Heparin

Heparin has been used to prevent intravascular thrombosis and clotting on the surface of equipment used during percutaneous coronary interventions (PCI) since Andreas Gruentzig performed the first angioplasty. In fact, the development of coronary angioplasty and of coronary artery bypass surgery would probably not have been possible without heparin. However, with the availability of low molecular weight heparin (LMWH) and the approval of bivalirudin, a direct thrombin inhibitor for use during PCI, the question is more and more frequently asked whether heparin should be replaced in PCI. The purpose of this paper is to critically review the evidence for the use of heparins (indirect thrombin inhibitors) and direct thrombin inhibitors during PCI.

Structure and mechanism of action of heparin.

Commercial heparin is prepared by extraction from either bovine lung or porcine intestine. The final purification and sanitation steps typically yield 30,000–50,000 U/animal when using porcine intestines. Heparin can vary with respect to molecular size and anticoagulant activity. It is a heterogeneous mixture of numerous polysaccharide chains with differing molecular weights ranging from 5,000 to over 40,000 daltons. Heparin obtained from different species or tissues differs structurally. Bovine lung heparin has greater affinity for thrombin than porcine intestinal heparin; this is partially due to bovine heparin's higher level of sulfation and higher molecular weight.

In order to inactivate thrombin, heparin must bind to both antithrombin (AT) and thrombin, forming a ternary complex. Heparin's anticoagulant effect relies upon a unique pentasaccharide sequence that binds with high affinity to AT; however, only 20–50% of the polysaccharide chains in heparin have this unique pentasaccharide sequence. These pentasaccharide-containing heparin chains must be at least 18 saccharide units in length to form the heparin:AT:thrombin complex (Figure 1). In the absence of heparin, AT is a naturally occurring but slow thrombin inhibitor. The heparin:AT interaction produces conformational changes in AT and accelerates its inhibition of thrombin, factor Xa, and factor IXa.

Heparin catalysis of factor Xa inhibition does not require bridging between factor Xa and AT. Since almost all the heparin chains are at least 18 units long, heparin has equivalent inhibitory activity against thrombin and factor Xa. However, when thrombin is bound to fibrin, the heparin:AT complex is less able to access and inhibit thrombin. Furthermore, with respect to anti Xa activity, the heparin:AT complex is unable to inhibit factor Xa bound to the surface of activated platelets.

Pharmacokinetics/pharmacodynamics.

Heparin must be given by injection since it is not absorbed when administered orally. Heparin is cleared via a biphasic process combining rapid saturable and slower first-order mechanisms. The saturable phase is influenced by heparin's non-specific binding to surface receptors on endothelial cells and macrophages, as well as heparin-binding proteins. The slower non-saturable clearance mechanism is predominantly renal. The clearance rate of heparin is dose-dependent with the apparent biologic half-life increasing from approximately 30 minutes following an intravenous (IV) bolus of 25 U/kg to approximately 60 minutes after an IV bolus dose of 100 U/kg. The variation in heparin molecular weight, ranging from 5,000–40,000 daltons, influences heparin clearance because higher molecular weight species are cleared from circulation more rapidly than low molecular weight species. Clearance of heparin thus depends on two primary sets of factors: 1) the dose administered; and 2) patient-related factors such as age, renal and hepatic function, and the presence of an inflammatory state that can increase the plasma concentration of heparin-binding proteins. These factors can result in increased variability of the pharmacokinetics of the drug and place these patients at increased risk for adverse events. Despite evidence of increased bleeding complications in patients with renal impairment, there is no recommendation for reduced heparin dosing in patients with renal impairment.
Laboratory monitoring of heparin. The anticoagulant effect of heparin is typically monitored using the activated partial thromboplastin time (aPTT). The aPTT test is sensitive to the inhibiting effects of heparin on thrombin, factor Xa and factor IXa with moderate correlation between aPTT levels and heparin concentrations. The aPTT is sensitive over a plasma heparin concentration range of 0.1–1.0 U/ml and is therefore a useful test to monitor heparin therapy in patients receiving prolonged infusions of heparin. The aPTT becomes prolonged beyond measurable levels at heparin concentrations > 1.0 U/ml. Therefore, the aPTT is not suitable for monitoring patients undergoing PCI where plasma levels may be in the range of 1.0–5.0 U/ml. For PCI, the activated clotting time (ACT) is the standard monitoring test. At the latter range of heparin concentrations, the correlation between heparin levels and ACT is superior to that with aPTT.

Limitations of heparin. Heparin remains the most widely used indirect thrombin inhibitor in clinical practice despite its well-known limitations (Table 1).

Low molecular weight heparins. Commercially produced low molecular weight heparins (LMWHs) are prepared from standard unfractionated heparin (UFH) through a chemical or enzymatic depolymerization process. The type of heparin initially chosen, the purity of the starting material, and the technology used to achieve depolymerization all contribute to variations in the final LMWH preparation. LMWHs are widely used in Europe for the prevention or treatment of thrombosis in the venous system and in recent years have gained wider use in the United States. Data demonstrating the utility of LMWH in the medical management of unstable coronary syndromes have led to a further increase in their use.

Structure and mechanism of action of low molecular weight heparin. LMWHs have a mean molecular weight of 4,000–5,000 daltons, about one third the size of UFH. Like UFH, they are heterogeneous in molecular size (ranging from 1,000–10,000 daltons) and in anticoagulant activity. Because LMWHs are comprised predominantly of smaller polysaccharide chains that take longer to clear from plasma, they possess a longer half-life than UFH. The plasma half-life of LMWH ranges from 2–4 hours after intravenous injection and 3–6 hours after a subcutaneous injection. LMWHs produce their anticoagulant effect by binding to AT via the same pentasaccharide sequence found in UFH (Figure 1). Much like UFH, this unique pentasaccharide sequence is found on fewer than one third of the LMWH molecules. Only 25–50% of the LMWH chains are long enough to bridge antithrombin to thrombin; consequently, LMWHs have less inhibitory activity against thrombin than against factor Xa. Factor Xa inhibition does not require bridging between factor Xa and AT. Therefore, the smaller pentasaccharide-containing chains in LMWH retain their ability to catalyze factor Xa inhibition. LMWHs bind to non-specific proteins less avidly than heparin, a property that contributes to better bioavailability and more predictable anticoagulation with LMWH compared to UFH.

Figure 1. Only heparin and low molecular weight heparins (LMWH) that possess the pentasaccharide sequence and have a chain length of at least 18 saccharide units are long enough to bridge antithrombin to thrombin. LMWHs have greater anti-Xa activity than antithrombin activity because no bridging is necessary to inhibit factor Xa.
Because nearly all UFH molecules contain at least 18 saccharide units, the antifactor Xa:antifactor IIa ratio is 1:1. Commercially available LMWHs have anti Xa to anti IIa ratios that vary between 4:1 and 2:1. The molecular size distribution in LMWHs can predict their antifactor Xa:antifactor IIa ratio. LMWHs with a greater proportion of shorter chains (under 18 saccharide units) have higher antifactor Xa:antifactor IIa ratios. The clinical consequences of these differences, however, are unknown.

Pharmacokinetics/pharmacodynamics of LMWH. LMWHs exhibit less non-specific protein binding, less interaction with platelets, and less antithrombin activity compared to unfractionated heparin. LMWHs are cleared predominantly by renal mechanisms, whereas UFH is cleared by a combination of renal and hepatic mechanisms. The biological half-life of LMWH increases in patients with renal failure.

Limitations of LMWH. Many of the limitations previously described for UFH may apply to LMWH. Although to a lesser extent, in comparison to UFH, LMWH demonstrates non-specific protein binding, and appears unable to effectively inhibit clot-bound thrombin. LMWH also cross-reacts with heparin antibodies and has been reported to cause thrombocytopenia. Specifically for the PCI setting, the perceived inability to measure the level of anticoagulation using the standard ACT test, as well as its longer plasma half-life, may make LMWH a less than ideal anticoagulant in the catheterization laboratory.

Clinical studies: Evidence for a relationship between ACT levels and clinical outcomes in PCI

<table>
<thead>
<tr>
<th>Limitation</th>
<th>Consequence</th>
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<tbody>
<tr>
<td>Non-specific binding to plasma proteins and endothelial cells</td>
<td>Variability in anticoagulant effect, especially in seriously ill patients</td>
</tr>
<tr>
<td>Release of Platelet factor 4 and von Willibrand factor from platelets during clotting</td>
<td>Results in heparin resistance and a need for higher levels of heparin</td>
</tr>
<tr>
<td>Inability of heparin to inactivate fibrin-bound thrombin</td>
<td>Thrombin remains active when bound to fibrin and continues to activate platelets</td>
</tr>
<tr>
<td>Heparin:AT complex cannot inhibit factor Xa bound to activated platelets</td>
<td>Incomplete inhibition of coagulation</td>
</tr>
<tr>
<td>Heparin induces platelet activation</td>
<td>Further activates the clotting cascade and release of heparin-binding proteins</td>
</tr>
<tr>
<td>Forms heparin antibodies</td>
<td>Can result in heparin-induced thrombocytopenia and thrombosis syndrome</td>
</tr>
<tr>
<td>Dose-dependent half-life</td>
<td>Non-linear increase in half-life as dose increases</td>
</tr>
<tr>
<td>Patient-to-patient variability</td>
<td>Standard heparin doses not equally effective</td>
</tr>
<tr>
<td>Ill-defined dose to achieve target ACT level in PCI</td>
<td>Supra-anticoagulation resulting in increased bleeding risk or suboptimal anticoagulation resulting in increased risk of ischemic complications</td>
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</table>

Laboratory monitoring of LMWH. Unlike UFH, the anticoagulant effect of LMWH, as a class, is not widely perceived to be measurable by using the aPTT or the ACT. The uncertainty regarding measurements of the anticoagulant activity of LMWH with these tests can become a critical issue in acute coronary syndromes where the need for PCI may require exact understanding of the patient’s anticoagulation status before and during the procedure. Currently, the only test that is broadly accepted to gauge the anticoagulation status of a patient who has received a LMWH is an anti-factor Xa test. The test is time-consuming, costly and not readily available at point of care, leaving the cardiologist without a rapid and reliable test for determining anticoagulation levels in patients receiving LMWH.

Limitations of LMWH. Many of the limitations previously described for UFH may apply to LMWH. Although to a lesser extent, in comparison to UFH, LMWH demonstrates non-specific protein binding, and appears unable to effectively inhibit clot-bound thrombin. LMWH also cross-reacts with heparin antibodies and has been reported to cause thrombocytopenia. Specifically for the PCI setting, the perceived inability to measure the level of anticoagulation using the standard ACT test, as well as its longer plasma half-life, may make LMWH a less than ideal anticoagulant in the catheterization laboratory.

Clinical studies: Evidence for a relationship between ACT levels and clinical outcomes in PCI

Measuring anticoagulant effect. The activated clotting time is the preferred point of care test for monitoring the anticoagulant effect of heparin in the cardiac catheterization laboratory. ACT values are linearly related to heparin concentrations in the range used in PCI. Additionally, the ACT can provide a rapid measure of the level of anticoagulation while in the catheterization lab. The HemoTec (HemoTec, Inc., Englewood, Colorado) and Hemochron devices (International Technidyne Corporation, Edison, New Jersey) are the two most commonly used for measuring ACT in the cardiac catheterization laboratories in the United States.
PCI without a glycoprotein (GP) IIb/IIIa antagonist: Case-control studies. Heparin is widely used in the PCI setting despite a dearth of information from well-controlled randomized trials. After decades of use and a large volume of clinical experience, the optimal dose for heparin in PCI remains unclear. Two small randomized studies compared low versus high doses of heparin for anticoagulation during elective PCI. Although lacking consistency, data from these studies support the perception that UFH’s ability to prevent thrombosis is dose dependent, i.e., that higher plasma levels of heparin achieve higher ACTs, and that these higher heparin concentrations are more likely to be protective against ischemic complications. However, this protection appears to be associated with an increased risk of hemorrhage.

Although there have been no trials in which patients were randomized to undergo PCI at different ACT values, data from three case-controlled studies provide evidence that patients with higher ACT or aPTT values had fewer ischemic events compared to patients with lower ACT or aPTT values (Table 2). When these data are pooled, the combined odds ratio for death or ischemic complications was 0.25 [95% confidence interval (CI), 0.17–0.37; p < 0.00001]. To define a threshold ACT above which adverse clinical outcomes become less likely and more intense heparin anticoagulation is of no added benefit, Narins et al. used this population to construct a multivariable binary logistic regression model to characterize the activated clotting time as a predictor of ischemic outcomes. The relationship between the initial ACT and adverse outcomes was highly statistically significant (p = 0.015). Moving from the 25th percentile of ACT (324 seconds) to the 75th percentile (413 seconds), the probability of adverse ischemic outcomes declined from 7.9% to 4.5% (Figure 2).

Randomized trials. A retrospective analysis of randomized studies supports the findings of the case-control studies. In 1,863 heparin-treated patients, there was an inverse relation between the ACT values measured five minutes after an initial heparin bolus and the risk of abrupt closure. For every 10-second increase in ACT, the probability of abrupt closure decreased by 1.3%. The relationship between the maximal ACT and the risk of abrupt vessel closure was most striking in patients undergoing brief procedures (odds ratio, 1.6% for every decrease of 10 seconds in maximal ACT).

A pooled analysis of recent major clinical trials in patients treated with heparin also provides evidence that higher ACT values ranging from 350–375 seconds result in greater protection against ischemic events. In this analysis, data from 6 contemporary randomized controlled trials of adjunctive antithrombotic regimens for PCI where UFH and aspirin constituted the control arm were analyzed using similar definitions for

<table>
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<th>Study</th>
<th>No. patients</th>
<th>Median ACT (s)</th>
<th>p-value</th>
</tr>
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<tr>
<td>Narins et al., 1996</td>
<td>62</td>
<td>350</td>
<td>&gt;0.004</td>
</tr>
<tr>
<td>Ferguson et al., 1994</td>
<td>103</td>
<td>229</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Figure 2. Activated clotting time is inversely proportional to the probability of death, myocardial infarction, and revascularization. Top line (hashed) indicates upper 95% confidence interval (CI). Middle line (solid) indicates initial activated clotting time. Lower line (hashed) indicates lower 95% CI. Reprinted with permission from Narins CR et al. Circulation 1996;93:667–671.
ischemic endpoints. In a total of 5,216 patients, the incidence of death, myocardial infarction, or any revascularization at 7 days was calculated for each ACT group. An ACT in the range of 350–375 seconds provided the lowest composite ischemic event rate of 6.6%, or a 34% relative risk reduction in 7-day ischemic events, compared to a rate of 11.6% observed between 171–295 seconds ($p = 0.001$) (Figure 3). The current trend toward lower heparin dosing to achieve lower ACT values of approximately 250–275 seconds may not provide optimal effectiveness in the absence of GP IIb/IIIa receptor inhibitors. However, in the presence of a GP IIb/IIIa inhibitor (abciximab), this pooled analysis did demonstrate that lower ACT values are beneficial, resulting in less bleeding risk and no increased risk in ischemic complications (Figure 4).

This same pooled analysis demonstrated that in order to achieve the lowest rate of bleeding, in the absence of a GP IIb/IIIa inhibitor, ACTs must be kept in a lower range (325–350 seconds) than the range to prevent ischemic complications (350–375 seconds), underscoring the fact that reductions in ischemic effects when targeting for maximal efficacy with heparin is a strategy that is associated with a cost of increased bleeding. This inability to achieve a low rate of both ischemic and hemorrhagic complications underscores an important limitation in the management of patients undergoing PCI.

The excess in thrombotic risk at higher ACTs observed in the analysis by Chew et al. may represent a consequence of platelet activation that has been reported with high doses of unfractionated heparin.24,33,56

Heparin dosing during PCI in conjunction with a GP IIb/IIIa antagonist. The trend in recent years has been to reduce the dose of heparin during PCI, particularly in patients treated with GP IIb/IIIa antagonists. Data from the EPIC trial57 suggested an unfavorable relationship between the prevailing heparin dose strategy (fixed dose of 10,000–12,000 U bolus IV) and bleeding in patients who were treated with abciximab. The odds ratio for major bleeding risk was 1.22 (95% CI, 0.28–5.38) for patients receiving < 70 U/kg of heparin; 3.75 (95% CI, 1.2–11.75) for patients receiving 70–120 U/kg; and 3.88 (95% CI, 2.15–7) for patients receiving > 120 U/kg. Patients who received relatively high doses of heparin did not experience a reduction in the rate of peri-procedural ischemic events.19 This observation prompted the initiation of the PROLOG10 and EPILOG10 studies, which established that reduction of the heparin dose from 100 U/kg to 70 U/kg in patients receiving abciximab lowered the rate of hemorrhage [non-CABG related major bleeding, 1.9% versus 1.1% ($p = 0.7$); minor bleeding, 7.6% versus 4.0% ($p < 0.001$)].19 Findings from EPILOG suggested that patients with diabetes may represent an exception to this finding; event rates were lowest in diabetics receiving abciximab combined with standard dose heparin (100 U/kg).32 However, significant event rate reductions among diabetics assigned to abciximab with low-dose, weight-adjusted heparin in the subsequent EPISTENT trial60 cast doubt on the applicability of these observations. In the ESPRIT trial,64 the heparin dose used in patients receiving eptifibatide was 60 U/kg. No relationship between ACT and the frequency of ischemic events was observed in patients receiving the GP IIb/IIIa antagonist.64 Therefore, experience from a number of studies using a variety of GP IIb/IIIa inhibitors suggests that among patients who are treated with a GP IIb/IIIa antagonist, reduction of the heparin dose to achieve an ACT of just over 200 seconds is necessary to avoid an increase in hemorrhagic events.65 However, the preponderance of evidence suggests that this is not the case when PCI is performed in the absence of a GP IIb/IIIa antagonist.
Low molecular weight heparins

Low molecular weight heparins have become increasingly popular within the last several years, in large part as a consequence of two trials suggesting superior outcomes with enoxaparin compared to UFH in the medical management of patients with unstable angina and non-Q wave myocardial infarction.66,67 Pooled analysis of the two studies for major and minor bleeding events, however, showed no reduction of bleeding for enoxaparin versus heparin (major, 1.3% enoxaparin versus 1.1% heparin; minor, 10% enoxaparin versus 4.3% heparin); if a PCI was required during either of these trials, enoxaparin was discontinued prior to the procedure. Consequently, the use of LMWH during PCI was not extensively studied.

To assess whether LMWH can be used in PCI, subsequent registry studies have investigated the use of enoxaparin in patients undergoing PCI. In NICE-1 (enoxaparin, IV bolus of 1.0 mg/kg)68 and NICE-4 (enoxaparin, 0.75 mg/kg plus abciximab),69 levels of anti Xa activity were similar to levels reported in patients treated with a 10,000 U UFH bolus.69 The rates of ischemic and bleeding complications were lower than historical controls from the EPILOG low-dose population, leading to the conclusion that enoxaparin, with or without abciximab, appeared to provide safe and effective anticoagulation during PCI. Similar results have been reported for the NICE 3 registry, in which ACS patients receiving enoxaparin were treated with one of the three available GP IIb/IIIa antagonists. Although the study suggests that it is feasible to extend the use of enoxaparin to the cath lab during PCI, no conclusions can be drawn about the benefits of using enoxaparin during the PCI procedure compared to UFH.70 Since the data in these open-label registries were compared to historical controls and comparative trials have not been performed, additional prospective studies are needed to establish the relative safety and efficacy of enoxaparin in PCI.

In one randomized study where LMWH (reviparin) was compared to UFH, reviparin did not reduce the composite of ischemic events at 6 months.71 Reviparin administered at 7,000 U bolus followed by infusion and subcutaneous injection was compared with UFH at 10,500 U bolus followed by infusion in 612 patients without the use of GP IIb/IIIa antagonists and with stent implantation performed only for salvage purposes. The rate of rescue stent implantation on the day of PCI was reduced from 6.9% to 2.0% with reviparin.71 However, because of the lack of benefit at 6 months, the product was not further developed for this indication.

Direct thrombin inhibitors as a potential alternative to heparin in PCI

Currently available direct thrombin inhibitors include bivalirudin, hirudin and argatroban. Each of these inhibitors binds directly to thrombin without the need for the cofactor antithrombin and are effective at inhibiting both fibrin-bound and free circulating thrombin. Hirudin and bivalirudin are bivalent inhibitors that bind to thrombin at exosite 1 (the substrate recognition site) and at the active site.72–74 In contrast, argatroban binds thrombin only at its active site in a univalent fashion. Hirudin and argatroban have received clinical approval for treatment and management of patients with heparin-induced thrombocytopenia. Bivalirudin is the only direct thrombin inhibitor that is indicated for use in patients with unstable angina undergoing percutaneous coronary angioplasty.

**Lepirudin.** Hirudin, a 65-amino acid polypeptide originally isolated from the salivary glands of the medicinal leech Hirudo medicinalis, is now available through recombinant DNA technology. Recombinant hirudin (lepirudin) binds tightly to thrombin to form a slowly reversible complex.75 Lepirudin is cleared via renal mechanisms and has a half-life of approximately 50–60 minutes (increasing up to 3 hours depending on patient characteristics and disease states).75

There have been no randomized trials of lepirudin in HIT patients undergoing PCI, although several lepirudin-treated patients in the clinical studies HAT-1 and HAT-2 also underwent successful PCI. In 2 trials of ACS (without ST-elevation myocardial infarction),76,77 clinical thrombotic outcomes were better with lepirudin, but the risk of major bleeding was substantially increased. A recent analysis of the larger of the two studies has shown that the increased risk of bleeding may relate to the development of thrombocytopenia with hirudin (0.9%), which was similar to the incidence reported for heparin (1.1%).78

Desirudin has been studied in 3 large trials of acute coronary syndromes (ACS), including a PCI trial, but
at present, desirudin is not approved for any use in the United States. Results from 1 trial demonstrated significant reductions in the incidence of acute ischemic episodes following PCI. This improvement over heparin was particularly evident among patients considered to be at high risk for ischemic complications, but bleeding complication rates were not reduced. The finding of improved efficacy of hirudin over heparin (but with an increased risk of bleeding) is consistent across many studies, including those in acute myocardial infarction and ACS without ST elevation.

**Argatroban.** Argatroban is a synthetic derivative of arginine. The drug binds reversibly to the catalytic site of thrombin with a terminal elimination half-life of 39–51 minutes. The primary route of clearance is liver metabolism. Unlike the selective bivalent direct thrombin inhibitors lepirudin and bivalirudin, 54% of the argatroban dose given binds to human serum proteins, with binding to albumin and α1-acid glycoprotein at 20% and 34%, respectively.

In a prospective study with historical controls, the composite endpoint of all-cause death, all-cause amputation, or new thrombosis was reduced from 38.8% in the historical control group to 25.6% in argatroban-treated patients. Bleeding was similar in both groups (~ 2%) and hematuria occurred in ~ 12% of argatroban patients compared to ~ 1% of the historical control group.
3) the ability to profoundly inhibit thrombin-mediated platelet aggregation. In vitro, thrombin-mediated platelet aggregation is fully inhibited at 1/500th of the plasma concentrations typically achieved in PCI, and
4) the ability to achieve high levels of anticoagulation without causing platelet activation. On the contrary, given thrombin’s central importance to platelet activation, it is likely that by virtue of its antithrombin effect bivalirudin attenuates platelet activation during PCI.

The safety and efficacy of bivalirudin in PCI were evaluated in 2 trials. In the first, bivalirudin was used as an alternative to heparin in a dose-finding trial of 291 patients undergoing angioplasty. Bivalirudin produced dose-dependent prolongation of the ACT and aPTT. In the second study, the Bivalirudin Angioplasty Trial (BAT), a total of 4,312 patients with unstable angina or MI requiring PCI were randomized in a double-blind fashion to receive bivalirudin or heparin during the procedure. Evaluation of the adjudicated data demonstrated a 22% relative risk reduction with bivalirudin in the rate of death, MI, or repeat revascularization at 7 days compared to heparin (7.9% versus 9.3%, respectively; p = 0.038) and significantly less major bleeding (3.5% versus 9.3%, respectively, a 62% relative reduction; p < 0.001). This unique reduction of both ischemic and hemorrhagic events was even more pronounced in a prespecified and randomized subgroup of post-MI patients where those treated with bivalirudin had a 51% relative risk reduction in death, MI or revascularization versus heparin (4.9% versus 9.9%, respectively; p = 0.009) and a relative risk reduction of 73% for major bleeding (2.4% versus 11.8%, respectively; p < 0.001). Clinically significant hemorrhage was defined as overt bleeding with a fall in hemoglobin level of 3 g/dl or more, or transfusion of ≥ 2 units of blood, or retroperitoneal or intracranial bleeding.

The reduced rate of hemorrhage in patients treated with bivalirudin compared to heparin-treated patients was found at all ACT levels (Figure 6A). This suggests that bivalirudin may reduce bleeding even in those settings where heparin doses are titrated to lower levels of ACT. Similarly, the incidence of the combined endpoints of death, MI, or repeat revascularization was lower in bivalirudin-treated patients compared to those treated with heparin across the ACT levels (Figure 6B). To further substantiate the claim that bivalirudin results in a reduction in bleeding complications in comparison to heparin independent of the precise dose of heparin administered, the incidence of major bleeding utilizing TIMI criteria was calculated for both the BAT and the heparin arm of a series of contemporary PCI trials. Double-blind, randomized clinical trials of anticoagulant agents used in PTCA performed predominantly in North America and coordinated by The Cleveland Clinic Foundation and/or Duke Clinical Research Institute.

### Table 1: TIMI major hemorrhage

<table>
<thead>
<tr>
<th>Study</th>
<th>Heparin (n)</th>
<th>Bivalirudin (n)</th>
<th>TIMI Major Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAPPORT</td>
<td>181</td>
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<tr>
<td>EPIC</td>
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<tr>
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<td>809</td>
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<td>2.2%</td>
</tr>
<tr>
<td>BAT</td>
<td>2151</td>
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<td>2.9%</td>
</tr>
<tr>
<td>BAT bivalirudin (2161)</td>
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</table>

Figure 7. In a comparison of TIMI major hemorrhage rates for the heparin-only control arm of several randomized PCI trials conducted between 1993–1998, both bivalirudin and heparin in the BAT trial demonstrated a relatively low rate of TIMI major hemorrhage.

Arugatroban has been evaluated for PCI in 2 trials of patients with HIT (total, n = 50). Of the patients who underwent PCI, > 98% had a successful procedure. The significant complications in patients given argatroban included 1 retroperitoneal hematoma and 1 abrupt vessel closure that required bypass surgery. The anticoagulant effect of the drug appeared to be adequate for all but 1 patient. Based on historical controls, argatroban appears to provide adequate anticoagulation but little bleeding advantage over UFH in clinical trials to date.

**Bivalirudin.** Bivalirudin is a synthetic, 20-amino acid polypeptide modeled after hirudin and comprised of an active site-directed peptide, D-Phe-Pro-Arg-Pro, linked via a tetraglycine spacer to a dodecapeptide analogue of the carboxy-terminal of hirudin (Figure 5). Bivalirudin interacts with thrombin at both the active site and exosite 1, forming a 1:1 stoichiometric complex. Once bound, however, thrombin slowly cleaves the Arg3-Pro4 bond of bivalirudin, resulting in recovery of thrombin’s active site function. Bivalirudin’s carboxy-terminal dodecapeptide remains bound to exosite 1, but with low affinity, such that bivalirudin initially acts as a non-competitive inhibitor of thrombin, then becomes a competitive inhibitor enabling thrombin to subsequently participate in hemostatic reactions. Thus, the biochemical properties of bivalirudin confer to the molecule a unique combination of features that appear favorable for PCI patients including:

1) the ability to inhibit thrombin regardless of its location (fibrin-bound versus soluble thrombin), a property of potential importance to patients with visible thrombus on angiography prior to stent placement;
2) rapid return to hemostatic competence upon cessation of infusion (i.e., ultra-short plasma and biologic half-life) due to vulnerability of bivalirudin at active site;
3) the ability to profoundly inhibit thrombin-mediated...
between 1993 and 1998 were included in the pooled analysis alongside the Bivalirudin Angioplasty Trial. The selection criteria excluded one US-based clinical trial (RESTORE) and a small number of clinical trials performed predominantly outside the US (HELVETICA, REDUCE) as well as trials conducted after 1998.

The TIMI major hemorrhage rate in the heparin arm of the BAT trial was well within the range of the rate observed in the heparin-only control arm of the more recent PCI trials in this pooled analysis (Figure 7).

A reduced rate of bleeding risk among patients treated with bivalirudin has been reported in other trials as well. In a systematic overview (meta-analysis) of clinical outcomes that included three additional trials comparing bivalirudin to heparin, Kong et al. reported a significant reduction in major hemorrhage (odds ratio, 0.41; 95% CI, 0.32–0.52; \( p < 0.001 \)), or 58 fewer events per 1,000 patients treated with bivalirudin rather than heparin.\(^9\)

Finally, bivalirudin may provide an attractive alternative to UFH for the treatment of coronary patients referred for catheterization after receiving subcutaneous LMWH. In a small, open-labeled, randomized trial of 40 patients treated with LMWH for ACS, patients were switched to either UFH or bivalirudin prior to angioplasty. Coagulation parameters and adverse effects were assessed. In these patients, the last dose of LMWH was administered at least 8 hours prior to randomization. The increases in ACT values were more predictable, and the return to normal ACT levels was more rapid in bivalirudin-treated patients than in heparin-treated patients. The median aPTT was higher with UFH than with bivalirudin and remained elevated at sheath removal time (89 seconds versus 44 seconds). Consistent with these observations, anti-Xa levels remained persistently elevated up to the time of sheath removal in UFH-treated patients. In contrast, anti-Xa levels in patients treated with bivalirudin declined steadily throughout the study period. Adverse events were comparable between groups. One patient in the UFH group had a post-procedure MI; no deaths or major hemorrhages occurred in either group.\(^2\) A complete report of this study awaits publication.

**Summary.** Heparin remains the most widely used anti-coagulant in interventional cardiology, but is limited by its inability to inhibit clot-bound thrombin and by its propensity to activate platelets. Furthermore, when attempts are made to overcome these limitations by increasing the dose of heparin, bleeding complications ensue.

LMWH represents a theoretic advance in antithrombotic therapy by virtue of its greater pharmacokinetic predictability and reduced propensity to stimulate platelet aggregation. However, with respect to PCI, the extended half-life of LMWH (particularly when administered subcutaneously) relative to UFH represents a major theoretic disadvantage.

Direct thrombin inhibitors, such as bivalirudin, that possess shorter half-lives and potentially more potent antithrombotic activity than UFH in a broad range of coronary lesion morphologies may provide interventionalists agents with more desirable pharmacokinetic profiles, particularly in an era characterized by shorter procedure times due to improvements in stent technology.

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