular interventions using unfractionated heparin as the primary anticoagulant. *J Invasive Cardiol* 2003;15:242–246.
53. Shammas NW, Lemke JH, Dippel EJ, et al. Bivalirudin in peripheral vascular interventions: A single center experience. *J Invasive Cardiol* 2003;15:401–404.
54. Starin E. Adoption of Angiomax at Christus Santa Rosa Medical Center decreases costs and increases satisfaction. *J Cardiovasc Manag* 2005;16:14–18.
55. Stone GW, Bertrand M, Colombo A, et al. Acute Catheterization and Urgent Intervention StrategY (ACUITY) trial: Study design and rationale. *Am Heart J* 2004;148:764–765
56. Veale JJ, McCarthy HM, Palmer G, Dyke CM. Use of bivalirudin as an anticoagulant during cardiopulmonary bypass. *J Extra Corpor Technol* 2005;37:296–302.
57. Warkentin TE, Koster A. Bivalirudin: A review. *Exp Opin Pharmacother* 2005;6:1349–1371.
58. Wasowicz M, Vegas A, Borger MA, Harwood S. Bivalirudin anticoagulation for cardiopulmonary bypass in a patient with heparin-induced thrombocytopenia. *Can J Anaesth* 2005;52:1093–1098.

59. White H; Hirulog and Early Reperfusion or Occlusion (HERO)-2 Trial Investigators. Thrombin-specific anticoagulation with bivalirudin vs. heparin in patients receiving fibrinolytic therapy for acute myocardial infarction: The HERO-2 randomised trial. *Lancet* 2001;358:1855–1863.
60. White HD, Aylward PE, Frey MJ, et al. Randomized, double-blind comparison of hirulog vs. heparin in patients receiving streptokinase and aspirin for acute myocardial infarction (HERO). Hirulog Early Reperfusion/Occlusion (HERO) Trial Investigators. *Circulation* 1997;96:2155–2161.