

Direct Thrombin Inhibitor Use During Percutaneous Coronary Intervention

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Abstract: Direct thrombin inhibitors (DTI) are emerging as alternative anticoagulants to unfractionated heparin and indirect thrombin inhibitors in patients undergoing percutaneous coronary intervention (PCI). We review the pharmacological properties of these newer antithrombotic agents and evaluate the clinical data demonstrating their use in patients undergoing PCI.

Key Words: bivalirudin, angioplasty, percutaneous coronary intervention

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Although unfractionated heparin (UFH) has served as the primary anticoagulant for nearly 50 years, it has several well-established limitations^{1,2} (Table 1). In recent years, an increasing number of anticoagulants have become available as alternatives to UFH for treatment of patients with acute coronary syndromes (ACS) and for percutaneous coronary intervention (PCI). From an interventional cardiologist's point of view, the most significant of these limitations is the ability of UFH to activate platelets. In part to compensate for these limitations, a number of new therapies and strategies have been implemented in the treatment of ACS (eg, glycoprotein IIb/IIIa antagonists, thienopyridines, stents).

An alternative strategy to deal with the problems associated with UFH is to replace this agent with antithrombins such as the direct thrombin inhibitors (DTIs). The purpose of this review is to examine the mechanisms of action, pharmacological properties, and clinical data for DTIs.

INDIRECT THROMBIN INHIBITORS

Heparin

UFH is a heterogeneous preparation of heparin molecules ranging in size from about 5000 to 40,000 daltons, and is typically extracted from porcine intestine or bovine lung.³ Heparin is a large polysaccharide polymer that contains negatively charged sulfate and carboxylic acid groups. The effects of heparin can be rapidly reversed with protamine, a basic

molecule (Table 2).² UFH is administered parenterally (intravenously or subcutaneously) and exerts its therapeutic effect by indirectly inhibiting coagulation factor IIa (thrombin), a critical mediator in clot formation. Thrombin is characterized by 2 binding sites (exosites 1 and 2) in addition to its active catalytic site, as shown in Figure 1. These sites are essential for the binding of thrombin substrates such as fibrinogen.⁴ Thrombin cleaves fibrinogen to form fibrin and carries out other actions that promote the formation, expansion and organization of blood clots such as conversion of factors V to Va and VIII to VIIIa.

To inactivate thrombin, the heparin molecule must bind to both antithrombin (AT) and thrombin, forming a ternary complex. AT is an α -globulin occurring naturally in the body that, in the absence of heparin, acts over the course of a few hours to inactivate thrombin. Once heparin binds to AT, a molecular change occurs in the heparin:AT complex that accelerates the ability of AT to bind to thrombin. Binding of the heparin molecule to thrombin at exosite 2, with "bridging" between AT and thrombin as shown in Figure 1, is also necessary for thrombin inhibition. Approximately one third of the heparin molecules in an UFH preparation contain the specific pentasaccharide sequence necessary for binding to AT, and most of these have polysaccharide chains long enough (at least 18 saccharide units) to bind to thrombin.^{1,5}

Like thrombin, factor X is also inhibited indirectly by heparin through the binding of AT. However, unlike thrombin, factor X does not require direct heparin binding for inactivation (ie, ternary complex formation). Thus, very short heparin molecules (<18 saccharide units in length) that contain the pentasaccharide sequence allowing binding to AT can inhibit factor X but not thrombin.

Excretion and Bioavailability of Heparin

After parenteral administration, heparin molecules are degraded into inactive compounds by the reticuloendothelial system of the body and then excreted via the kidneys. Liver failure and renal insufficiency prolong the half-life of UFH. Heparin is a large molecule that cannot cross the placenta barrier and, as a result, is considered an acceptable anticoagulant for use during pregnancy.

Low-Molecular-Weight Heparins

Low-molecular-weight heparins (LMWHs) are characterized by a mean molecular weight of 4000 to 5000 daltons but range in size from 1000 to 10,000 daltons. Similar to UFH, LMWHs show heterogeneous anticoagulant activity.¹ LMWHs are derived from UFH through a chemical and enzymatic depolymerization process resulting in preparations of

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TABLE 1. Limitations of Unfractionated Heparin

Limitation	Consequence
Nonspecific binding to plasma proteins and endothelial cells ^{25,55}	Variability in anticoagulant effect, especially in seriously ill patients ⁷⁴
Release of platelet factor 4 and von Willibrand factor from platelets during clotting	Results in heparin resistance and a need for higher levels of heparin ³⁵
Inability of heparin to inactivate fibrin-bound thrombin ⁶	Thrombin remains active when bound to fibrin and continues to activate platelets ⁷⁵
Heparin induces platelet activation ⁴⁹	Further activates the clotting cascade and release of heparin-binding proteins
Forms heparin antibodies	Can result in heparin-induced thrombocytopenia and thrombosis syndrome ⁴²
Dose-dependent half-life ⁶⁷	Nonlinear increase in half-life as dose increases
Ill-defined dose to achieve target ACT level in PCI	Super anticoagulation resulting in increased bleeding risk or suboptimal anticoagulation resulting in increase risk of ischemic complications ⁷⁶

shorter heparin molecules⁶ and consist of chains of alternating residues of D-glucosamine and uronic acid, similar to UFH.⁷

The LMWHs are also indirect thrombin inhibitors that bind to antithrombin via the same pentasaccharide sequence found in UFH.⁸ The anticoagulant effects of LMWHs result from their inhibition of factor Xa and thrombin as well as other factors including factors XIIa, XIa, and IXa, and TFPI. LMWHs demonstrate less inhibitory activity against thrombin than against factor X because only 25%–50% of the LMWH chains are long enough to bridge antithrombin to thrombin.^{8–12} Because factor Xa inhibition does not require bridging between factor Xa and AT, the smaller (<18 saccharide units) pentasaccharide-containing heparin chains in LMWH preparations can inactivate factor Xa but not thrombin (Fig. 1). LMWHs have anti-Xa to anti-IIa (thrombin) ratios that vary between 4:1 and 2:1, whereas UFH has nearly equal inhibitory effects on factor Xa and thrombin⁸ for an anti-Xa:anti-IIa ratio of 1:1.

One of the major disadvantages of indirect thrombin inhibition by UFH and LMWH is their inability to inactivate thrombin bound to fibrin or to the soluble fibrin degradation products that increase in concentration after t-PA-induced lysis.¹³ At lower concentrations, heparin molecules are unable to inhibit clot- or fibrin-bound thrombin molecules because the heparin binding site may be less accessible when these thrombin complexes occur. This clot-bound thrombin is still enzymatically active. The inability to fully inhibit clot-bound thrombin may be one of the potential mechanisms for the 3%–6% reinfarction rate following initially successful coronary thrombolysis.

TABLE 2. Protamine Neutralization of LMWH¹⁴

Heparin	% Anti-Xa Neutralized	% Sulfate
Fraxiparin	58	35
Tinzaparin	86	39
Dalteparin	74	37
Clivarin	51	35
Enoxaparin	54	32
Supersulfonated LMWH	100	42

DIRECT THROMBIN INHIBITORS

Direct thrombin inhibitors (DTIs) (eg, bivalirudin, argatroban, hirudin, ximelagatran) are able to inhibit thrombin directly without the need for the cofactor antithrombin and are able to inhibit both fibrin-bound and soluble thrombin, in contrast to UFH and LMWH.

Because of their relatively small size, the interaction of the DTIs with the active site of thrombin is not compromised following binding of thrombin to fibrin at exosite 1.¹⁵ Thus, they are able to inactivate both free thrombin and thrombin bound to fibrin or fibrin degradation products. This may be because of a greater affinity of thrombin for exosite 1 (Table 3).

Bivalirudin, lepirudin, and hirudin are bivalent DTIs that bind to thrombin at exosite 1 (the substrate recognition site) and at the active site^{16–18} (Figs. 2 and 3). The univalent DTI argatroban binds thrombin only at its active site¹⁹ (Fig. 4).

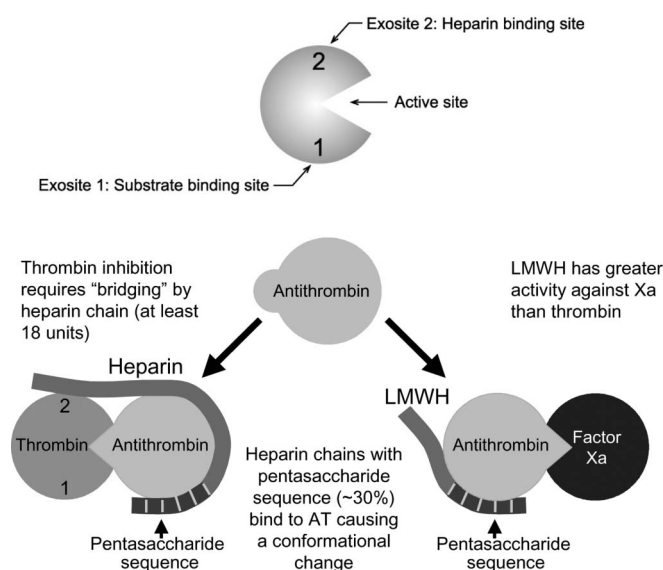


FIGURE 1. Thrombin binding sites and the inhibition of thrombin and factor Xa by UFH and LMWH. [Used with permission from Marmur J. *J Invasive Cardiol.* 2002;14(Suppl B): 8B–18B.]

TABLE 3. Binding Characteristics of Direct Thrombin Inhibitors

Drug	Molecular Weight	Mode of Binding	Thrombin Binding Site
Bivalirudin	~2.2 Kda (20 amino acids)	Reversible, bivalent	Active site, exosite 1
r-hirudin (lepirudin, desirudin)	~7.0 Kda (65 amino acids)	Irreversible, bivalent	Active site, exosite 1
Argatroban	~527 Daltons (Da)	Reversible, univalent	Adjacent to active site

In the direct thrombin inhibitor trialists' collaborative group, hirudin and heparin were associated with an increased major bleeding complication. However, the bivalent inhibitor, bivalirudin was associated with fewer major bleeding complications, probably because of its shorter half-life. Bivalirudin was also associated with a lower death rate when compared with hirudin or to univalent inhibitors²⁰ (Fig. 5).

Bivalirudin

Bivalirudin is a synthetic 20-amino-acid polypeptide modeled after hirudin and comprised of an active site-directed peptide linked via a tetraglycine spacer to a dodecapeptide analogue of the carboxy terminal of hirudin.¹⁸ Bivalirudin binds thrombin with high affinity at both the active site and exosite 1. Once bound, thrombin slowly cleaves bivalirudin at the active site, resulting in recovery of the function of thrombin's active site.¹⁸ The carboxy-terminal dodecapeptide portion of the bivalirudin molecule remains bound to exosite 1 with low affinity. Therefore, bivalirudin initially acts as a noncompetitive inhibitor of thrombin but then becomes a competitive inhibitor, enabling thrombin to subsequently participate in hemostatic reactions (see Fig. 2).

Pharmacodynamics of Bivalirudin

Bivalirudin is cleared by a combination of proteolytic cleavage and renal mechanisms.²¹ Bivalirudin has a half-life of about 25 minutes²² in patients with normal renal function, with prolongation seen in patients with moderate (34 minutes) or severe (57 minutes) renal impairment (30–59 mL/min and less than 30 mL/min, respectively). Dose adjustments of the bivalirudin infusion may be required for patients with severe renal impairment and for dialysis-dependent patients.²¹ Although there is no antidote to counteract the anticoagulant effects, this does not appear to be a major concern with bivalirudin because of its short half-life. The short half-life of bivalirudin distinguishes it from lepirudin (recombinant hirudin) and may contribute to a more favorable safety profile.

Bivalirudin exhibits linear dose-proportional plasma concentration responses with a positive correlation between dose and anticoagulant effect. The anticoagulant effect of bivalirudin is readily measured by both the ACT or the aPTT, making this agent easy to use in the catheterization laboratory.

Bivalirudin has not demonstrated any cross-reactivity with heparin-induced antibodies in the serum of patients with HIT.

Lepirudin

The recombinant agent lepirudin (hirudin), originally isolated from the salivary glands of the medicinal leech (*Hirudo medicinalis*), is a 65-amino-acid polypeptide.²³ Lepirudin specifically binds to thrombin with such high affinity that the lepirudin/thrombin complex is considered irreversible, a potential disadvantage for this agent because there is no antidote to reverse its anticoagulant activity.²⁴

Pharmacodynamics of Lepirudin

Lepirudin is cleared primarily via renal mechanisms.²⁵ After intravenous injection, the half-life is approximately 50–60 minutes, increasing up to 3 hours depending on patient comorbid diseases.²⁶ Because the drug is cleared via the kidneys, drug accumulation occurs in patients with renal insufficiency. Consequently, both the bolus and infusion dose must be reduced in patients with renal impairment (creatinine clearance <60 mL/min), and the agent is not recommended for use in patients with creatinine clearance <15 mL/min.^{26–28}

The plasma concentrations of lepirudin increase proportionally to the dose administered. The standard ACT assay method, however, is unsuitable for routine monitoring of the anticoagulant effects of lepirudin. In general, an aPTT ratio (the patient's aPTT value at any given time divided by an aPTT reference value) is the method recommended for monitoring the anticoagulant with lepirudin. The ecarin clotting time (ECT) assay has also been reported as successful in predicting anticoagulant effect.²⁹

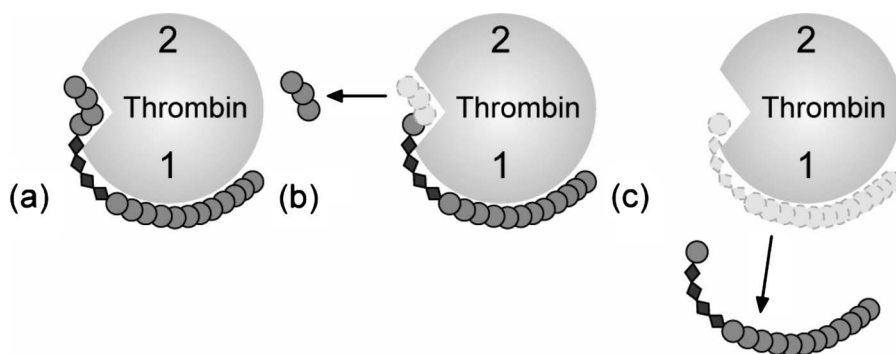
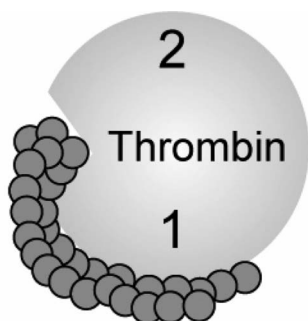


FIGURE 2. Molecular interactions between the bivalent direct thrombin inhibitor bivalirudin and thrombin. A, Bivalirudin binds to 2 sites on the thrombin molecule: its active site and exosite 1. B, Bivalirudin is cleaved by thrombin at the active site. C, The bond between thrombin and the remaining portion of bivalirudin is now weaker, allowing thrombin to resume its hemostatic function.



Hirudin

FIGURE 3. The bivalent binding of hirudin, a direct thrombin inhibitor. Hirudin binding is highly specific and almost irreversible. Like hirudin, lepirudin is also a bivalent direct thrombin inhibitor and also demonstrates nearly irreversible binding to thrombin.

Lepirudin antibodies have been detected in approximately 40% of treated patients^{25,30} and appear to have an effect on anticoagulant status. Some of these antibodies bind to lepirudin and potentially prolong its half-life, leading to drug accumulation and subsequent hemorrhagic complications, while other antibodies reportedly neutralize lepirudin's anticoagulant effect.³¹

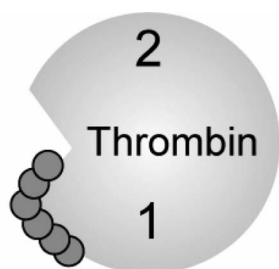
Argatroban

Argatroban is a synthetic derivative of arginine that binds reversibly to the catalytic site of thrombin.¹⁹ Argatroban does not inhibit other serine proteases, but 54% of the argatroban dose binds to human serum proteins, albumin and 1-acid glycoprotein.³²

Pharmacodynamics of Argatroban

The primary route of clearance for argatroban is by liver metabolism, with a half-life approximately 54 minutes after IV administration. Hepatic impairment significantly decreases argatroban clearance (approximately 4-fold) and increases its half-life to approximately 181 minutes.

The anticoagulant effect of argatroban can be measured using the ACT or the aPTT. Plasma concentrations, dose, and



Argatroban

FIGURE 4. The univalent binding of argatroban. Argatroban reversibly binds only near the active site on thrombin and is characterized by a short half-life.

anticoagulant effects are well correlated. Argatroban has not demonstrated any cross-reactivity to heparin-induced antibodies.

Ximelagatran

The DTIs described above are administered parenterally. Ximelagatran is an orally administered DTI. This compound represents an alternative to warfarin or LMWH for antithrombotic therapy. It was developed for use in venous thromboembolism, stroke secondary to atrial fibrillation, and recurrent ischemic events after acute myocardial infarction.³³

Pharmacodynamics of Ximelagatran

Ximelagatran is metabolized to melagatran after oral ingestion. When melagatran has a hydroxyl and an ester group added, its prodrug form, ximelagatran, is created. This allows oral ximelagatran to have increased lipophilicity and permeability across cells, which leads to a consistent oral bioavailability in humans.³³ After oral absorption, ximelagatran will be reduced and hydrolyzed to melagatran.³⁴ Melagatran binds only to thrombin's active site.³⁵ Melagatran is a DTI that provides anticoagulation when given parenterally but has poor bioavailability if given orally.^{33,34}

Ximelagatran achieves a peak concentration in 2–3 hours after oral ingestion. Melagatran is eliminated primarily via the kidneys (~80%), and its elimination half-life is 1.7 to 2.7 hours.^{33,34} Therefore, in patients with severe renal impairment, its elimination half-life is increased to 9 hours, and the dose of ximelagatran should be decreased or the dosing interval increased.³³

In the fall of 2004, the Food and Drug Administration (FDA) did not approve ximelagatran for use in the United States. The FDA panel was concerned about the elevations in liver enzymes with treatment with this drug, including 3 deaths related to liver failure that were reported in patients treated with ximelagatran.

Univalent Versus Bivalent Direct Thrombin Inhibitors

According to a recent meta-analysis of 11 randomized trials comparing DTIs to UFH in the management of patients with acute coronary syndromes,³⁶ the authors found a 15% reduction in death/MI in patients treated with a DTI, compared with treatment with UFH. A 0.8% absolute risk reduction, maintained at 30 days, was also found. Similar benefits were seen with the DTIs hirudin and bivalirudin, but not with the univalent DTI argatroban.

In accord with various other trialists, the investigators found univalent DTIs (argatroban and 2 other univalent agents, efegatran and inogatran) to be less effective than the bivalent DTIs (hirudin, bivalirudin) in preventing recurrent ischemic events. However, the bivalent DTI hirudin was associated with a higher cost and increased risk of bleeding compared with UFH.³⁶ Hirudin was associated with an increased risk of major bleeding in patients presenting with ST segment elevation MI. In contrast to these findings, bivalirudin was associated with a 50% reduction in major bleeding in patients with acute coronary syndromes. In a subgroup analysis, there was a benefit of direct thrombin inhibitors on death or myocardial infarction in trials of both acute coronary syndromes and percutaneous

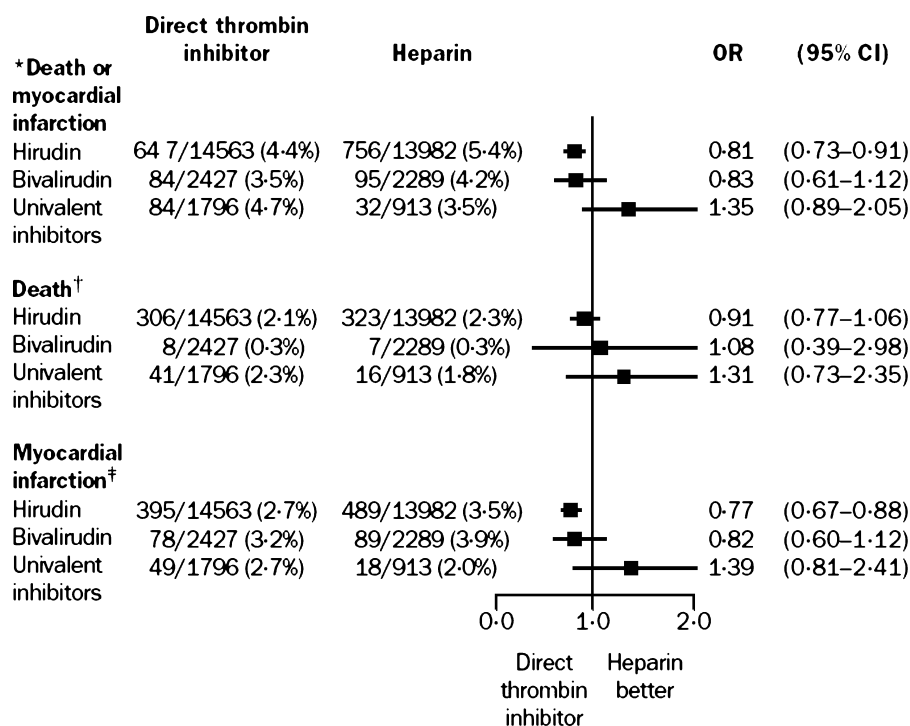


FIGURE 5. Direct thrombin inhibitor in acute coronary syndrome meta-analysis.²⁰

coronary interventions. In contrast, the univalent DTIs showed a less robust decrease in major bleeding.³⁶

CLINICAL DATA IN PCI

Unfractionated Heparin and Low-Molecular-Weight Heparin in PCI

Large clinical trials evaluating LMWH in the management of patients with unstable angina and non-Q-wave myocardial infarctions have been promising.^{37–42} Clinical data from two of these trials comparing enoxaparin to UFH demonstrated reductions in ischemic events with LMWH versus UFH. However, there appeared to be moderate increases in major and minor bleeding with LMWH compared with UFH.^{37,42}

Evidence for the clinical value of LMWH in PCI is much less clear than that supporting use in ACS. There are a number of publications reporting the use of LMWH in PCI,^{43–48} but none are large-scale, randomized controlled trials that provide convincing evidence of a meaningful benefit over UFH.

Direct Thrombin Inhibitors in PCI

Bivalirudin, lepirudin, and argatroban are the only DTIs approved in the United States. Lepirudin and argatroban are approved for treatment and management of patients with HIT. Argatroban is also approved for use in patients with HIT or at risk for HIT undergoing PCI. Bivalirudin is indicated for use in a broader population of patients with unstable angina undergoing PCI.

Bivalirudin

Of all the available DTIs, bivalirudin appears to offer an alternative to UFH in PCI. In the Bivalirudin Angioplasty Trial

(BAT), 4312 patients with unstable angina or post-MI, requiring PCI, were randomized in a double-blind fashion to receive bivalirudin or heparin during the procedure.⁵⁰ This trial demonstrated a 22% relative risk reduction with bivalirudin in the rate of the composite endpoint of death/MI/repeat revascularization at 7 days (6.2% versus 7.9%, $P = 0.039$) when compared with heparin. In addition, there was significantly less major bleeding (3.5% versus 9.3%, $P < 0.001$), with a 62% relative risk reduction in this endpoint (Table 4). Major bleeding was defined as overt bleeding resulting in a hemoglobin drop of ≥ 3 g/dL, the need for transfusion of at least 2 units, and either retroperitoneal or intracranial bleeding.

In addition, reduction of both ischemic and hemorrhagic events was observed in a randomized subgroup of post-MI patients ($n = 741$). Those treated with bivalirudin had a 51% relative risk reduction in death, MI, or revascularization versus heparin (4.9% versus 9.9%, $P = 0.009$) and a 73% relative risk reduction for major bleeding⁵⁰ (2.4% versus 11.8%, $P < 0.001$).

The BAT trial was conducted before the widespread use of stents and GP IIb/IIIa inhibitors. The results provided information and suggestions of improved outcomes with the use of bivalirudin over heparin. To assess bivalirudin in the modern interventional setting, several pilot trials have been conducted. Three randomized studies evaluating the safety of bivalirudin and GP IIb/IIIa inhibitors versus UFH and GP IIb/IIIa inhibitors have been completed. Although the number of patients in these studies is small, bivalirudin plus abciximab ($n = 60$), eptifibatide ($n = 42$), and tirofiban ($n = 33$) all provide positive safety data consistent with the results seen in BAT for combining bivalirudin with GP IIb/IIIa inhibitors.^{51–53}

The CACHET B/C and REPLACE-1 trials^{54–55} provide additional preliminary results with bivalirudin in the setting of

TABLE 4. Bivalirudin Comparative PCI Trials

Trial	N	Population	Outcomes (%)	Biv vs UFH
Bat, ⁵⁰ 2001	4312	PCI	D/MI/R at 7 days	6.2 vs 7.9
			Major bleeding	3.5 vs 9.3
CACHET, ⁵⁶ 2002	288	PCI	D/MI/R at days	2.8 vs 7.8
			Major bleeding	1.4 vs 6.3
REPLACE-1, ⁵⁵ 2002	1056	PCI	D/MI/R at 48 hr	5.6 vs 6.9
			Major bleeding	2.2 vs 2.7
REPLACE-2, ⁵⁷ 2003	6010	PCI	D/MI/R/in-hospital major bleed at 30 days	9.2 vs 10.0
			D/MI/R at 30 days	7.6 vs 7.1
			Major bleeding	2.4 vs 4.1

R, repeat revascularization.

stents and GPIIb/IIIa inhibition. CACHET B/C (n = 208) was an open-label trial of patients undergoing elective PCI, randomized to receive either heparin plus abciximab or bivalirudin with provisional abciximab.^{54,56} The bivalirudin arm (n = 144) had only 24% abciximab use. The CACHET B/C demonstrated a 64% relative risk reduction of death/MI/revascularization for bivalirudin compared with UFH plus abciximab (n = 64; 2.8% versus 7.8%). Similarly, bivalirudin treatment resulted in a 74% relative risk reduction of major bleeding (1.4% versus 6.3%). This small trial provided preliminary evidence of a unique reduction in both ischemic and hemorrhagic events associated with the use of bivalirudin.

REPLACE-1, a slightly larger trial⁵⁵ of 1056 patients, provided continued evidence of reduced ischemic and hemorrhagic complications in patients undergoing elective or urgent PCI. Stents were used in 85% of patients, and GPIIb/IIIa inhibition was administered to 72% of patients at the discretion of the operator. As found in prior investigations, this large pilot study demonstrated a simultaneous reduction in both ischemic and bleeding complications. There was a relative risk reduction of 19% for the composite 48-hour endpoint death/MI/revascularization and a 22% reduction in major bleeding events observed⁵⁵ (Table 4).

The REPLACE-2 trial⁵⁷ was a randomized, double-blind trial of bivalirudin conducted in 6010 patients. The use of bivalirudin plus provisional administration of GP IIb/IIIa inhibitors was compared with UFH with planned GP IIb/IIIa inhibition in patients undergoing PCI. Bivalirudin with provisional GP IIb/IIIa inhibitor use demonstrated a numerically reduced incidence of the composite endpoint (death, myocardial infarction, revascularization, major bleeding) compared with heparin and GP IIb/IIIa inhibitors. With respect to more traditional endpoints, the incidences of death and revascularization were lower for bivalirudin-treated patients. However, the incidence of non-Q-wave MIs in this group was higher. No statistically significant differences were found. The incidences of bleeding, transfusions and thrombocytopenia, however, were significantly lower in patients receiving bivalirudin, compared with heparin and provisional GP IIb/IIIa arm (Table 4). The 6-month follow-up data from the REPLACE-2 trial demonstrated that patients randomized to heparin with GPIIb/IIIa inhibitor and bivalirudin experienced very similar rates of myocardial infarction (1.5%) and revascularization (9%).

Although it did not reach statistical significance, the death rate at 6 months and 1 year was numerically lower in the bivalirudin arm compared with UFH and glycoprotein IIb/IIIa inhibitors. This suggests that bivalirudin plus a glycoprotein IIb/IIIa inhibitor administered on a provisional basis only may be an appropriate anticoagulation strategy in a large portion of PCI patients.

Bivalirudin has also been evaluated in 50 patients with HIT undergoing PCI, in the Anticoagulant Therapy with Bivalirudin to Assist in percutaneous coronary intervention in patients with heparin-induced Thrombocytopenia (ATBAT) trial. Bivalirudin was well tolerated in these patients. A report on the interim data from the first 11 patients in this study, in addition to data from 39 additional patients in previous studies, suggests that bivalirudin may provide a superior alternative to currently available agents.^{58,59}

Bivalirudin appears to be well tolerated in high-risk patient populations. Women, patients over 65, and patients with serum creatinine >1.2 mg/dL have been observed to experience fewer adverse clinical events, in comparison with UFH treatment.^{60,61} Although a reduced dose of bivalirudin may be considered for patients with severe renal insufficiency or for patients on renal dialysis, it is noteworthy that with dose adjustment in patients with renal impairment in the BAT trial, patients with any degree of renal impairment had fewer bleeding complications than similar patients treated with UFH.

Lepirudin (Hirudin)

Although thrombotic complications are lower with lepirudin than with heparin when they are used to treat ACS patients, the risk of major bleeding appears greater.⁶² To date, lepirudin is not indicated for use in PCI patients. A recent analysis suggests 1 reason for the increased risk of bleeding may be related to the development of thrombocytopenia with lepirudin (0.9%), which was similar to the incidence reported for heparin (1.1%).⁶³

A single large randomized trial of 1141 unstable angina patients treated with desirudin or UFH was conducted. Like lepirudin, desirudin is a recombinant DTI based on hirudin. After undergoing angioplasty, patients in the study demonstrated significant reduction in death/MI/revascularization at 96 hours. However, there were no significant differences at 7 months for event-free survival.⁶⁴

Argatroban

Argatroban has been evaluated in small clinical trials for a number of uses. Two studies have evaluated the use of argatroban for PCI in HIT patients. Fifty patients with a current or historical HIT diagnosis were evaluated by Matthai and colleagues.⁶⁵ Patients who needed CABG, who were receiving GP IIb/IIIa inhibitors, or who had hepatic dysfunction were excluded. Argatroban was administered as a bolus of 350 µg/kg and followed by an IV infusion of 25–30 µg/kg/min to maintain an ACT of 300–450 seconds. The result was a 98% success rate, defined as less than 50% stenosis of the vessel postprocedure and the absence of bypass surgery, AMI, or death. Significant complications in patients given argatroban included 1 retroperitoneal hematoma and 1 abrupt vessel closure that required bypass surgery. Because this was a HIT population, inclusion of a control group was considered unethical.

Lewis et al⁶⁶ evaluated 91 HIT patients undergoing PCI in 3 similarly designed studies. They administered a bolus of 350 µg/kg that was followed by an IV infusion of 25 µg/kg/min, with a target ACT of 300–450 seconds. Among patients undergoing initial PCI (n = 91), 94.5% had a successful procedure defined as lack of death, emergency coronary bypass, or Q-wave MI. Adequate anticoagulation was demonstrated in 97.8% of the study population. Death/MI/revascularization occurred within 24 hours in 7.7% of patients. The rate of major bleeding, which was defined as overt bleeding resulting in a ≥ 5 g/dL drop in hemoglobin, a transfusion of ≥ 2 U, intracranial or retroperitoneal bleeding, or bleeding into a major prosthetic joint, was 1.1%. Minor bleeding was defined as overt bleeding that failed the criteria for major bleeding and occurred in 32% of initial patients who were treated. It is difficult to assess the overall effectiveness of this agent, given the short 24-hour time point for the primary endpoint, and there was no direct comparison group.

Because patients with HIT cannot receive heparin, argatroban offers an alternative anticoagulant in this special population.⁶⁷ There are no published clinical trial data establishing the comparative efficacy of argatroban in PCI for patients with a history of HIT.

In a meta-analysis of 35,970 patients in comparative trials of DTIs versus heparin in patients with ACS or undergoing PCI, reductions in death or MI with hirudin or bivalirudin were observed. However, similar findings were not observed with univalent agents such as argatroban.³⁶ These differences may result from statistical power, but no comparative studies between DTIs exist to establish clear superiority for one agent over the other.

There are no data suggesting limitations of argatroban use in patients with renal impairment. However, the use of argatroban in patients with hepatic dysfunction may increase the risk of bleeding complications. Even moderate liver dysfunction can prolong the half-life of argatroban by more than double compared with its half-life in patients with normal hepatic function.⁶⁸

STRATEGIES FOR TREATMENT IN PCI

The limitations of heparins include unpredictable anticoagulant effects, inability to inhibit fibrin-bound thrombin,

activation of platelets, and the lack of a defined optimal dose. This has led to the addition of aspirin, thienopyridines, GPIIb/IIIa inhibitors, and closure devices with PCI procedures to reduce ischemic events while attempting to maintain an acceptable rate of hemorrhagic complications.

It is important to assess ischemic outcomes and bleeding complications in evaluating optimal strategies for coagulation in PCI. Assessing bleeding complications between trials is difficult because of varying definitions for major and minor bleeding, such as the definitions used by the GUSTO and the TIMI trials.^{69,70} Many PCI investigations, including the majority of the LMWH studies, use the Thrombolysis in Myocardial Infarction (TIMI) definitions for the bleeding endpoint.⁷⁰

TIMI criteria were initially established for the evaluation of bleeding complications in thrombolytic trials where relatively high rates of such complications were expected. However, the use of the TIMI criteria for bleeding in the setting of PCI may not be most appropriate measure for a procedure where the extent of bleeding complications is not as high. Furthermore, it has been well established that bleeding resulting in a 3 g/dL or greater drop in hemoglobin, as well as the need for transfusions, have significant adverse implications for patient morbidity and mortality, as well as for hospital costs. Studies have shown an increased length of stay with TIMI minor bleeding and increased risk of morbidity and mortality with transfusions.⁷¹ There are also some data to suggest that bleeding complications can actually result in ischemic complications.⁷² Consequently, minor bleeding events should not be dismissed as an insignificant consequence in evaluating outcomes in clinical trials.

Heparin allows for a simplified administration scheme (subcutaneous injections twice daily rather than continuous IV infusions) for management of ACS patients. LMWHs represent a theoretical advance in antithrombotic therapy because of their greater pharmacokinetic predictability and reduced propensity to stimulate platelet aggregation. Whether these theoretical advantages translate into clinical benefits in PCI remains to be demonstrated. To date, the most appropriate doses of LMWHs and how to combine them optimally with GPIIb/IIIa inhibitors in the cardiac catheterization laboratory have not been adequately established in a large-scale randomized clinical trial.

LMWH use in open-label pilot and registry PCI studies and in ACS patients has been interpreted as indicating that they provide a benefit over UFH. However, critical review of these data suggests that there is no difference from UFH in benefit for ischemic and major bleeding complications. In some investigations, LMWH use has been demonstrated to markedly increase the risk of minor bleeding and transfusion.^{46,47}

Among the available direct thrombin inhibitors, bivalirudin represents the agent with the most robust data in support of superior benefits over UFH in PCI. When the BAT data or more contemporary trials and registry data are evaluated, bivalirudin remains consistent in providing reductions in ischemic and hemorrhagic events across all patient populations studied (Table 5).

Although the management of anticoagulation in patients treated with subcutaneous LMWH remains unclear, data with bivalirudin suggest that patients receiving either UFH or LMWH

TABLE 5. Bivalirudin PCI Registry Studies

Trial	N	Population	Outcomes (%)	Biv vs UFH
Adamian, ⁷⁷ 2002	28	Renal impaired Baseline Cr 1.9 + 0.7 mg/dL undergoing PCI	CIN Major vascular comps Bleeding comps	0 0 0
Adamian, ⁷⁸ 2002	146	Diabetes undergoing PCI	Major vascular comps Transfusion Hematoma	0 vs 1.4 1.4 vs 0 0 vs 1.4
Cho, ⁷⁹ 2003	162 bival 172 historical hep	Elective or urgent PCI	D/MI/R at 120 days Bleeding	4.2 vs 12.7 4.3 vs 6.4

before PCI may be safely switched to bivalirudin for the PCI procedure. In 1006 patients pretreated with heparin and switched to bivalirudin, Bittl⁷³ found that patients treated with bivalirudin (n = 512) compared with heparin (n = 494) had fewer ischemic events (6.3% versus 9.5%; $P = 0.043$) and fewer bleeding complications (4.1% versus 11.9%, $P < 0.001$). The significant difference in adverse clinical outcomes may be linked to heparin's inability to effectively inhibit fibrin-bound thrombin in the high-risk ACS population.

These data suggest that switching from heparin to bivalirudin for PCI procedures is feasible and may be advantageous. However, additional investigations are needed to confirm these results.

SUMMARY

There is a paucity of data in favor of LMWH during PCI despite the evidence supporting the superiority of LMWH over UFH in the non-PCI setting. Adequate, well-controlled, randomized trials involving numbers of patients large enough to establish the comparative benefit and optimal use of LMWHs in PCI are lacking. In contrast, the advantages of DTIs in the PCI setting have been well established in the literature. In particular, the REPLACE-2 trial demonstrates the unequivocal superiority of the direct thrombin inhibitor bivalirudin over UFH in PCI.

DTIs have been available to clinicians for a number of decades. Although they have been effective in decreasing thrombotic complications, their use was limited because of the increased incidence of bleeding. Bivalirudin, a molecule modeled on hirudin, has the unusual pharmacological property of retaining a high degree of thrombotic inhibition with a markedly reduced biologic half-life. In the current stenting era where procedures are usually completed within 30 minutes, bivalirudin may be particularly well suited to coronary interventions.

Thus, at present, a stronger case can be made in favor of bivalirudin than LMWH to replace UFH. A head-to-head trial of bivalirudin versus a high-dose intravenous bolus of LMWH in PCI would be of interest to the cardiovascular and interventional communities.

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