Anticoagulation Strategies for Patients Undergoing Percutaneous Coronary Intervention: Unfractionated Heparin, Low-Molecular-Weight Heparins, and Direct Thrombin Inhibitors

Spyros Kokolis, Erdal Cavusoglu, Luther T. Clark, and Jonathan D. Marmur

Low-molecular-weight heparins and direct thrombin inhibitors are emerging as alternative anticoagulants to unfractionated heparin in patients undergoing percutaneous coronary intervention (PCI). This paper reviews the pharmacologic properties of these newer antithrombotic agents and evaluates the clinical data demonstrating their use in patients undergoing PCI.

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In recent years, an increasing number of anticoagulants have become available as alternatives to unfractionated heparin (UFH) for treatment of patients with acute coronary syndromes (ACS) and for percutaneous coronary intervention (PCI). Although UFH has served as the primary anticoagulant for nearly 50 years, it has several well-established limitations1 (Table 1). From the perspective of an interventional cardiologist, perhaps 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 (e.g., glycoprotein IIb/IIIa antagonists, thienopyridines, stents).

An alternative strategy to deal with the problems associated with UFH is to substitute this agent with antithrombins such as the low-molecular-weight heparins (LMWHs) and direct thrombin inhibitors (DTIs). The purpose of this review is to examine the mechanisms of action, pharmacologic properties and clinical uses for UFH, LMWHs, and DTIs.

Indirect Thrombin Inhibitors

Heparin

Heparin is a large polymer, averaging approximately 15,000 daltons in size, which contains negatively charged sulfate and carboxylic acid groups. The effects of heparin can be rapidly reversed with protamine, a basic molecule.2 UFH is a heterogeneous preparation of heparin molecules ranging in size from about 5,000 to 40,000 daltons, and typically extracted from porcine intestine or bovine lung.3 UFH is administered parenterally (intravenously [IV] or subcutaneously [SQ]) and exerts its therapeutic effect by indirectly inhibiting coagulation factor IIa (thrombin), a critical mediator in clot formation. Thrombin is characterized by two binding sites (exosites 1 and 2), in addition to its active catalytic site, as shown in Fig 1. These sites are essential for the binding of thrombin substrates such as fibrinogen.4 Thrombin cleaves fibrinogen to form fibrin, activates other coagulation factors, and carries out other actions mediated by its binding sites to promote the formation, expansion, and organization of blood clots.
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

### Table 1. Limitations of Unfractionated Heparin

<table>
<thead>
<tr>
<th>Limitation</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonspecific binding to plasma proteins and endothelial cells⁶⁴,⁶⁹</td>
<td>Variability in anticoagulant effect, especially in seriously ill patients⁵⁸</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 heparin⁴⁴</td>
</tr>
<tr>
<td>Inability of heparin to inactivate fibrin-bound thrombin⁶</td>
<td>Thrombin remains active when bound to fibrin and continues to activate platelets⁶⁹</td>
</tr>
<tr>
<td>Heparin induces platelet activation⁶⁰</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 syndrome⁶⁸</td>
</tr>
<tr>
<td>Dose-dependent half-life⁶¹</td>
<td>Nonlinear increase in half-life as dose increases</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 increase risk of ischemic complications⁵⁰</td>
</tr>
</tbody>
</table>

Abbreviations: ACT, activated clotting time; PCI, percutaneous coronary intervention.

**Fig 1.** Thrombin binding sites and the inhibition of thrombin and factor Xa by UHF and LMWH. Abbreviations: AT, antithrombin; LMWH, low-molecular-weight heparins. (Source: J Invasive Cardiol;14:8B-18B, 2002 [Suppl B]).
bind to thrombin. Binding of the heparin molecule to thrombin at exosite 2, with bridging between AT and thrombin as shown in Fig 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 (i.e., 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
After parenteral administration, heparin molecules are degraded into inactive compounds by the reticuloendothelial system, 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 placental barrier, and is therefore considered an acceptable anticoagulant for use during pregnancy.

Low-Molecular-Weight Heparins
LMWHs are derived from UFH through a chemical and enzymatic depolymerization process resulting in preparations of shorter heparin molecules,6 which like UFH, consist of chains of alternating residues of D-glucosamine and uronic acid.7 LMWHs are characterized by a mean molecular weight of 4000 to 5000 daltons but range in size from 1,000 to 10,000 daltons. Similar to UFH, LMWHs show heterogeneous anticoagulant activity.1

The LMWHs are also indirect thrombin inhibitors that bind to AT 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, Xla, and IXa, and tissue factor pathway inhibitor (TFPI). LMWHs demonstrate less inhibitory activity against thrombin than against factor X, because only 25% to 50% of the LMWH chains are long enough to bridge AT 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 (see 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% to 6% reinfarction rate following initially successful coronary thrombolysis.

Monitoring of Anticoagulation Activity
Activated clotting time (ACT) and activated partial thromboplastin time (aPTT) are not routinely used to measure the anticoagulant effect of LMWHs. Because only 25% of LMWH molecules are large enough to inactivate thrombin, LMWHs do not prolong the ACT or the aPTT to the same extent as UFH. This is especially true for the agents with shorter chain lengths and higher anti-Xa:anti-IIa ratios.14 The uncertainty regarding measurements of LMWH anticoagulant activity with bedside tests such as the ACT has become a critical issue in the settings of ACS and PCI. An accepted method to gauge the anticoagulation status of a patient treated with LMWHs is anti-factor Xa testing. However, the test is time consuming, costly, and not readily available as a point-of-care testing. Furthermore, clinical studies have demonstrated weak correlations between anti-Xa levels and thrombin formation.15-17

Recently, a new test known as ENOX (enoxaparin test card) has become available. This test specifically measures the anticoagulant effects of enoxaparin (>1.0 IU/mL) using a factor Xa-activated clotting method. However, this test has
never been formally validated in patients under-
going PCI. Furthermore, deficiencies in factors X, V, or prothrombin can result in a prolongation of
the ENOX clotting test, even in the absence of
enoxaparin. UFH has also been found to interfere
with the test results.18 In general, assays of antico-
agulation activity are dependent both on tech-
nique and laboratory standardization, and are dif-
ficult to compare and evaluate owing to their
variability.

In addition, the premise of using anti-factor Xa
to gauge the activity of LMWH may in itself be
incorrect because it focuses on an isolated step in
the coagulation cascade. Anti-factor Xa measure-
ment would not effectively ascertain the extent of
anticoagulation exerted by LMWHs at multiple
levels, through factors XIIa, XIa, and IXa, and TFPI.

In contrast, assays such as the ACT and the PTT
give a more global assessment of the anticoagulant
effects and more recent data suggest that these
assays may be useful when LMWH are adminis-
tered IV as opposed to SQ.15 Data supporting the
ACT to monitor LMWH on PCI are presented in
the “Clinical Data in PCI” section.

Pharmacodynamics

LMWHs are cleared predominantly by renal
mechanisms.8 The plasma half-life of LMWH
ranges from 2 to 4 hours after IV injection and 3 to
6 hours following a SQ injection.6 The half-life of
LMWH increases in patients with renal failure.
LMWH dose should be reduced by approximately
50% in patients with severe renal impairment
(creatinine clearance <30 mL/min), owing to the
risk of accumulation that may lead to major bleed-
ing, particularly at the sites of instrumentation.19-21

LMWHs have a longer half-life and, compared
to UFH, show less nonspecific binding to endo-
thelial cells, platelet factor 4 released from acti-
vated platelets, and other plasma proteins. Follow-
ing a dose of LMWH, the ability to inhibit
factor Xa persists longer than the ability to sup-
press thrombin, owing to more rapid clearance of
the longer LMWH chain units.

Heparin-Induced Thrombocytopenia and
Heparin-Induced Thrombocytopenia and
Thrombosis Syndrome

Heparin-induced thrombocytopenia (HIT) may
occur following the formation of platelet antibod-
ies as a consequence of heparin therapy. The dis-
order is characterized by a reduction in the num-
ber of platelets approximately 6 to 10 days after
the initiation of therapy, necessitating the imme-
diate discontinuation of heparin. Heparin-in-
duced thrombocytopenia and thrombosis syn-
drome (HITTS) is characterized by decreased
numbers of circulating platelets and thrombosis
within the vasculature. The chronic use of UFH
may lead to a decrease in the production and ac-
tivity of AT, which thus increases the risk of
thrombosis.

LMWH is presumed to have a lower incidence
of HIT/HITTS. However, LMWHs do cross-react
with HIT antibodies and have been reported to
cause thrombocytopenia in a small percentage of
patients.22

Reversibility

Protamine is the reversal agent for UFH. The
mechanism through which protamine inhibits
UFH is dependent on the degree of sulfonation
of the molecule. The protamine-resistant fraction in
LMWH is due to the lower-molecular-weight frac-
tion with a low sulphate charge density. The
amount of anti-Xa neutralized is directly propor-
tional to the number of sulphate groups attached
to the LMWH. LMWHs are at least partially re-
versible by protamine and therefore should be
given if a reversal state is needed rapidly in pa-
tients who had LMWH administered23 (Table 2).

Direct Thrombin Inhibitors

In contrast to UFH and LMWH, DTIs (e.g., biva-
lirudin, argatroban, hirudin) are able to inhibit
thrombin directly without the need for the cofac-

<table>
<thead>
<tr>
<th>Table 2. Protamine Neutralization of LMWH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
</tr>
<tr>
<td>Fraxiparin</td>
</tr>
<tr>
<td>Tinzaparin</td>
</tr>
<tr>
<td>Dalteparin</td>
</tr>
<tr>
<td>Clivarin</td>
</tr>
<tr>
<td>Enoxaparin</td>
</tr>
<tr>
<td>Super-sulphonated LMWH</td>
</tr>
</tbody>
</table>

Source: From Crowther et al.23
tor AT, and are able to inhibit both fibrin-bound and soluble thrombin.

Because of their relatively small size, the interaction of the DTI’s with the active site of thrombin is not compromised following binding of thrombin to fibrin at exosite 1. Thus, they are able to inactivate both free thrombin and thrombin bound to fibrin or fibrin degradation products. This may be due to 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 (Figs 2 and 3). The univalent DTI argatroban binds thrombin only at its active site (Fig 4).

In the direct thrombin inhibitor trialists’ collaborative group, hirudin and heparin were associated with an increase in major bleeding complications. 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 to hirudin, or to univalent inhibitors (Fig 5).

### Table 3. Binding Characteristics of Direct Thrombin Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Molecular Weight</th>
<th>Mode of Binding</th>
<th>Thrombin Binding Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bivalirudin</td>
<td>2.2 Kda (20 amino acids)</td>
<td>Reversible bivalent</td>
<td>Active site, exosite 1</td>
</tr>
<tr>
<td>r-Hirudin (lepirudin, desirudin)</td>
<td>7.0 Kda (65 amino acids)</td>
<td>Irreversible, bivalent</td>
<td>Active site, exosite 1</td>
</tr>
<tr>
<td>Argatroban</td>
<td>827 Daltons</td>
<td>Reversible, univalent</td>
<td>Adjacent to active site</td>
</tr>
</tbody>
</table>

**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 analog of the carboxy-terminal of hirudin. 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. 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 (Fig 2).

**Pharmacodynamics**

Bivalirudin is cleared by a combination of proteolytic cleavage and renal mechanisms. Bivalirudin has a half-life of about 25 minutes in patients with normal renal function, with prolongation seen in patients with moderate (34 min) or severe...
renal impairment (creatinine clearance of 30 to 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. 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. 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. Lepirudin is cleared primarily via renal mechanisms. After IV injection, the half-life is approximately 50 to 60 minutes, increasing up to 3 hours depending on comorbid diseases. 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.

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 assay has also been reported as successful in predicting anticoagulant effect.

**Pharmacodynamics**

Lepirudin antibodies have been detected in approximately 40% of treated patients 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, and other antibodies reportedly neutralize lepirudin’s anticoagulant effect.

**Argatroban**

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

**Pharmacodynamics**

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

**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 ACS, the authors found a 15% reduction in death/myocardial infarction (MI) in patients treated with a DTI, compared to treatment with UFH. An 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 two other univalent agents, efegasatan and inogatrpan) 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. 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 ACS. In a subgroup analysis, there was a benefit of DTIs on death or MI in trials of both ACS and PCI. In contrast, the univalent DTIs showed a less robust decrease in major bleeding.

**Clinical Data**

Unfractionated Heparin and Low-Molecular-Weight Heparin

Large clinical trials evaluating LMWH in the management of patients with unstable angina and non–Q-wave MIs have been promising. 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 to UFH.

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, but none are large-scale, randomized controlled trials that provide convincing evidence of a meaningful benefit over UFH.

The Coronary Revascularization Using Integrilin and Single Bolus Enoxaparin (CRUISE) study evaluated a total of 261 patients comparing enoxaparin plus eptifibatide with UFH plus eptifibatide. The study was too small to reach meaningful conclusions, but there was no evident benefit for enoxaparin in ischemic events (8.5 versus 7.6, \(p = .82\)) or major bleeding (2.5 versus 1.6, \(p = .68\)) compared to UFH. This is in contrast to Thrombolysis in Myocardial Infarction (TIMI), where major bleeding occurred more frequently among patients receiving enoxaparin and TIMI minor bleeding was more frequent with UFH compared with enoxaparin (Table 4).

Dalteparin, a LMWH, in doses of 40 IU/kg (\(n = 27\)) or 60 IU/kg (\(n = 76\)), was evaluated in a small, nonrandomized pilot study of patients undergoing PCI. Early assessment determined that the 40 IU/kg dose appeared inadequate to provide optimal protection from ischemic events and consequently the majority of patients in this pilot study received the 60 IU/kg dose. In this study, the composite endpoint of death/Q-wave MI/revascularization occurred at a rate of 3.7%, major bleeding at 2.8%, minor bleeding at 10.3%, and transfusion at 2.8%.

Another study with dalteparin evaluated 110 patients who were undergoing PCI received doses of dalteparin 60 or 80 IU/kg alone or followed by abciximab infusion. This study evaluated whether the ACT could be used to monitor IV dalteparin during PCI. In this trial, dalteparin induced a significant rise in the ACT with a smaller degree of variance as compared to UFH. This study had no

### Table 4. LMWH Comparative Studies in PCI

<table>
<thead>
<tr>
<th>Trial/Study</th>
<th>N</th>
<th>Study Population</th>
<th>Outcomes (%)</th>
<th>LMWH vs UFH</th>
</tr>
</thead>
<tbody>
<tr>
<td>REDUCE,54</td>
<td>612</td>
<td>Elective PCI; single lesion</td>
<td>Acute coronary events</td>
<td>At 24 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Major bleeding</td>
<td>2.3 vs 2.6</td>
</tr>
<tr>
<td>CRUISE,52</td>
<td>261</td>
<td>Elective or urgent PCI</td>
<td>D/Mi/Revas at 30 days</td>
<td>8.5 vs 7.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TIMI major</td>
<td>2.5 vs 1.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TIMI minor</td>
<td>4.1 vs 10.5</td>
</tr>
<tr>
<td>Legalery et al,57</td>
<td>584 enox</td>
<td>Unselected PCI</td>
<td>D/Mi/Revas</td>
<td>1.3 vs 2.0</td>
</tr>
<tr>
<td></td>
<td>581 UFH (historical control)</td>
<td></td>
<td>Major bleeding</td>
<td>1.0 vs 0.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hematoma</td>
<td>2.6 vs 1.7</td>
</tr>
</tbody>
</table>

**Abbreviations:** CRUISE, Coronary Revascularization Using Integrilin and Single Bolus Enoxaparin; D, death; LMWH, low-molecular-weight heparin; MI, myocardial infarction; PCI, percutaneous coronary intervention; REDUCE, Reduction of Restenosis After PTCA. Early Administration of Reviparin in a Double-Blind Unfractionated Heparin and Placebo-Controlled Evaluation; Revasc, revascularization; TIMI, Thrombolysis in Myocardial Infarction; UFH, unfractionated heparin.
death or urgent revascularization during the hospital course of the study population. Two of the 96 PCI patients had MI (2.1%), major bleeding with transfusion occurred at a rate of 1.0%, and minor bleeding at a rate of 4.2%. This was the first study to demonstrate that the ACT may be useful in monitoring the anticoagulant effect of IV administered dalteparin during PCI. Similar degrees of elevation of the ACT have been seen with enoxaparin in 26 PCI patients with the ACT at 150 seconds at baseline to 208 seconds post-10 minutes when enoxaparin was given at a dose of 0.5 mg/kg IV bolus.56

One randomized study compared reviparin, another LMWH, to UFH in 612 patients.34 Reviparin (n = 306) was administered as a 7000-U bolus followed by a 10,500-U infusion for 24 hours and a twice-daily 3500-U SQ injection. UFH (n = 306) was given as a 10,000-U bolus followed by a 24,000-U infusion for 24 hours. No GP IIb/IIIa inhibitors were used, and stent implantation was performed only for bailout purposes. The rate of rescue stent implantation on the day of PCI was reduced with UFH compared to reviparin, from 6.9% to 2.0%. However, reviparin did not reduce the composite of ischemic events at 6 months when compared to heparin (1.3% versus 2.0%). Therefore, the agent was not promoted further for this indication.

Another comparative study employed a historical control as a basis for assessing the relative safety and efficacy of enoxaparin in PCI.57 This study compared 584 unselected ACS patient undergoing PCI with enoxaparin versus a historical UFH control group of 581 patients. There were no significant differences between the two groups (Table 4).

Table 5. LMWH Registry Studies in PCI

<table>
<thead>
<tr>
<th></th>
<th>EPISTENT Control (UFH) (N = 809)</th>
<th>NICE-1 (Enox 1 mg/kg) (N = 828)</th>
<th>EPISTENT Treated (UFH + abciximab) (N = 794)</th>
<th>NICE-4 (Enox 0.75 mg/kg + abciximab) (N = 813)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D/MI/Revasc at 30 days</td>
<td>10.8</td>
<td>7.7</td>
<td>5.3</td>
<td>6.8</td>
</tr>
<tr>
<td>TIMI major, all</td>
<td>2.2</td>
<td>1.1</td>
<td>1.5</td>
<td>0.4</td>
</tr>
<tr>
<td>TIMI major non-CABG</td>
<td>1.0</td>
<td>0.5</td>
<td>0.8</td>
<td>0.2</td>
</tr>
<tr>
<td>TIMI minor all</td>
<td>1.7</td>
<td>6.2</td>
<td>2.9</td>
<td>7.0</td>
</tr>
<tr>
<td>Transfusion all</td>
<td>2.2</td>
<td>2.7</td>
<td>2.8</td>
<td>1.8</td>
</tr>
</tbody>
</table>

aThe EPISTENT Investigators, 1998.59
bKereiakes, 2001.51

Abbreviations: CABG, coronary artery bypass graft; D, death; MI, myocardial infarction; Revasc, revascularization; TIMI, Thrombolysis in Myocardial Infarction; MI, myocardial infarction.

A series of registry studies, National Investigators Collaboration on Enoxaparin (NICE),50,51,58 provide the majority of patient exposure to enoxaparin in ACS patients undergoing PCI. The NICE registries are open label and noncomparative in nature and continue to suggest relative equivalence to UFH in ACS patients undergoing elective or urgent PCI.

The primary endpoint of both NICE-1 (1.0 mg/kg IV bolus of enoxaparin) and NICE-4 (0.75 mg/kg enoxaparin plus abciximab) was major bleeding (in-hospital and at 30 days) defined as a drop in hemoglobin ≥5 g/dL, a drop in hematocrit of ≥15%, or intracranial bleeding.51,58 Secondary endpoints included death/MI/revascularization, need for transfusion, and minor bleeding, which was defined as spontaneous and observed hematuria or hematemia, ≥3 g/dL in hemoglobin or hematocrit drop of ≥10%. The investigators found an absolute reduction in the composite endpoint of death/MI/revascularization and in major bleeding compared to the historical UFH control arm of the EPISTENT trial (a trial of similar design). In addition, a corresponding increased absolute risk in minor bleeding and in transfusion rates was also reported for NICE-1 (Table 5). Similar observations were made when results of NICE-4 were compared to the abciximab-treated group of EPISTENT (Table 5).

The NICE-3 registry assessed the safety of enoxaparin in conjunction with one of the three available GP IIb/IIIa antagonists in ACS patients.50 This study also addressed the feasibility of bringing ACS patients treated with enoxaparin to the catheterization laboratory without further anticoagulation using UFH. The NICE-3 study included 661 ACS patients with documented coro-
Anticoagulation for PCI

Table 6. Combined Event Rates (UFH + LMWH)

<table>
<thead>
<tr>
<th>Control (N = 1833)</th>
<th>Treated (N = 1834)</th>
<th>All ACS (616)</th>
<th>PCI only (292)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D/Mi/Revasc at 30 days</td>
<td>10.6</td>
<td>6.2</td>
<td>5.7</td>
</tr>
<tr>
<td>TIMI major, all</td>
<td>1.3</td>
<td>1.25</td>
<td>4.5</td>
</tr>
<tr>
<td>TIMI major non-CABG</td>
<td>NR</td>
<td>NR</td>
<td>1.9</td>
</tr>
<tr>
<td>TIMI minor all</td>
<td>1.7</td>
<td>2.8</td>
<td>25.0</td>
</tr>
<tr>
<td>Transfusion all</td>
<td>1.6</td>
<td>1.9</td>
<td>10.5</td>
</tr>
</tbody>
</table>


Abbreviations: ACS, acute coronary syndrome; CABG, coronary artery bypass graft; D, death; MI, myocardial infarction; NR, not reported; PCI, percutaneous coronary intervention; Revasc, revascularization.

Table 7. LMWH Studies in PCI

<table>
<thead>
<tr>
<th>Trial/Study</th>
<th>N</th>
<th>Study Population</th>
<th>Outcomes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kereiakes et al.56 2001 (dalteparin) 40 IU/kg and 60 IU/kg</td>
<td>103</td>
<td>Elective PCI</td>
<td>D/Mi/Revasc 3.7 Major bleed 2.8 Minor bleed 10.3 Transfusion 2.8</td>
</tr>
<tr>
<td>Choussat,61 2002 (enoxaparin) 0.5 mg/kg IV</td>
<td>180</td>
<td>Elective PCI</td>
<td>D/Mi/Revasc 3.9 Major bleed 0.6 Minor bleed 2.2</td>
</tr>
<tr>
<td>Collet et al.60 2001 (enoxaparin) 1 mg/kg q 12 h</td>
<td>132/451</td>
<td>Unselected population of ACS patients undergoing PCI</td>
<td>D/Mi 3.0 Major bleed 0.8 Minor bleed 2.4</td>
</tr>
</tbody>
</table>

Abbreviations: ACS, acute coronary syndrome; D, death; MI, myocardial infarction; PCI, percutaneous coronary intervention; Revasc, revascularization.
versus patients with normal renal function \( (n = 500) \) (51% versus 22%, \( P < .01 \)). Collet et al\(^{63} \) report that patients with severe renal impairment undergoing angioplasty should have 64% of the standard dose of enoxaparin administered.

Thus, to date, the results of available LMWH studies have yet to provide convincing clinical evidence of the therapeutic benefit of LMWH over and above the use of UFH as a base anticoagulant.

**Direct Thrombin Inhibitors**

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.\(^{64} \) 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%, \( P = .039 \)) when compared to heparin. In addition, there was significantly less major bleeding (3.5% versus 9.3%, \( P < .001 \)), with a 62% relative risk reduction in this endpoint \( (\text{Table 8}) \). Major bleeding was defined as overt bleeding resulting in a hemoglobin drop of \( \geq 3 \text{ g/dL} \), the need for transfusion of \( \geq 2 \text{ U} \), 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%, \( P = .009 \)) and a 73% relative risk reduction for major bleeding\(^{64} \) (2.4% versus 11.8%, \( P < .001 \)).

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.\(^{65-67} \)

The CACHET B/C and REPLACE-1 trials\(^{68,69} \) provide additional preliminary results with bivalirudin in the setting of stents and GP IIb/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.\(^{68,70} \) 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 ab-

### Table 8. Bivalirudin Comparative PCI Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Outcomes (%)</th>
<th>Biv vs UFH</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAT,(^{64} ) 2001</td>
<td>PCI</td>
<td>D/MI/R at 7 days</td>
<td>6.2 vs 7.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Major bleeding</td>
<td>3.5 vs 9.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D/MI/R at 7 days</td>
<td>2.8 vs 7.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Major bleeding</td>
<td>1.4 vs 6.3</td>
</tr>
<tr>
<td>CACHET,(^{70} ) 2002</td>
<td>PCI</td>
<td>D/MI/R at 48 h</td>
<td>5.6 vs 6.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Major bleeding</td>
<td>2.2 vs 2.7</td>
</tr>
<tr>
<td>REPLACE-1,(^{69} ) 2002</td>
<td>PCI</td>
<td>D/MI/R at 30 days</td>
<td>9.2 vs 10.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Major bleeding</td>
<td>7.6 vs 7.1</td>
</tr>
<tr>
<td>REPLACE-2,(^{71} ) 2003</td>
<td>PCI</td>
<td>D/MI/R at 30 days</td>
<td>2.4 vs 4.1</td>
</tr>
</tbody>
</table>

Abbreviations: D, death; MI, myocardial infarction; PCI, percutaneous coronary intervention; R, revascularization.
ciximab (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 trial 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 observed (Table 8).

The REPLACE-2 trial 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 to 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, MI, revascularization, and 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 8). 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 MI (1.5%) and revascularization (9.0%). Although it did not reach statistical significance, the death rate at 6 months and 1 year was numerically lower in the bivalirudin arm compared to 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, suggest that bivalirudin may provide a superior alternative to currently available agents.

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. 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 compared to heparin when used to treat ACS patients, the risk of major bleeding appears greater. 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%).

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.

Argatroban

Argatroban has been evaluated in small clinical trials for a number of uses. Two studies have eval-
uated the use of argatroban for PCI in HIT patients. Fifty patients with a current or historical HIT diagnosis were evaluated by Matthai et al. Patients who required CABG, who were receiving GP IIb/IIIa inhibitors, or had hepatic dysfunction were excluded. Argatroban was administered as a bolus of 350 μg/kg and followed by an IV infusion of 25 to 30 μg/kg/min to maintain an ACT of 300 to 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, acute MI, 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 al.80 evaluated 91 HIT patients undergoing PCI in 3 similarly designed studies. They administered a bolus of 350 μg/kg was followed by an IV infusion of 25 μg/kg/min, with a target ACT of 300 to 450 seconds. Among patients undergoing initial PCI (n = 91), 94.5% had a successful procedure defined as 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 prostatic 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 that 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.81 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.42 These differences may be because of statistical power, but no comparative studies between DTIs exist to establish clear superiority for 1 agent over the other.

There are no data suggesting limitations of argatroban use in patients with renal impairment. However, the use of argatroban use 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 to its half-life in patients with normal hepatic function.82

### Strategies for Treatment

Heparin has been used as the standard anticoagulant in PCI since the 1970s. Its limitations 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 acceptable rate of hemorrhagic complications.

In evaluating optimal strategies for coagulation in PCI, it is important to assess ischemic outcomes and bleeding complications. Assessing bleeding complications between trials is difficult owing to various definitions for major and minor bleeding, such as the definitions used by the GUSTO and the TIMI trials.83,84 Many PCI investigations, including the majority of the LMWH studies, utilize the TIMI definitions for the bleeding endpoint.84

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 ≥3 g/dL drop in hemoglobin, as well as the need for transfusions, have significant adverse implications for the 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.85 There are also some data to suggest that bleeding complications can actually result in ischemic complications.86 Consequently, minor bleeding
events should not be dismissed as an insignificant consequence when evaluating outcomes in clinical trials.

LMWHs represent a theoretical advance in antithrombotic therapy because of their greater pharmacokinetic predictability and reduced propensity to stimulate platelet aggregation. This allows for a simplified administration scheme (SQ injections twice daily rather than continuous IV infusions) for management of ACS patients. Whether these theoretical advantages translate into clinical benefits in PCI remains to be demonstrated. Although there are convincing data that support the use of LMWH in ACS, such data are still lacking in PCI. 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, have been interpreted as indicating that they provide a benefit over UFH. However, critical review of this data suggests that the benefit is limited to being no worse than UFH for ischemic and major bleeding complications. In some investigations, LMWH use has been demonstrated to markedly increase the risk of minor bleeding and transfusion.52,53

Among the available DTIs, 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.

Although the management of anticoagulation in patients treated with SQ LMWH remains unclear, data with bivalirudin suggest that patients receiving either UFH or LMWH prior to PCI may be safely switched to bivalirudin for the PCI procedure. In 1006 patients pretreated with heparin and switched to bivalirudin, Bittl87 found that patients treated with bivalirudin (n = 512) compared to heparin (n = 494) had fewer ischemic events (6.3% versus 9.5%; P = .043) and fewer bleeding complications (4.1% versus 11.9%, p < .001). The significant difference in adverse clinical outcomes may be because of heparin’s inability to effectively inhibit fibrin-bound thrombin in the high-risk ACS population.

Another small pilot study investigated the possibility that bivalirudin may provide an alternative to UFH in PCI for ACS patients initially treated with SQ LMWH. In this open-label trial of 40 patients treated with LMWH for management of ACS, patients were randomized to either UFH or bivalirudin prior to angioplasty. The last dose of LMWH was administered at least 8 hours prior to randomization. Coagulation parameters and adverse events were assessed. Adverse events were found to be comparable between the two groups. One patient in the UFH group had a postprocedure MI; no deaths or major hemorrhages occurred in either group. Coagulation parameters were more predictable in bivalirudin-treated patients compared with the heparin-treated patients, with 2 to 3 times less variability, and returned to a normal level rapidly in patients receiving bivalirudin (L. Wallentin, MD, unpublished data, data on file with The Medicines Co., June 2003). These data suggest that switching from LMWH to bivalirudin for PCI procedures is feasible and may be advantageous. However, additional investigations are needed to confirm these preliminary results.

Summary

The evidence supporting the superiority of LMWH over UFH in the non-PCI setting is overwhelming. However, the data favoring the use of LMWH over UFH during PCI are more limited. 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 theory, benefits and advantages of LMWH in PCI should be similar to that observed in non-PCI. The use of LMWHs via IV administration allows for the achievement of a rapid and controlled anticoagulation during PCI. Contrary to traditional belief, recent studies suggest that the level of anticoagulation induced by LMWHs can in fact be measured using the standard ACT test.15 In addition, LMWH does not appear to activate platelets, thereby potentially reducing the need for administration of concomitant glycoprotein IIb/IIIa inhibitors. Such a reduction could lead to reduced bleeding and costs associated with PCI. LMWHs, unlike DTIs, are at least partially reversible with protamine. As a re-
sult, LMWH agents appear to represent an anticoagulation option during PCI. This needs further investigation to ascertain their relative benefit in comparison to UFH, as well as to novel DTIs, such as bivalirudin.

In contrast to LMWH, the advantages of the DTI, bivalirudin, have been well established. In particular, the REPLACE-2 trial demonstrated the unequivocal superiority of the DTI, bivalirudin, compared to UFH in PCI. Thus, at present, a stronger case can be made in favor of bivalirudin than LMWH to replace UFH. Whether or not DTI is superior to LMWH in patients undergoing PCI has not been established. A head-to-head randomized double blind clinical trial of bivalirudin versus a high-dose IV bolus of LMWH in PCI (ideally with ACT guidance) would be of interest to the cardiovascular and interventional communities.

Table 9

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Population</th>
<th>Outcomes (%)</th>
<th>Biv vs UFH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adamian,91 2002</td>
<td>28</td>
<td>Renal impaired</td>
<td>CIN</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Baseline Cr 1.9 + 0.7 mg/dL</td>
<td>Major vascular complications</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>undergoing PCI</td>
<td>Bleeding comps</td>
<td>0</td>
</tr>
<tr>
<td>Adamian,92 2002</td>
<td>146</td>
<td>Diabetes undergoing PCI</td>
<td>Major vascular comps</td>
<td>0 vs 1.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Transfusion</td>
<td>1.4 vs 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hematoma</td>
<td>0 vs 1.4</td>
</tr>
<tr>
<td>Cho,93 2003</td>
<td>162 biv</td>
<td>Elective or urgent PCI</td>
<td>D/MI/R at 120 days</td>
<td>4.2 vs 12.7</td>
</tr>
<tr>
<td></td>
<td>172 historical heparin</td>
<td></td>
<td>Bleeding</td>
<td>4.3 vs 6.4</td>
</tr>
</tbody>
</table>

Abbreviations: biv, bivalirudin; Cr, creatinine; D, death; MI, myocardial infarction; PCI, percutaneous coronary intervention; R, revascularization.

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