

# **Heparin-induced Thrombocytopenia (HIT) in Cardiovascular Medicine**

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## Abbreviations/Glossary

<i>ACS</i>	<i>acute coronary syndromes, includes unstable angina, heart attack</i>	<i>HIT</i>	<i>heparin-induced thrombocytopenia, a reduced platelet count in patients given heparin</i>
<i>ACT</i>	<i>activated clotting time, a measure of how fast blood clots</i>	<i>HITTS</i>	<i>heparin-induced thrombocytopenia and thrombosis syndrome, a more severe form of HIT</i>
<i>aPTT</i>	<i>activated partial thromboplastin time, a measure of how fast blood clots</i>	<i>IL-8</i>	<i>interleukin 8, a protein signaller involved in the immune system</i>
<i>ADP</i>	<i>adenosine diphosphate, a substance that can bind to and activate platelets</i>	<i>LMWHs</i>	<i>low-molecular-weight heparins, a variation of standard heparin</i>
<i>DVT</i>	<i>deep-vein thrombosis, clotting within the major veins</i>	<i>MI</i>	<i>myocardial infarction, heart attack</i>
<i>ELISA</i>	<i>enzyme-linked immunosorbent assay, a laboratory test for HIT</i>	<i>NAP-2</i>	<i>neutrophil-activating peptide, a protein that influences the immune system</i>
<i>FDA</i>	<i>the U.S. Food and Drug Administration, which approves drugs for sale in the U.S.</i>	<i>PAT</i>	<i>platelet-aggregation test, a laboratory test for HIT</i>
<i>GP IIb/IIa</i>	<i>glycoprotein IIb/IIa, a receptor within the surface membranes of platelets</i>	<i>PCI</i>	<i>percutaneous coronary intervention, includes angioplasty, stents, atherectomy</i>
<i>HAT</i>	<i>heparin-associated thrombocytopenia, former name for HIT</i>	<i>PF4</i>	<i>platelet factor 4, a protein involved in the development of HIT</i>
<i>HIPA</i>	<i>heparin-induced platelet-activation assay, a laboratory test for HIT</i>	<i>SRA</i>	<i>serotonin-release assay, a laboratory test for HIT</i>

# 1 Historical Perspectives

Physicians in general, and cardiologists in particular, are increasingly facing the problem of heparin-induced thrombocytopenia (HIT), the complications of which can be severe or life threatening. This white paper describes the incidence of this problem and methods used in its prevention and treatment.

## 1.1 Heparin

Heparin, discovered in 1916, has been used as an anticoagulant since the late 1930s. It has become the cornerstone of therapy for many venous and arterial thrombotic (clot-caused) disorders. In the United States alone, more than 12 million patients receive heparin each year.<sup>1</sup>

In cardiology, heparin is a key element in the treatment of the acute coronary syndromes (ACS), which range from unstable angina to heart attack (acute myocardial infarction [MI]). It also plays a critical adjunctive role in percutaneous and surgical coronary interventions.<sup>2,3</sup> Many patients also receive heparin for treatment of irregular heart rhythms, valvular disease, deep-vein thrombosis (DVT), clots in the lungs (pulmonary emboli), and as a preventive measure with surgery.

When patients arrive at the hospital with ACS, heparin therapy begins almost immediately. Heparin is required for both of the typical treatment strategies for patients with acute MI: intravenous thrombolytic ("clot-busting") therapy, and percutaneous coronary intervention (PCI), which includes angioplasty, stent implantation, or both.<sup>3</sup> Patients with coronary disease may have repeat hospital admissions for treatment of ACS or repeat PCI and therefore may have many exposures to heparin.

As early as 1942, however, Copley and Robb noted a decrease in the platelet count (thrombocytopenia) in the blood of dogs treated with heparin.<sup>4</sup> Eventually, clinically significant thrombocytopenia was reported in people treated with heparin.<sup>5</sup> In 1958,

Weismann and Tobin noted thrombotic complications in patients who were given heparin.<sup>6</sup> Such complications can include blood clots in the arms or legs (thrombus), pulmonary emboli, chest pain from clot-obstructed coronary arteries, and myocardial or cerebral infarction.

Rhodes and colleagues proposed that the thrombocytopenia related to heparin use was connected with the thrombotic events seen in heparin-treated patients.<sup>7</sup> In 1976, Bell and colleagues conducted the first prospective study to investigate the incidence of thrombocytopenia during heparin therapy in humans.<sup>8</sup> Since this work, our understanding of heparin-induced thrombocytopenia and its complications has expanded greatly.

## 1.2 Incidence of HIT

Heparin-induced thrombocytopenia has 2 distinct clinical forms. The milder and more common form, type I, can occur in up to 35% of patients, typically within the first few days of treatment.<sup>9,10</sup> This type usually is not associated with thrombotic complications and can resolve even if heparin treatment continues.

Type II HIT occurs less often but can be associated with life-threatening complications. It typically appears after 4 to 5 days of heparin treatment, sometimes earlier if the patient has received heparin before.<sup>11</sup> One prospective study defined HIT as a platelet count of  $<150,000/\text{mm}^3$  (the normal platelet count is  $150,000\text{--}300,000/\text{mm}^3$ ) occurring  $\geq 5$  days after the start of standard heparin therapy, with antiheparin antibodies also being present.<sup>12</sup> In all, 3.3% of the 332 patients, who were receiving the heparin after elective hip surgery, fulfilled this definition.

Type II HIT often is associated with thrombotic complications. For example, 8 of the 9 patients with type II HIT in the 332-patient study (89%) also suffered a thrombotic event.<sup>12</sup> More recently, 2 studies have shown rates of thrombotic complications of 39%–52% within 30 days

after a diagnosis of HIT.<sup>13,14</sup> This situation is sometimes referred to as HITTS (heparin-induced thrombocytopenia and thrombosis syndrome).

Thrombotic complications can range from venous blood clots to a severe form of HIT-related thrombosis known as "white-clot syndrome," which involves widespread clotting within the arteries and veins. This syndrome is rare, occurring in about 0.6% of patients who develop type II HIT, but confers a 20% risk of limb amputation and up to 30% mortality.<sup>15-18</sup>

The incidences of both types of HIT may be increasing, because of the greater use of procedures requiring adjunctive heparin treatment and the fact that patients now are living long enough to undergo many such procedures.<sup>19</sup> Although there is no firm evidence that previous heparin exposure will predispose patients to develop HIT,<sup>20</sup> small studies have noted that patients with previous exposure to heparin may develop HIT sooner after heparin therapy begins than patients with no previous heparin exposure.<sup>16,21-24</sup>

### 1.3 Type I HIT

As noted above, type I HIT (also known as heparin-associated thrombocytopenia, or HAT) is relatively common, occurring in up to 1 in 3 patients. It is associated with mild

thrombocytopenia (100,000–150,000/mm<sup>3</sup>) that typically emerges within the first 4 days of heparin therapy (**Table 1**).<sup>19</sup> It often resolves even when heparin therapy continues.<sup>14,25</sup> Type I HIT occurs most often in patients receiving high doses of heparin and rarely occurs at lower doses, such as those used to flush intravenous lines. The mechanism for this type of HIT is thought to reflect the direct effect of heparin on platelets, resulting in reversible clumping and removal from the circulation. No major adverse effects have been reported in connection with type I HIT, and this condition is generally benign. Patients still should be monitored, however, for progression from type I to type II HIT.

### 1.4 Type II HIT

#### 1.4.1 Description

Type II HIT is a more severe form of thrombocytopenia, with platelet counts often <100,000/mm<sup>3</sup>. The disorder is much more rare and occurs in only 2%–7% of patients.<sup>25</sup> The reduction in platelets usually occurs 5–14 days after heparin therapy begins, but it can occur earlier in patients who have been given heparin within the previous 3 months (**Table 1**).<sup>11,19</sup>

**Table 1. Characteristics of Type I versus Type II HIT**

Characteristic	Type I	Type II
Mechanism	Nonimmune	Immunological reaction
Reduction in platelet count	Mild	Severe (↓ by 50%)
Onset	Early (<4 days after exposure)	Delayed (>4–5 days after exposure)*
Persistence	Resolves, even if heparin continued	Resolves with heparin discontinuation
Thrombosis	Rare	Common
Symptoms	None	Possibly life-threatening

\*Unless previous exposure to heparin within 3 months, which can result in earlier onset because of immune memory.<sup>11</sup> Adapted from Brieger et al.<sup>19</sup>

In contrast to type I HIT, type II HIT can be provoked by any amount of heparin exposure, including heparin flushes and subcutaneous doses, and thrombocytopenia can persist until all heparin exposure has been removed.<sup>14,25</sup>

Type II HIT is mediated by an antibody that causes activation and destruction of platelets, which can result in severe thrombotic complications and high mortality. The remainder of this paper will focus on this type of HIT.

#### 1.4.2 Mechanism

**Figure 1** displays a schematic representing the possible mechanism of HIT development.<sup>26,27</sup> First, platelets store a positively-charged protein, platelet factor 4 (PF-4), within their alpha granules.<sup>28</sup> This molecule, which also is present on the inner surface of blood vessels and free in the circulation, has great affinity for heparin. Binding of PF4 with heparin promotes the formation of antibodies to the PF4-heparin complex and triggers the immune response.<sup>29-31</sup> Most of the antibody formed is of one subclass (IgG), but other subclasses (IgM and IgA) also have been reported in type II HIT.<sup>32,33</sup> These antibodies can react with other substances, such as dextran or low-molecular-weight heparins (LMWHs), which becomes important when a patient requires alternative anticoagulation.

Some patients with HIT have antibodies not to the PF4-heparin complex but to interleukin-8 (IL-8) or neutrophil-activating peptide (NAP-2). Whether these antibodies are produced in response to heparin exposure is unknown, but IL-8 and NAP-2 are structurally similar to PF4 and thus may induce an immune response similar to that induced by the PF4-heparin complex.<sup>34</sup> This may explain the thrombocytopenia and thrombosis in heparin-treated patients despite a lack of antibodies to PF4-heparin complexes.

In any event, the PF4-heparin-antibody complex then binds to circulating platelets via Fc receptors on the platelet surface.<sup>35</sup>

Most Fc receptors are of the  $\gamma$ R1IA subtype and seem to have great affinity for the immune complex, but this has not been directly measured and quantified.<sup>36,37</sup> The binding of the immune complex to platelets causes cross-linking of Fc receptors on the platelets and strong platelet activation. Activation of platelets by any mechanism, including that involved in HIT, results in platelet aggregation and clot formation.

The PF4-heparin-antibody complexes also can bind to cells on the inner surfaces of blood vessels (vascular endothelium), through heparin-like molecules (glycosaminoglycans) on the surface. Such binding activates the endothelial cells to release prothrombotic substances.<sup>38</sup> Through this mechanism, patients with HIT antibodies but a normal platelet count still may develop HIT-related thrombosis.

#### 1.4.3 Genetic Variations and Susceptibility to HIT

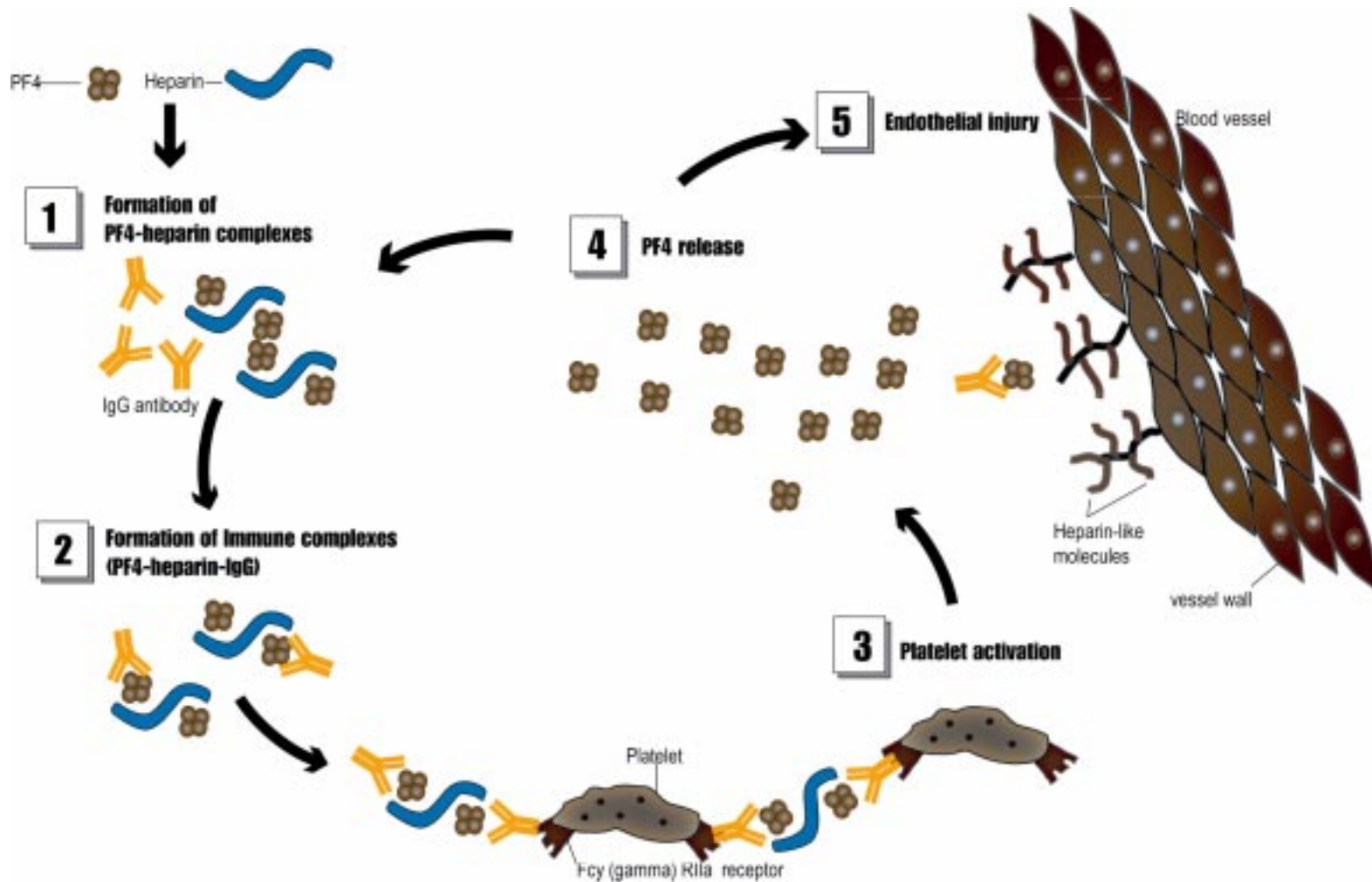
The key step in the development of HIT is the binding of the PF4-heparin-antibody complex to the Fc receptor on the platelet. In several small studies, genetic variations in the subtype of the Fc receptor<sup>39</sup> have correlated with both the likelihood and severity of HIT.<sup>37,40</sup>

The genetic variation delays the clearance of the immune complexes from the circulation, translating into longer activation of endothelial cells and platelets and thus an increased risk of thrombotic complications. More work is needed to further elucidate a genetic factor contributing to HIT.

### 1.5 Diagnosis of HIT

Physicians are likely to underdiagnose HIT in clinical practice.<sup>27</sup> The lack of routine, automated platelet counting until the mid-1970s may have prevented earlier recognition of the syndrome. Unfortunately, almost 50% of the patients with HIT are

Figure 1. Possible pathway for development of HIT/HITTS



Heparin induces mild platelet activation, causing platelets to release PF4 into the circulation. PF4 forms a complex with heparin (1), against which the body produces antibodies (2). The antibody tails of the PF4-heparin-antibody complex bind to the Fcγ1a receptor of platelets (3) and cause cross-linking and strong platelet activation, resulting in release of more PF4 (4) and of substances that promote clotting. The antibodies also attack PF4 bound to heparin-like molecules on the inner surface of blood vessels (5), resulting in injury to the vessel wall and further clotting. Adapted from Aster<sup>26</sup> and Warkentin.<sup>27</sup>

diagnosed only after a thrombotic complication has occurred.

HIT should be diagnosed first on clinical grounds (**Table 2**)<sup>41</sup> and then confirmed by laboratory testing (**Table 3**).<sup>42</sup> Therapy should not be delayed while awaiting the test results. The foundations for the diagnosis are:

- new thrombocytopenia (<100,000/mm<sup>3</sup> or a >50% decline from pre-heparin counts),
- exposure to heparin in the appropriate time window, and,
- exclusion of other causes of thrombocytopenia.<sup>9,12,42</sup>

Clinicians always must suspect HIT if the patient has received even the smallest amount of heparin.

HIT must be differentiated from thrombocytopenia caused by other drugs. With quinine derivatives, β-lactam antibiotics, and sulfa drugs, for example, the drug can bind to the platelet GP IIb/IIIa receptor, and antibodies can be produced against this drug-receptor complex.<sup>43,44</sup> Other drugs can cause thrombocytopenia by stimulating, directly or indirectly, the production of antiplatelet antibodies.<sup>45,46</sup> Finally, the antiplatelet drug, abciximab, is itself an antibody to the platelet GP IIb/IIIa

receptor. Severe thrombocytopenia (<50,000/mm<sup>3</sup>) has been reported with this drug, although the precise mechanism is unclear.<sup>47,48</sup> Because many cardiovascular patients with thrombocytopenia receive GP IIb/IIIa inhibitors simultaneously with heparin, identifying the responsible drug (if any) can be difficult.

Laboratory diagnosis of HIT can be made by 2 classes of assays, the functional (or activation) assays and immunoassays (**Table 3**).<sup>27,49,50</sup> The functional assays measure heparin-induced, antibody-specific platelet activation *in vitro*, and include the <sup>14</sup>C serotonin-release assay (SRA), the heparin-induced platelet-activation assay (HIPA), and the platelet-aggregation test (PAT). Flow cytometry also has been used as a functional assay to detect type II HIT antibodies.<sup>51,52</sup>

In the <sup>14</sup>C SRA, serum from a patient with possible HIT is incubated with heparin and radioactively labeled platelets from a normal donor. If the HIT antibodies are present, they activate the platelets to release radiolabeled <sup>14</sup>C from their dense granules, which is then measured. This assay is very sensitive and specific (both >90%) but is technically demanding and is used more as a research tool than as a clinical assay.<sup>49,53</sup>

**Table 2. Diagnostic Criteria for HIT**

Clinical	Immunological
New, unexpected thrombocytopenia within the appropriate time frame	Heparin-dependent, platelet-activating HIT antibodies
Thrombosis (controversial)	Antibodies against the PF4/heparin complex (or heparin/IL-8 or heparin/NAP-2 complexes)
Heparin-induced skin lesions	
Acute systemic reaction after intravenous heparin bolus	

Reprinted from Warkentin.<sup>27</sup>

**Table 3. Diagnostic Tests for HIT Antibodies**

Test	Advantages	Drawbacks
<sup>14</sup> C Serotonin-release assay (SRA)	↑ sensitivity	washed platelets (technically demanding), needs radioactivity
Platelet aggregation test (PAT)	rapid, simple	↓ sensitivity, unsuitable for testing multiple samples
Heparin-induced platelet aggregation test (HIPA)	rapid, ↑ sensitivity	washed platelets (technically demanding)
ELISA	↑ sensitivity, also detects IgA and IgM	↑ cost, ↓ specificity for clinically significant HIT

Adapted from Warkentin.<sup>42</sup>

The HIPA is a similar assay, using platelets from normal donors. The test is positive when the patient's serum induces clumping of platelets from many donors, in at least 2 different concentrations of heparin. The HIPA's sensitivity and specificity are similar to those of the SRA only if several donors are used, the platelets are washed, and a positive control is available.<sup>54</sup> It is much easier to perform than the SRA, however, and results are rapidly available.

With the PAT, platelet-rich plasma from normal donors is incubated with the patient's serum and heparin. In type II HIT, platelets in the assay will clump in heparin but not in buffer solution.<sup>54,55</sup> Because it is simple, this assay is widely used, but it has low sensitivity (30%–50%). Sensitivity can be improved by using washed platelets, donors with platelets known to be highly sensitive to HIT antibodies, and adequate heparin concentrations in the assay. Specificity can be improved by showing that platelet clumping is inhibited in high concentrations of heparin.<sup>54,56</sup>

The second class of assay for HIT is the immunoassay, ie, an enzyme-linked immunosorbent assay (ELISA). This test measures antibodies (IgG, IgA, and IgM subclasses) that bind to the PF4-heparin complexes adsorbed onto the wells of microtiter plates. The ELISA's sensitivity is nearly 90%;<sup>57,58</sup> thus the assay can detect

weaker antibodies, such as IgA and IgM, that usually are not detected by the functional assays. The functional assays, on the other hand, can detect HIT antibodies to targets other than the heparin-PF4 complex, such as IL-8 and NAP-2, although there is controversy about this issue.<sup>34</sup>

Given the strengths and weakness of both types of tests, most laboratories use both. A functional assay is recommended for initial screening, reserving use of the ELISA for patients with a strong suspicion of HIT but negative results on functional assay. Since neither class of test has 100% sensitivity, the use of complementary assays improves the ability to make the correct diagnosis.<sup>53,59</sup>

## 1.6 Outcomes of HIT

The most severe complications of HIT are thrombotic events, which can be arterial or venous, local or widespread.<sup>13</sup> Venous clotting is most common, occurring in roughly a 4:1 ratio to arterial events,<sup>27</sup> and includes pulmonary embolism and DVT.<sup>13</sup> Other venous events include cerebral sinus thrombosis and adrenal-vein thrombosis, which leads to adrenal bleeding and the Waterhouse-Friedrickson syndrome.<sup>60-64</sup> Patients with this complication may have adrenal crisis and refractory hypotension.

Arterial thromboses can affect the arms, legs, brain, and heart, and other large and small systemic arteries. They occur most often at sites of previous vascular injury or



abnormality,<sup>65-67</sup> such as sites of arteriosclerosis and vascular puncture sites. Coronary thrombosis is not uncommon after PCI in patients with undiagnosed HIT, due to vascular injury from the angioplasty balloon or coronary stent.

Other complications relate to the heparin itself: skin lesions, acute systemic reactions, and transient global amnesia. The skin lesions most often are areas of redness or dead tissue at sites where heparin was given.<sup>68,69</sup> Patients who develop a skin reaction to heparin are 30% more likely to develop clinically significant HIT than patients without skin lesions, and those with skin lesions who develop HIT are much more likely to have thrombotic complications.<sup>68,69</sup>

Acute systemic reactions include fever/chills, faster heart rate, increased blood pressure, rapid and labored breathing, chest pain, sweating, nausea, vomiting, and diarrhea.<sup>27</sup> Some patients develop symptoms that mimic a pulmonary embolism, such as severe difficulty in breathing, after heparin is given.<sup>70</sup> Continuing systemic heparin in HIT patients with this complication, called "pseudo-pulmonary embolism," can be fatal.<sup>71</sup>

In 1994, Warkentin et al. reported on 2 patients, later discovered to have HIT, who developed transient global amnesia after they had received a large, intravenous dose of heparin. Both patients lost the ability to form memories, but they recovered within 24 hours. The investigators speculated that metabolic or ischemic disturbances spurred by the abrupt and marked platelet activation of HIT produced the temporary amnesia in these patients.<sup>72</sup> There have been no further reports of this phenomenon, however.

In summary, serologic HIT is not uncommon, but the proportion of HIT patients who go on to develop the most severe complications is quite small (0.6% in 1 series).<sup>12,18,73</sup> Much research is aimed at identifying the clinical and biochemical factors that can predict patients at higher risk of HIT complications, but for now,

clinicians should assume that all HIT patients are at high risk.

## 1.7 Management of HIT

Two goals take priority in the management of patients with HIT: to remove the antigenic stimulus and to prevent thrombotic complications. Achieving the first goal is fairly straightforward; it requires that all forms of heparin be removed immediately from the patient's system, including intravenous flushes and coated catheters.

Achieving the second goal requires something more than just stopping heparin.<sup>14</sup> First, the activated platelets and endothelial cells continue to induce clotting long after heparin is discontinued. Second, patients who develop HIT had been receiving an anticoagulant for an underlying condition (such as DVT, pulmonary embolism, ACS, or percutaneous or surgical cardiac interventions) that still may require treatment. These 2 factors direct the use of alternative anticoagulants.

## 2 Alternatives to Heparin

There are several alternatives to heparin for anticoagulation, but most of them are not appropriate for patients with HIT. This section summarizes the mechanisms, relative benefits, and risks of other available anticoagulants (**Table 4 and Figure 2**).

### 2.1 Low-molecular-weight Heparins (LMWHs)

The LMWHs, which include enoxaparin, dalteparin, nadroparin, fraxiparin, and tinzaparin, are formed by the depolymerization (fractionation) of standard heparin. In general, the LMWHs have several advantages over standard, unfractionated heparin: they produce more predictable anticoagulation, they do not result in platelet activation, monitoring is not required, and they are less likely to cause HIT. In fact, 1 study has reported *higher* platelet counts among 430 patients receiving preventive enoxaparin for general, thoracic, or orthopedic surgery, significantly

higher in some cases,<sup>74</sup> with no increase in thrombotic complications.

The LMWHs have been shown to be at least as good as unfractionated heparin for unstable angina, non-Q-wave MI, and PCI, and as an adjunct to thrombolysis.<sup>74-86</sup> In long-term follow-up, the data continue to show a benefit of enoxaparin over standard heparin and of dalteparin over placebo in PCI for acute coronary syndromes, and enoxaparin also has been shown to be cost-effective.<sup>75,80,81</sup>

Unfortunately, the LMWHs share much of their structure with heparin.<sup>87,88</sup> Thus, when a patient develops HIT with standard heparin, the LMWHs cannot be considered an alternative because of the high rate of cross-reactivity (~80%).<sup>89-93</sup>

## 2.2 Warfarin

Warfarin (Coumadin®, DuPont) is not useful in acute management of HIT for 2 reasons. First, it has very slow onset of action, typically 3–5 days. Second, and more important, it has been associated with a syndrome called "venous limb gangrene."<sup>94,95</sup> This syndrome results in a loss of arterial pulses, death of the tissue in the arm or leg, and (often) amputation.

Patients with HIT who receive warfarin and develop venous limb gangrene have been reported to have more thrombin generation and less protein C activity than control subjects, which may reflect a disturbance in the coagulant-anticoagulant balance that occurs during warfarin therapy in patients with HIT.<sup>95</sup> This imbalance may have more severe consequences in patients with HIT, because they already have increased thrombin generation, and released platelet microparticles induce coagulation. Further, warfarin may inhibit protein C synthesis more than it inhibits the synthesis of prothrombin or factor IX, which may worsen HIT and actually promote thrombosis in HIT patients.<sup>96</sup> Of note, venous limb gangrene occurs most often in patients receiving high doses of warfarin. Those receiving lower doses have a much lower incidence.<sup>96</sup>

Although warfarin has no role in the short-term management of HIT, it often is useful in long-term therapy for its complications.

## 2.3 Danaparoid

Danaparoid (Organon®, Organon Inc. USA) is a heparin-like compound that has been used successfully to treat HIT.<sup>27,97-103</sup> It is a mixture of glycosaminoglycans obtained from the intestinal tract of pigs. It contains no heparin fragments and has a structural backbone different from that of either standard heparin or LMWHs. Danaparoid exerts its antithrombotic effect mainly by antithrombin III inhibition of factor Xa, with minor anti-IIa activity.<sup>98,100</sup> It profoundly inhibits fibrin formation but has no antiplatelet or fibrinolytic activity. *In vitro*, danaparoid specifically inhibits platelet clumping induced by the HIT antibody, which offered a therapeutic advantage over the other agents available when it was introduced.

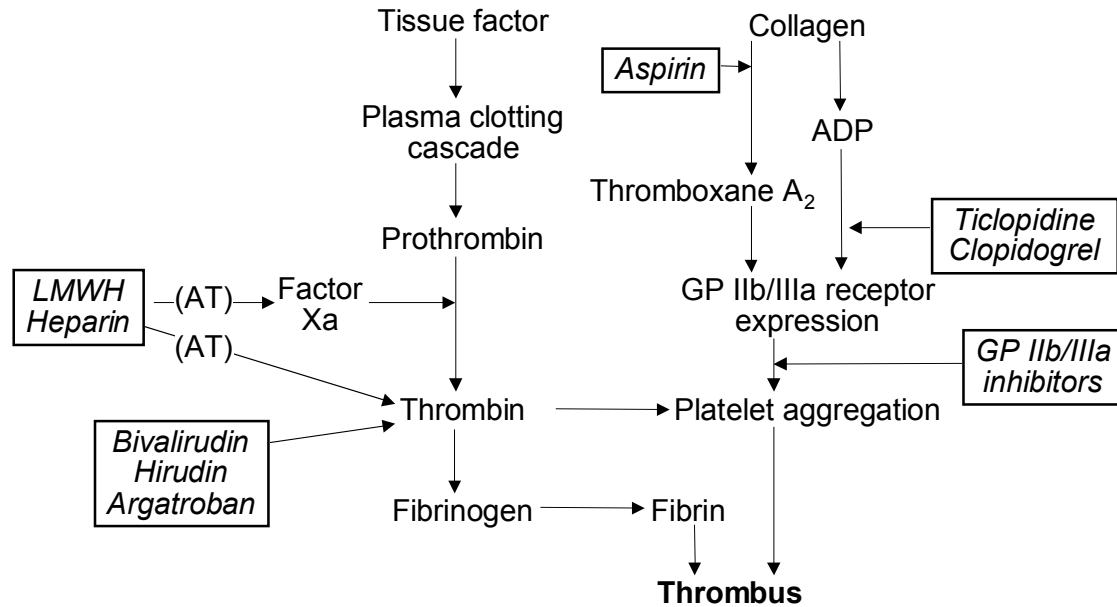
The cross-reactivity rate with heparin, however, is 10%–20%,<sup>97,99,103</sup> and the absence of cross-reacting antibodies to danaparoid in laboratory testing does not necessarily make the drug safe for use in HIT patients. Danaparoid also has a very long half-life, can be given only intravenously, and must be monitored with anti-factor Xa levels. There is no acceptable reversal agent for danaparoid.<sup>98,100</sup>

Nonetheless, before newer anticoagulants emerged (see below), danaparoid was the therapy of choice for HIT patients, and is approved in some countries for this use.<sup>27</sup> For patients with HIT undergoing PCI, however, there have been only case reports describing the use of danaparoid with abciximab.<sup>104,105</sup> Given the better alternatives available, danaparoid is no longer widely used in HIT and is not used during PCI.

**Table 4. Comparison of Heparin Alternatives**

<b>Drug</b>	<b>Advantages</b>	<b>Disadvantages</b>
Warfarin	<ul style="list-style-type: none"> <li>• No cross-reactivity</li> </ul>	<ul style="list-style-type: none"> <li>• Venous limb gangrene</li> <li>• Slow onset</li> </ul>
LMWHs	<ul style="list-style-type: none"> <li>• None</li> </ul>	<ul style="list-style-type: none"> <li>• High cross-reactivity</li> </ul>
Ancrod	<ul style="list-style-type: none"> <li>• Rapid anticoagulation</li> <li>• No cross-reactivity</li> </ul>	<ul style="list-style-type: none"> <li>• Unpredictable anticoagulation effect</li> <li>• Does not inhibit thrombin</li> <li>• Slow onset of action</li> <li>• No FDA-approved indication</li> </ul>
Danaparoid	<ul style="list-style-type: none"> <li>• Monitor with anti-Xa levels</li> <li>• Some available data and clinical experience</li> </ul>	<ul style="list-style-type: none"> <li>• 10%-20% cross-reactivity</li> <li>• No reliable reversal agent</li> <li>• Indirect thrombin inhibitor</li> <li>• Long half-life</li> <li>• Slow onset of action</li> </ul>
Argatroban	<ul style="list-style-type: none"> <li>• Direct thrombin inhibitor</li> <li>• No cross-reactivity</li> <li>• Not immunogenic</li> <li>• Rapid anticoagulation</li> <li>• Monitor with aPTT or ACT</li> </ul>	<ul style="list-style-type: none"> <li>• Hepatic clearance</li> <li>• No reversal agent</li> <li>• Long half-life</li> <li>• Unpredictable anticoagulant response</li> </ul>
Lepirudin	<ul style="list-style-type: none"> <li>• Direct thrombin inhibitor</li> <li>• No cross-reactivity</li> <li>• Rapid anticoagulation</li> <li>• Short half-life</li> <li>• Monitor with aPTT</li> <li>• Predictable anticoagulant response</li> </ul>	<ul style="list-style-type: none"> <li>• Can develop antibodies</li> <li>• Renal clearance</li> <li>• No reversal agent</li> <li>• Long half-life</li> </ul>
Bivalirudin	<ul style="list-style-type: none"> <li>• Direct thrombin inhibitor</li> <li>• No cross-reactivity</li> <li>• Short half-life</li> <li>• Rapid anticoagulation</li> <li>• Predictable anticoagulant response</li> <li>• Not immunogenic</li> <li>• Monitor with aPTT or ACT</li> </ul>	<ul style="list-style-type: none"> <li>• No reversal agent</li> </ul>

**Figure 2. Targets for Antithrombotic Therapies**



ADP, adenosine triphosphate.

## 2.4 Ancrod

Ancrod (Arvin®, Knoll Pharmaceuticals) is a defibrinogenating agent extracted from the venom of the Malayan pit viper.<sup>106,107</sup> It cleaves the  $\alpha$ -chain of fibrinogen-releasing fibrinopeptide A, thus producing an abnormal fibrin molecule. The abnormal molecules are rapidly cleared from circulation by macrophages and monocytes (the reticuloendothelial system) and by activation of the fibrinolytic system. Ancrod has been used to treat HIT in an uncontrolled trial in Europe and Canada,<sup>106</sup> but it is not recommended for treatment of acute HIT because of the better available alternatives.<sup>107</sup> Ancrod does not inhibit thrombin generation in all patients, and it takes a prolonged time to produce anticoagulation. It must be given slowly over 12–24 hours to suppress fibrinogen levels sufficiently and avoid formation of thrombi that could inhibit clearance. Most important, fibrin inhibition is unpredictable with Ancrod, and maintaining a safe and effective range of anticoagulation is difficult. Finally, because Ancrod is a foreign protein,

patients can develop antibodies and resistance to this agent after prolonged use.<sup>106,107</sup>

## 2.5 Antiplatelet agents

Most thrombotic complications of HIT result from platelet activation and thrombin generation. The discontinuation of heparin stops the generation of antibodies, but activated platelets and increased thrombin levels continue to promote thrombosis (**Figure 2**). Drugs that block the platelet adenosine diphosphate (ADP) or GP IIb/IIIa receptor theoretically could play a role in the treatment of patients with HIT.

The effects of ADP receptor blockers (such as ticlopidine [Ticlid®, Roche Labs] and clopidogrel [Plavix®, Sanofi-Synthelabo]) in HIT have been investigated mostly *in vitro* to date.<sup>108,109</sup> One study compared the effects of ticlopidine versus the GP IIb/IIIa inhibitor GPI 562 on 5 HIT-positive serum samples, 5 HIT-negative samples, and 4 donor platelet samples.<sup>108</sup> The effects on platelet aggregation were dose-dependent and similar between the agents. One patient who had been given ticlopidine 250 mg/day

also showed similar results *ex vivo*. In a comparison of the ADP receptor blocker AR-C66096, the GP IIb/IIIa inhibitor lamifiban (Hoffman-LaRoche), and the thromboxane receptor blocker daltroban (Bristol-Myers Squibb) on the serum from 11 patients with HIT, the ADP receptor blocker and lamifiban both blocked platelet aggregation, but daltroban had no effect.<sup>109</sup>

Several investigators have explored the use of GP IIb/IIIa inhibitors in patients with HIT,<sup>110-112</sup> although no randomized, controlled trials have been conducted. One case series has compared the use of a GP IIb/IIIa inhibitor plus a thrombin inhibitor versus historical controls given a thrombin inhibitor alone.<sup>110</sup> Despite being given a lower dose of thrombin inhibitor, the 3 patients who received combination therapy all recovered completely with no increase in bleeding or thrombotic complications. Further clinical trials of combination therapy are needed before the use of any antiplatelet agent can be recommended for treatment of patients with HIT.

## 2.6 Direct Thrombin Inhibitors

Because of the disadvantages of the other heparin alternatives, the best choice for anticoagulation in patients with HIT may be the direct thrombin inhibitors.<sup>113-123</sup> These drugs offer therapeutic advantages over alternative anticoagulants in that they neutralize excess thrombin generated by the HIT antibody-platelet complex and provide therapeutic anticoagulation for the underlying condition. These compounds have no similarities with heparin, LMWHs, or heparanoids such as danaparoid and thus pose no risk of cross-reactivity. Finally, they provide reliable, predictable anticoagulation. The direct thrombin inhibitors that have undergone the most study are argatroban, lepirudin/desirudin, and bivalirudin. Other such agents include efegatran, inogatran, and melagatran.

### 2.6.1 Argatroban

Argatroban (formerly Novastan®, Texas Biotechnology/GlaxoSmithKline) is a

reversible, direct, and selective synthetic thrombin inhibitor.<sup>113-115</sup> This small-molecule (527 Da) derivative of arginine reversibly binds to the catalytic site of thrombin. It has no similarity with heparin, so it does not cross-react with HIT antibodies.

Anticoagulation may be monitored simply with activated partial thromboplastin times (aPTT). The drug binds equally to both clot-bound and free thrombin and has a relatively short half-life (39–51 min). Argatroban is excreted normally even in patients with renal impairment. It is metabolized by the liver, however, and it should be used cautiously in patients with hepatic disease. The drug shows a predictable dose response and rapid anticoagulant effects, and the coagulation system rapidly returns to normal when therapy is stopped.<sup>113-115</sup>

A multicenter trial of 160 patients with HIT and 144 patients with HITTS compared argatroban therapy with 193 historical control patients treated with different agents. Argatroban reduced thrombotic events and death from thrombotic complications at 30 days with no increase in bleeding.<sup>114,124</sup> In June 2000, the U.S. Food and Drug Administration (FDA) approved argatroban as an anticoagulant for prevention or treatment of thrombosis in patients with HIT.

Argatroban also has been evaluated for PCI in 2 trials of patients with HIT (total n=50).<sup>125,126</sup> Of note, although GP IIb/IIIa inhibitors often are used in PCI today, the studies did not include these drugs. Patients received a bolus dose of argatroban to reach an activated clotting time (ACT) of 300–450 seconds. Of the patients who underwent PCI, >98% showed procedural success, and 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.<sup>125-127</sup> In December 2000, the manufacturer filed a supplementary regulatory application for approval of

argatroban for PCI in patients at risk of developing HIT.

## 2.6.2 Lepirudin and Desirudin

Lepirudin (Refludan®, Aventis Pharma) and desirudin (Revasc®, Aventis Pharma) are nearly identical, recombinant forms of hirudin, a direct, specific thrombin inhibitor extracted from the salivary gland of the medicinal leech, *Hirudo medicinalis*.<sup>116-118,121</sup> Hirudin has no structural similarity with heparin and thus no cross-reactivity. Hirudin inactivates both clot-bound and free thrombin by forming a tight, 1:1 complex with it. As a result, it has a relatively long half-life. Lepirudin has a molecular weight of 7.0 kDa; desirudin, 7.1 kDa. Both drugs are excreted by the kidneys, so bleeding complications and drug accumulation are more common in patients with renal impairment.

Although there is no cross-reactivity with HIT antibodies, antibodies to lepirudin have been reported to form in up to 50% of patients treated for >5 days.<sup>118,122</sup> The clinical importance of these antibodies is unknown but they have not been associated with serious adverse events thus far.<sup>120-122</sup> The antihirudin antibodies actually may potentiate the effects of lepirudin and increase the aPTT.<sup>122</sup>

Lepirudin has been well studied in patients with HIT. In a series conducted in 1995, all 6 patients with HIT or HITTS in 1 series treated with lepirudin responded with increased platelet counts with no deaths or amputations.<sup>118</sup> In the first Heparin-Associated Thrombocytopenia study (HAT-1), 86% of the 71 HIT patients treated with lepirudin showed increasing or maintained platelet counts compared with 120 historical controls, and the 35-day incidence of death, thromboembolic complications, or amputation was reduced by >50% with lepirudin.<sup>120</sup> In the HAT-2 study, the adjusted risk ratio for thromboembolic complications, limb amputation, or death at 35 days was 0.71 for the 95 patients given lepirudin compared with 120 historical controls treated with danaparoid, warfarin,

or no anticoagulation.<sup>120,121</sup> The risk of bleeding was increased with lepirudin, however: 39.6% versus 35% by day 28 in HAT-1 and 45% versus 27% by day 35 in HAT-2. Nonetheless, the efficacy shown in these and other studies led to the March 1998 FDA approval of lepirudin as an anticoagulant for patients with HIT.

There have been no randomized trials of lepirudin or desirudin in HIT patients with ACS or undergoing PCI. Lepirudin has been studied in 2 trials of ACS (without ST-elevation MI); 1 enrolling 909 patients,<sup>128</sup> the other enrolling 10,141 patients.<sup>129</sup> Although clinical outcomes were somewhat better with lepirudin, the risk of major bleeding was increased. A recent analysis from the larger of the 2 studies has shown that the increased risk may relate to the development of thrombocytopenia with hirudin (0.9%), which was similar to the incidence reported for heparin (1.1%).<sup>130</sup> The Advisory Committee to the FDA recommended against approval of lepirudin for anticoagulation in adult ACS in May 2000.

Desirudin has been studied in 3 large trials of ACS (total n=16,285): 1 to prevent restenosis after angioplasty,<sup>131</sup> 1 with fibrinolytic therapy for ST-elevation MI,<sup>132</sup> and 1 across the spectrum of patients with ACS, including a primary angioplasty substudy for acute MI.<sup>133,134</sup> Desirudin showed a modest, nonsignificant advantage over heparin in the primary endpoints of these trials. Moreover, desirudin was associated with significantly fewer early adverse events in both trials that included PCI and more consistent anticoagulant effects compared with heparin.<sup>131,133</sup> Several lepirudin-treated patients in HAT-1 and -2 also underwent successful PCI.

Neither agent is approved for use in HIT patients undergoing PCI, and at present, desirudin is approved for use in the U.K. only for prevention of DVT. Because these agents are excreted by the kidneys, it may be difficult to maintain safe and effective anticoagulation in patients with renal

impairment, particularly in those who also receive contrast media in conjunction with PCI.

### 2.6.3 Bivalirudin

Bivalirudin (Angiomax®, The Medicines Company), formerly known as Hirulog, is a newer direct thrombin inhibitor. This hirudin-like compound is a 20-amino-acid polypeptide with a molecular weight of 2.18 kDa.<sup>123</sup> Much smaller than hirudin, bivalirudin has an active site-directed region (moiety) connected to a moiety that binds to the substrate-binding site of thrombin. Bivalirudin has great binding affinity for thrombin, but once bound, the active site-directed moiety is split off, allowing recovery of thrombin function. Bivalirudin has a half-life of 25 minutes in patients with normal renal function and produces rapid, dose-dependent anticoagulation. Most drug is eliminated by the kidneys and by proteolytic cleavage; only 20% is eliminated unchanged in the urine. As with all direct thrombin inhibitors, bivalirudin has no structural similarities to heparin and has no cross-reactivity with HIT antibodies. Because it is smaller and lacks a secondary protein structure, bivalirudin is less likely than other direct thrombin inhibitors to induce an antibody response.<sup>123</sup>

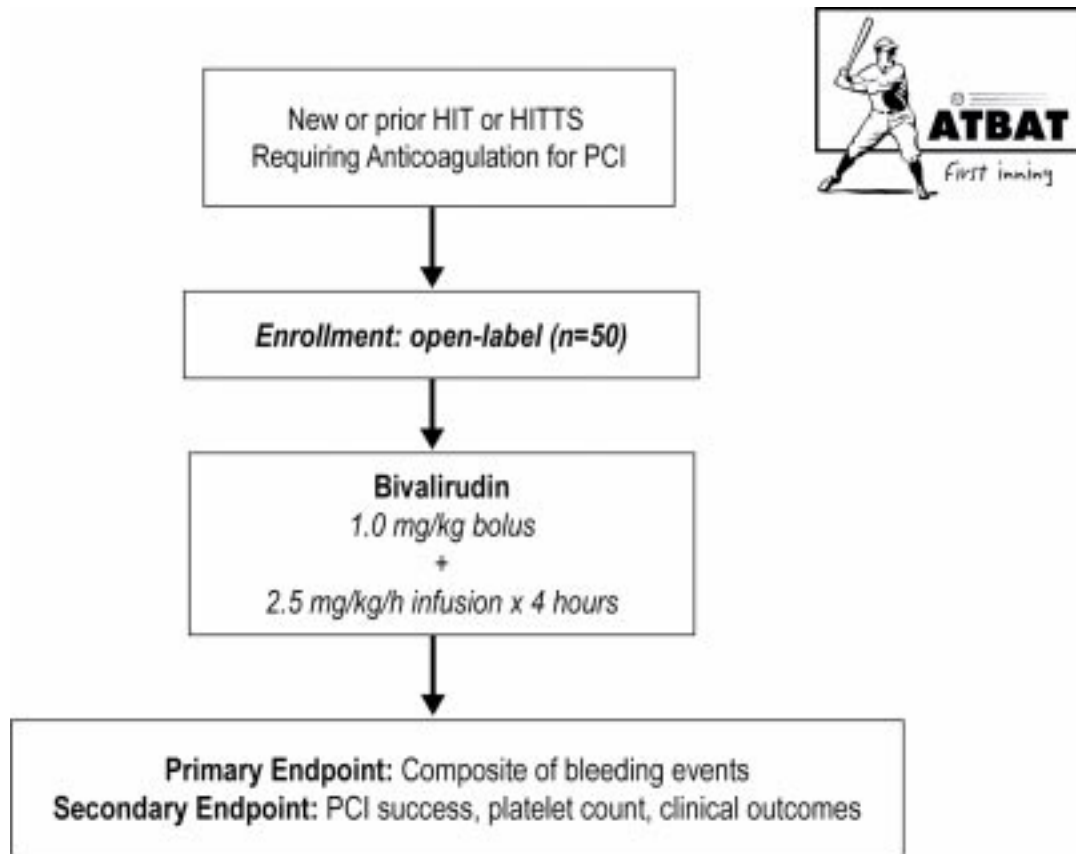
The safety and efficacy of bivalirudin for patients with unstable angina undergoing PCI were evaluated in 2 trials. In the first, bivalirudin was used as an alternative to heparin in an open-label, dose-finding trial of 291 patients undergoing angioplasty.<sup>135,136</sup> The primary endpoint, abrupt vessel closure within 24 hours, occurred in only 18 patients (6.2%), and there were no significant bleeding complications. Bivalirudin produced a predictable, dose-dependent prolongation of the ACT and aPTT in this study.<sup>135</sup> In the second trial, the Bivalirudin Angioplasty Trial (BAT), 4312 patients with unstable angina or MI requiring PCI were randomized in a double-blind fashion to receive bivalirudin or heparin during the procedure.<sup>137,138</sup> Initial analysis showed no difference in the

composite primary endpoint (in-hospital death, MI, abrupt vessel closure, rapid clinical deterioration of cardiac origin) between groups: 11.4% for bivalirudin vs. 12.4% for heparin.<sup>137</sup> After further evaluation and adjudication of the data by independent investigators, however, bivalirudin was associated with a significantly lower rate of death, MI, or repeat revascularization at 7 days (7.9% versus 9.3%, a 22% relative reduction) and significantly less major bleeding (3.5% vs. 9.3%, a 62% relative reduction).<sup>138</sup> In December 2000, the FDA approved bivalirudin for use in patients with unstable angina undergoing PCI. The drug currently is being studied in Phase III trials of anticoagulant treatment in acute MI.

Bivalirudin has been studied in a total of 39 patients with HIT in 2 studies.<sup>123</sup> The patients had multiple indications for anticoagulation, but almost half (17/39, 44%) were undergoing PCI. The overall mortality in the studies was 10% (4/39); the deaths resulted from complications of HIT-related thromboses and none was considered related to bivalirudin therapy.<sup>123</sup> All but 1 of the 17 patients who underwent PCI (15 angioplasty, 2 angioplasty with stent implantation) had a successful procedure. An intra-aortic balloon pump was placed in 2 patients, and anticoagulation was maintained with bivalirudin. Four of the 39 patients underwent successful bypass surgery. There were few bleeding complications seen in the 39 bivalirudin-treated patients.<sup>123</sup> These outcomes are consistent with historical datasets.

To further evaluate bivalirudin in patients with HIT undergoing PCI, the Anticoagulant Therapy with Bivalirudin to Assist in the performance of percutaneous coronary intervention in patients with heparin-induced Thrombocytopenia (ATBAT) trial began enrollment in 1999. This continuing trial is a multicenter, open-label, single-arm registry being coordinated by the Duke Clinical Research Institute. Patients with new or previous HIT who require anticoagulation during PCI are included (**Figure 3**), and the target enrollment is 50 patients. The primary

**Figure 3. Study Design for the ATBAT Trial**



endpoint is the composite incidence of major bleeding (intracranial bleeding, retroperitoneal bleeding, bleeding that results in hemodynamic impairment) during or within 48 hours after completion of bivalirudin infusion or hospital discharge, whichever occurs first. Secondary endpoints are the components of the composite endpoint, the ACT before and after PCI, and platelet counts before and after PCI. Bivalirudin is given as a 1-mg/kg intravenous bolus dose followed by a 2.5-mg/kg/h infusion for 4 hours. A reduced-dose infusion may be continued for up to 20 more hours if clinically indicated.

Interim data are available for 11 patients.<sup>123</sup> Of these, 7 are female, and most have had prior MI (82%) and active anginal symptoms (91%). All 11 patients have had successful procedures, defined as Thrombolysis In Myocardial Infarction (TIMI) grade 3 blood

flow in the blocked artery or <50% residual occlusion (stenosis) at the end of the procedure. No major bleeding has occurred, and only 2 patients have had minor bleeding. There have been no deaths, MIs, strokes, or abrupt closures to date. These interim results are encouraging, and enrollment continues. The results of ATBAT will provide important information about the safety and efficacy of bivalirudin in patients with HIT undergoing PCI.

#### 2.6.4 Limitations of Data for Thrombin Inhibition

The trials to date for the direct thrombin inhibitors have been limited in 3 substantial aspects: they have enrolled relatively few patients, most have been registries, and most have compared patients against historical controls. Many of the studies on anticoagulants in HIT were performed



before standard treatment options existed for these patients, and placebo-controlled trials were thought to be unethical. Given the patient population, some of these limitations can be only partially overcome.

Currently, no test can reliably determine who will develop HIT. This prevents prospective randomization of patients in trials of drugs to prevent HIT. At best, alternative anticoagulant trials can assess the incidence of thrombocytopenia and thrombosis only in patients already known to have HIT.

Survivors of HIT who need repeat anticoagulation, although increasing, still have been rare enough such that enrollment in the largest trial of a direct thrombin inhibitor in HIT patients has enrolled <200 patients. Better identification of patients with prior HIT may improve the situation. Finally, the cross-reactivity of many agents to heparin limits options for comparative trials, resulting in the development of registries and comparisons with historical controls.

### 3 Future Investigations

We clearly need to further our understanding of pathophysiology of HIT. The promising results with GP IIb/IIIa and ADP receptor blockers, for example, may indicate that the mechanism of HIT involves not only generation of PF4-heparin-antibody complexes but also platelet-specific processes.<sup>108</sup> That iloprost, a prostacyclin analog, has been used successfully in patients with HIT undergoing surgery also may reflect a multifactorial mechanism for HIT.<sup>139</sup> Better understanding of the pathophysiology of HIT could allow development of targeted therapies at various points in the process. The discovery of a possible genetic component to the development of HIT also might allow development of a screening test.

The alternatives to heparin remain limited for several indications, including the spectrum of acute coronary syndromes (unstable angina, non-Q-wave MI, and ST-elevation MI) and most cardiovascular

procedures. Much investigation continues into alternative anticoagulants, the newest of which are the factor Xa inhibitors.<sup>140,141</sup>

Alternative anticoagulants for patients with HIT must undergo rigorous study, in larger, randomized trials, if possible. With too-small sample sizes, the ability to detect both rare adverse events and clinically meaningful differences in treatment effect is diminished.

### 4 Conclusions

As people are living longer and undergoing more procedures requiring heparin anticoagulation, the problem of HIT is becoming more and more prevalent. The complications of HIT can be quite severe and include thrombosis, amputation, and death. This disorder must be recognized promptly and treated if the patient is to survive without major consequences.

The diagnosis should be made on clinical grounds and confirmed by laboratory tests. Therapy should not be delayed while awaiting the laboratory results. The best initial laboratory test currently is the HIPA or PAT, depending on availability. If the result of either test is equivocal or negative, and the clinical suspicion is high, confirmatory testing by ELISA should be performed.

Treatment goals are to remove all heparin exposures, prevent thrombosis, and provide safe, alternative anticoagulation for the underlying disorder. All current alternatives have disadvantages, but the best therapy at present is a direct thrombin inhibitor.

Cardiovascular patients with HIT are particularly challenging, given that anticoagulation is required therapy for unstable angina and ACS, and many of these patients will require high levels of anticoagulation for PCI. Patients with ACS and those undergoing PCI may be successfully treated with argatroban, lepirudin, or bivalirudin. Investigations such as the ATBAT trial, and continued study into the pathophysiology of HIT, should identify better anticoagulant strategies for cardiovascular patients at risk for this serious disorder.

## 5 References

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