When Heparins Promote Thrombosis

Review of Heparin-Induced Thrombocytopenia

Ik-Kyung Jang, MD, PhD; Marcie J. Hursting, PhD

Heparin-induced thrombocytopenia (HIT; sometimes known as HIT type II) is a serious, immune system–mediated complication of heparin therapy often resulting in devastating thromboembolic outcomes. Although nomenclature distinctions have been made historically between this condition and the non–immune system–mediated, asymptomatic transient drop in platelet count in some patients receiving heparin (sometimes known as HIT type I), the term “HIT” is now preferably reserved for the immune system–mediated condition. An estimated 1 in 100 patients who receive heparin (sometimes known as HIT type II) is a serious, immune system–mediated complication of heparin therapy often resulting in devastating thromboembolic outcomes. Although nomenclature distinctions have been made historically between this condition and the non–immune system–mediated, asymptomatic transient drop in platelet count in some patients receiving heparin (sometimes known as HIT type I), the term “HIT” is now preferably reserved for the immune system–mediated condition.

An estimated 1 in 100 patients who receive unfractionated heparin for at least 5 days will develop HIT-associated thrombosis. The pervasive use of heparins makes HIT one of the most important adverse drug reactions confronting physicians. Heparin is routinely used for thromboprophylaxis or treatment in many clinical settings, including cardiovascular surgery and interventional procedures, acute coronary syndromes, venous thromboembolism, atrial fibrillation, peripheral occlusive disease, dialysis, and extracorporeal circulation. It is among the most frequently prescribed medications in the United States, with >1 trillion units used and 12 million patients treated annually.

Because thrombocytopenia is common in hospitalized patients, occurring in up to 58% of critically ill patients, and can be caused by a variety of factors, HIT unfortunately often remains unrecognized. However, consistent with standard clinical practice for life-threatening conditions, HIT should be suspected in a heparin-treated patient who has thrombocytopenia with or without thrombosis. Increased awareness and a high degree of suspicion for HIT are critical to ensure its prompt recognition, diagnosis, and treatment. Advances in understanding the pathophysiology of HIT and its natural history have led to current treatment recommendations—specifically, that heparin must be discontinued immediately and alternative anticoagulation must be initiated.

Herein we review the pathogenesis, frequency, natural history, diagnosis, and treatment of HIT.

Pathogenesis

Unfractionated heparin is a heterogeneous group of negatively charged, sulfated glycosaminoglycans (molecular weight 3000 to 30 000 Da) from animal sources. Low-molecular-weight heparins (LMWHs; molecular weight, 2000 to 10 000 Da) are produced from unfractionated heparin by chemical or enzymatic processes. Heparin has high affinity for platelet factor 4 (PF4), a positively charged protein found in platelet α-granules and on some cell surfaces, including platelets and endothelial cells. The extent of binding of heparin and PF4 depends on the heparin’s chain length, or molecular weight (optimally, at least 14 to 16 saccharides, molecular weight =4500 Da), and its degree of sulfation.

When heparins and PF4 bind, PF4 undergoes a conformational change, exposing neoeptopes that act as immunogens and lead to the generation of heparin-PF4 antibodies. HIT is caused by the antibodies, most frequently IgG, binding to the heparin-PF4 complex (Figure 1). Heparin-PF4 antibodies (sometimes called “HIT antibodies”) in the resultant multimolecular immune complex activate platelets via their FcγRIa receptors, causing the release of prothrombotic platelet-derived microparticles, platelet consumption, and thrombocytopenia.

The microparticles in turn promote excessive thrombin generation, frequently resulting in thrombosis. The antibody-antigen complexes also interact with monocytes, leading to tissue factor production, and antibody-mediated endothelial injury may occur. Both of these latter processes may contribute further to thrombosis.

No distinguishing clinical or laboratory feature has yet been identified to predict which individual with heparin-PF4 antibodies will progress to HIT. Patients with anti–heparin-PF4 IgG of high titer often, but not always, have HIT, perhaps associated with differential platelet activation abilities by antibody type and titer. Heparin-PF4 antibodies that fail to induce HIT appear to remain clinically significant in some patients. In patients with acute coronary syndromes and normal platelet counts, the presence of heparin-PF4 antibodies is associated with significantly higher rates of myocardial infarction at 30 days and with thrombotic outcomes at 1 year.

Frequency

The at-risk population for HIT includes patients with heparin-PF4 antibodies. The frequency of heparin-PF4 antibodies depends on various factors, including the patient population, the heparin used, the duration of heparin therapy, and the antibody detection method. In general, the antibodies occur...
more often in cardiovascular surgical patients than in orthopedic surgical patients, in postsurgical patients than in medical patients, in those treated with bovine heparin than porcine heparin, and in those treated with unfractionated heparin than LMWH.14,17–19 Depending on the assay and type of heparin used, heparin-PF4 antibodies occur in 0% to 61% of cardiovascular surgery patients postoperatively,14,17–19 0% to 12% of patients undergoing hemodialysis,20 and 2% to 8% of patients with cardiovascular disease.21

HIT occurs in 0.5% to 5% of patients treated with heparin, again depending on various factors, including the patient population and heparin type used14,22 (Table 1). The frequency of HIT appears to be notably higher (11%), by exception, in cardiac transplant recipients.23 Generally similar to the frequency trends of the HIT antibodies, the frequency of HIT is greater with bovine versus porcine heparin, with unfractionated heparin versus LMWH, and in postsurgical versus medical or obstetric patients.6 However, orthopedic surgery patients, despite having a lower frequency of HIT antibodies, are more likely than cardiac surgery patients to develop HIT.14 In cardiac surgery patients, the frequency of HIT in pediatrics (1.3%)24 is generally comparable to that estimated in adults in combined-study analyses (2.4%).25

Prospective studies indicate that HIT occurs in 0.3% to 3% of medical patients receiving heparin therapy.21,26–28 HIT, while reported in obstetric patients,29 is rare, occurring in one study in no (0/244) heparin-treated pregnant females yet in 4% (10/244) of nonpregnant controls.30

Despite variability in the frequency of HIT, patients of any age receiving any type of heparin at any dose by any route of administration can develop HIT.31 According to hospital-wide surveillance studies of 32- to 36-month duration, HIT occurred in 1.2% of all patients who received heparin for 4 days32 and in 1.0% of all inpatients receiving any form of heparin.30

**Clinical Features and Natural History**

Patients with HIT usually experience a platelet count drop of at least 50%, often to <150×10^9/L, typically starting 5 to 14 days after initiation of heparin.6,33 Rapid-onset HIT and delayed-onset HIT are alternative presentations that are increasingly being recognized. If a patient has heparin-PF4 antibodies from a recent heparin exposure, the platelet count

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**TABLE 1. Frequency of HIT**

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Frequency</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults (unfractionated heparin postoperatively)</td>
<td>1.0% to 2.4%</td>
<td>14, 25</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>1.3%</td>
<td>24</td>
</tr>
<tr>
<td>Cardiac transplantation</td>
<td>11%</td>
<td>23</td>
</tr>
<tr>
<td>Orthopedic surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unfractionated heparin postoperatively</td>
<td>4.8%</td>
<td>22</td>
</tr>
<tr>
<td>LMWH postoperatively</td>
<td>0.6%</td>
<td>22</td>
</tr>
<tr>
<td><strong>Medical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>0.3%</td>
<td>21</td>
</tr>
<tr>
<td>Critical care</td>
<td>0.4%</td>
<td>26</td>
</tr>
<tr>
<td>Those treated with subcutaneous, unfractionated heparin</td>
<td>0.8%</td>
<td>27</td>
</tr>
<tr>
<td>Newly treated with hemodialysis</td>
<td>3.2%</td>
<td>28</td>
</tr>
<tr>
<td>Obstetrics</td>
<td>Rare</td>
<td>29, 30</td>
</tr>
<tr>
<td><strong>Overall (hospital-wide surveillance studies)</strong></td>
<td>1.0% to 1.2%</td>
<td>31, 32</td>
</tr>
</tbody>
</table>

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Figure 1. Model of pathogenesis of HIT. Heparin binds with PF4, which exposes neoepitopes on PF4 and leads to antibody production (1). Heparin-PF4-IgG immune complexes form (2), and IgG in multimolecular complex triggers platelet activation via binding to Fc receptors (3). Activated platelet releases additional PF4 (4a) and prothrombotic platelet microparticles (4b). Thrombotic risk is further promoted by binding of PF4 to heparin-like molecules on endothelial cells (EC), contributing to immune system–mediated endothelial damage (5). Reprinted with author and publisher permission from: Januzzi JL Jr, Jang IK. Heparin induced thrombocytopenia: diagnosis and contemporary antithrombin management. J Thromb Thrombolysis. 1999;7:259–264.
The thromboembolic complications of HIT contribute to the high mortality. Cessation is 38% to 76%.41–44 In HIT patients without progression to adverse outcomes in HIT include skin lesions and acute systemic reactions. Erythematous or necrotizing skin lesions occur at the heparin injection site in 10% to 20% of patients who develop heparin-PF4 antibodies during subcutaneous heparin therapy. Thrombocytopenia develops in approximately 4-fold over arterial thrombosis associated with heparin.27,33 Acute systemic reactions, including fever, chills, hypertension, tachycardia, chest pain, dyspnea, or other symptoms, occur 5 to 30 minutes after administration of an intravenous heparin bolus in up to 25% of patients with circulating HIT antibodies. The platelet count usually falls suddenly, and prompt suspicion of HIT is critical, as cardiopulmonary fatalities have occurred.57

Circulating heparin-PF4 antibodies remain detectable for 4 months after the diagnosis of HIT in approximately 10% to 40% of patients, depending on the assay used.33 The antibody longevity thereafter remains unclear. Data suggest that enduring antibodies, rather than an anamnestic immune response to heparin, precipitate the rapid thrombocytopenia that can occur when patients with recent, previous heparin exposure are reexposed to heparin.27,33

**Diagnosis**

The diagnosis of HIT is based on its typical clinical picture, ie, isolated thrombocytopenia in a patient treated for at least 5 days with a heparin product, or acute thrombosis associated with thrombocytopenia and a similar history, and after other causes of thrombocytopenia have been excluded. The “4 Ts” of HIT may be useful for assessing patients with suspected HIT and provide a catchy memory device for the salient clinical features of HIT (Table 2).57 The point system considers the degree of thrombocytopenia (maximum points for a platelet count fall of >50% or a nadir of 20 to 100×10^9/L), the Timing of the platelet fall (maximum points for an onset 5 to 10 days after starting heparin or within 1 day if there has been recent heparin exposure), the presence of thrombosis or other sequelae (maximum points for new thrombosis, skin lesions, or acute systemic reactions), and other causes for thrombocytopenia excluded (maximum points for no other cause evident). As discussed subsequently,
Risk of HIT 0.1% to 1% Medical/obstetric patients receiving prophylactic-dose UFH, or intravenous UFH bolus

Acute, systemic reactions after intravenous UFH bolus Patients with acute inflammatory, cardiorespiratory, neurological, or other unusual symptoms and signs within 30 minutes after an intravenous UFH bolus

Risk of HIT >1% Patients receiving UFH at therapeutic doses Postoperative patients receiving UFH antithrombotic prophylaxis

Risk of HIT 0.1% to 1% Medical/obstetric patients receiving prophylactic-dose UFH, or LMWH after first receiving UFH; postoperative patients receiving prophylactic-dose LMWH, or intravascular catheter UFH flushes

Risk of HIT <0.1% Medical/obstetric patients receiving only LMWH; medical patients receiving catheter UFH flushes

TABLE 3. Consensus Guidelines for Platelet Count Monitoring for HIT

<table>
<thead>
<tr>
<th>Population</th>
<th>Examples</th>
<th>Monitoring Guideline*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent heparin exposure</td>
<td>Patients starting UFH or LMWH and who received UFH within the previous 100 days; patients whose heparin exposure history is unknown</td>
<td>Obtain baseline platelet count and repeat platelet count within 24 hours of starting heparin</td>
</tr>
<tr>
<td>Acute, systemic reactions after intravenous UFH bolus</td>
<td>Patients with acute inflammatory, cardiorespiratory, neurological, or other unusual symptoms and signs within 30 minutes after an intravenous UFH bolus</td>
<td>Obtain platelet count immediately to compare with recent prior platelet counts</td>
</tr>
<tr>
<td>Risk of HIT &gt;1%</td>
<td>Patients receiving UFH at therapeutic doses</td>
<td>Monitor at least every 2 days until day 14 of therapy or until UFH is stopped, whichever comes first</td>
</tr>
<tr>
<td>Risk of HIT 0.1% to 1%</td>
<td>Postoperative patients receiving UFH antithrombotic prophylaxis</td>
<td>Monitor at least every 2 days between postoperative days 4 and 14† or until UFH is stopped, whichever comes first</td>
</tr>
<tr>
<td>Risk of HIT &lt;0.1%</td>
<td>Medical/obstetric patients receiving prophylactic-dose UFH, or LMWH after first receiving UFH; postoperative patients receiving prophylactic-dose LMWH, or intravascular catheter UFH flushes</td>
<td>Monitor every 2 or 3 days from days 4 to 14† or until UFH is stopped, whichever comes first, when practical</td>
</tr>
<tr>
<td>Risk of HIT &lt;0.1%</td>
<td>Medical/obstetric patients receiving only LMWH; medical patients receiving catheter UFH flushes</td>
<td>As clinically indicated (no routine monitoring)</td>
</tr>
</tbody>
</table>

UFH indicates unfractionated heparin.

*As recommended by the College of American Pathologists (Warkentin58; adapted with permission from Archives of Pathology & Laboratory Medicine. Copyright 2004, College of American Pathologists) and the 7th ACCP Conference on Antithrombotic and Thrombolytic Therapy (Warkentin and Greinacher6; adapted with permission from Chest. Copyright 2004).

†Days 4 to 10, with additional monitoring if platelet count falls in that time window, according to the College of American Pathologists guidelines.

Laboratory tests are available for confirming the clinical diagnosis; however, initiation of proper treatment must never be delayed pending results.

Because the drop in platelet count is a primary way of recognizing HIT, routine monitoring of the platelet count is recommended for most patients receiving heparin therapy, ie, in patients whose risk of HIT is at least 0.1% (Table 3).6,58 A baseline platelet count before initiating heparin treatment is important to allow estimation of relative changes. In higher-risk patients, such as individuals receiving unfractionated heparin at therapeutic doses, the platelet count should be checked at least every other day until day 14 of therapy (or until heparin is stopped, whichever is sooner). In lower-risk patients, monitoring should be at least every 2 or 3 days between days 4 and 14 while on heparin therapy.6

Because it is a potentially life-threatening condition, HIT should be considered with priority among the possible causes of thrombocytopenia with or without thrombosis in a heparin-treated patient. Obvious alternative causes of thrombocytopenia, such as sepsis (with or without disseminated intravascular coagulation) or primary bone marrow disorder, may suggest against HIT but also may confound the diagnosis. Thrombocytopenia may also be associated with the use of intra-aortic balloon pumps or on-pump cardiac surgery. Nonimmune heparin-associated thrombocytopenia is a mild, transient decline in platelet count that occurs 1 to 4 days after initiating heparin in 10% to 20% of patients; it is relatively benign and usually resolves spontaneously despite continuation of heparin. Pseudothrombocytopenia, a laboratory artifact, can result from platelet clumping in EDTA-containing tubes. Quinine- or other drug-induced immune thrombocytopenic purpura, as well as glycoprotein Ib/IIa antagonist–induced thrombocytopenia, typically has more severe thrombocytopenia than that of HIT. Patients with massive, acute venous thromboembolism occasionally develop thrombocytopenia because of platelet consumption on the thrombus surface; their platelet count nadir usually happens within 1 day of heparin initiation.59 Besides HIT, thrombotic “storms” also occur in the anti-phospholipid antibody syndrome, Trousseau’s syndrome, cholesterol emboli syndrome, and infective or nonbacterial thrombotic endocarditis. HIT should be also considered if a recently hospitalized patient returns with thromboembolism.35,36,60 Approximately 10% of patients coming to the emergency department with symptoms of thrombosis and a recent history of heparin exposure have circulating heparin-PF4 antibodies.61

Laboratory Testing

The College of American Pathologists recommends heparin-PF4 antibody testing for patients in whom there is suspicion of HIT based on the temporal features of the thrombocytopenia or on the occurrence of new thrombosis during or soon after heparin treatment.38 Results from laboratory tests for HIT antibodies may not be obtained for hours to days after being ordered. Because of the increased thrombotic risk early in the progression of HIT,46,47 appropriate therapy in a patient with suspected HIT must not be delayed pending laboratory results.

Antigenic and functional tests for heparin-PF4 antibodies are available yet often are labor intensive and time intensive.58 Antigenic assays, such as the ELISA, measure antibodies to PF4 complexed with heparin or other polyanions. The ELISA has a sensitivity of >90%; however, it also detects antibodies that do not elicit HIT (false-positives) and has decreased specificity in certain populations such as cardiac surgery patients. Functional tests, including platelet aggregometry and the [14C]serotonin release assay, measure platelet activity in the presence of patient sera and heparin. Platelet aggregometry has a sensitivity of 35% to 85%, and
acute-phase reactants can cause false-positives; its sensitivity and specificity can be improved by using washed platelets from normal donors.\(^6\) The serotonin-release assay is sensitive and specific (>95%) yet is technically demanding, involves radioactivity, and is generally used as a confirmation test only. Flow cytometric assays, including methods to detect platelet microparticle release\(^1\) and annexin V binding,\(^8\) are described that are strongly correlated with the serotonin-release assay yet do not use radioactivity. No single assay, however, has 100% sensitivity and specificity. Although testing becomes most effective when functional and antigen tests are done in combination and multiple samples are taken,\(^6\) this approach is often impractical, and results are unlikely to be available in a timely manner.

**Treatment**

When HIT is suspected, all heparins must be avoided, including LMWHs, heparin flushes, heparin-coated catheters, and any other sources, and alternative anticoagulation must be initiated immediately. This treatment recommendation applies to HIT patients diagnosed with thrombocytopenia alone or with thromboembolism.\(^6\) In the absence of alternative anticoagulation, the risk of thrombosis is \(\approx 5\%\) to 10% per day in the first few days after stopping heparin,\(^5\) increasing to a total risk of 38% to 76% within a month.\(^4\) Appropriate treatment therefore requires immediately removing the trigger (stop heparin) as well as controlling the thrombin storm of HIT (provide appropriate alternative anticoagulation).

Neither LMWH nor warfarin should be used for treatment of HIT.\(^6\) Although less likely than unfractionated heparin to induce HIT antibodies, LMWH cross-reacts substantially, approaching 100%, with existing HIT antibodies\(^7\) and hence, can propagate HIT. Warfarin is not recommended in HIT because it can paradoxically worsen the thrombosis and cause venous limb gangrene and skin necrosis.\(^6,35,65,66\) This appears to be due to an imbalance between the natural anticoagulant and procoagulant proteins associated with HIT-related consumption, which is exacerbated during warfarin induction. If a patient is receiving coumarin therapy when diagnosed with HIT, vitamin K administration is recommended to reverse the coumarin effects.\(^6\) Recommendations with regard to transitioning patients from parenteral alternative anticoagulation to warfarin, if needed for long-term therapy, are discussed later.

**Alternative Anticoagulants**

In the United States, the only approved anticoagulants for use in adult patients with HIT are the direct thrombin inhibitors argatroban, which is a synthetic molecule derived from \(L\)-arginine, and lepirudin, which is a recombinant protein derived from leech hirudin. In addition to its use in prophylaxis or treatment of thrombosis in HIT, argatroban is also approved for use in patients with or at risk for HIT who are undergoing percutaneous coronary intervention (PCI). Danaparoid, a heparinoid, is approved for use in pediatric HIT patients. Danaparoid can cross-react with HIT antibodies\(^67\) and is contraindicated in those patients. There is no alternative anticoagulant approved for use in pediatric HIT patients.

Direct thrombin inhibitors, including argatroban, lepirudin, and bivalirudin, are nonheparin anticoagulants that inhibit thrombin without need of a cofactor and that do not generate or interact with HIT antibodies.\(^58\) In prospective, historical controlled studies, argatroban\(^38,43\) and lepirudin\(^46,47,69\) significantly improved outcomes in HIT, particularly reducing new thrombosis (Figure 2). Major bleeding rates assessed by similar criteria were 6% to 7% with argatroban (7% with control)\(^38,43\) and 13% to 19% with lepirudin (control not reported).\(^46,47,69\) When the studies were conducted, no approved agent was available for use as a comparator, and placebo control was unethical; therefore, historical control groups were used for comparisons. These agents are routinely
<table>
<thead>
<tr>
<th>Feature</th>
<th>Argatroban</th>
<th>Lepirudin</th>
<th>Danaparoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of action</td>
<td>Direct thrombin inhibitor</td>
<td>Direct thrombin inhibitor</td>
<td>Indirect factor Xa inhibitor</td>
</tr>
<tr>
<td>Molecular weight, Da</td>
<td>526</td>
<td>6979</td>
<td>5500</td>
</tr>
<tr>
<td>Cross-reactivity with HIT sera</td>
<td>No</td>
<td>No</td>
<td>10% to 50%, depending on assay (contraindicated in patients with a positive in vitro test for antibodies in presence of danaparoid)</td>
</tr>
<tr>
<td>US indication</td>
<td>Anticoagulation for prophylaxis or treatment of thrombosis in patients with HIT</td>
<td>Anticoagulation for patients having HIT with associated thromboembolic disease to prevent further thromboembolic complications</td>
<td>HIT without thrombosis: 750 U administered subcutaneously twice or thrice daily</td>
</tr>
<tr>
<td>Recommended dose</td>
<td>2 μg/kg per minute, adjusted to achieve aPTTs 1.5 to 3 times the baseline value (reduced dose if hepatic impairment)</td>
<td>0.4-mg/kg initial bolus followed by a 0.15-mg/kg per hour infusion, adjusted to achieve aPTT ratios of 1.5 to 2.5 (reduced dose if renal impairment)</td>
<td>HIT with thrombosis: 1500- to 3750-U bolus (depending on body weight) followed by a 400-U/h infusion for 4 hours, then a 300-U/h infusion for 4 hours, then a 150- to 200-U/h infusion for at least 5 days, with a target of 0.5 to 0.8 anti–factor Xa U/mL in plasma (reduced doses if renal impairment)</td>
</tr>
<tr>
<td>Primary route of elimination</td>
<td>Hepatic</td>
<td>Renal</td>
<td>Renal</td>
</tr>
<tr>
<td>Elimination half-life</td>
<td>39 to 51 minutes</td>
<td>1.7 hours</td>
<td>25 hours</td>
</tr>
<tr>
<td>Monitoring</td>
<td>aPTT or ACT</td>
<td>aPTT or ECT</td>
<td>Anti–factor Xa activity</td>
</tr>
<tr>
<td>Antidote</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

*Reduced doses may be appropriate if used in combination with glycoprotein IIb/IIIa.76

Table 4. Comparison of Alternative Anticoagulants That Are Approved in the United States or Elsewhere for Use in HIT Patients

monitored with the activated partial thromboplastin time (aPTT) or, at higher levels of anticoagulation, the activated clotting time (ACT) for argatroban or ecarin clotting time (ECT) for lepirudin. No controlled studies have evaluated any other direct thrombin inhibitor in patients with HIT, although there are limited prospective data on the use of bivalirudin in HIT patients.4,70–72

Whereas direct thrombin inhibition reduces thrombin activity, factor Xa inhibition reduces thrombin generation. Danaparoid, which is a mixture of heparan, dermatan, and chondroitin sulfates, exerts its anticoagulant effects predominantly by inhibiting factor Xa (anti–factor Xa to anti–factor IIa activity of roughly 22:1) with anti-thrombin or heparin cofactor II as a cofactor. In vitro cross-reactivity of danaparoid with HIT sera is ≈10% to 50%, depending on the assay.67 Clinical experience with danaparoid in HIT includes a compassionate-use program,67,73 a randomized, controlled trial with dextran 70 as a comparator,45 and a retrospective comparative trial with lepirudin.74 When monitoring is needed, plasma anti–factor Xa levels are typically used because the aPTT and activated ACT are not significantly prolonged at clinically relevant doses. Fondaparinux is also an indirect, yet more selective, factor Xa inhibitor. In vitro cross-reactivity with HIT sera is significantly less with fondaparinux than with unfractionated heparin (0% to 5.9% versus 79.8% overall for a variety of tests).75 Fondaparinux is not approved for treating HIT and is contraindicated in patients with thrombocytopenia associated with a positive in vitro test for HIT antibody in the presence of fondaparinux. Limited data exist on its use in HIT.76,77

The choice of the alternative anticoagulant should consider its demonstrated efficacy and safety in the intended use, availability of the drug and methods for monitoring, and the patient’s clinical status, including renal and hepatic function. A retrospective comparison of danaparoid and lepirudin has been published,76 but no prospective “head-to-head” study of alternative anticoagulants in HIT has been conducted. Table 4 presents the key features of the 3 alternative anticoagulants, ie, argatroban, lepirudin, and danaparoid, that are approved for use in this setting in the United States or elsewhere. Clinical data from HIT patients for these anticoagulants as well as bivalirudin and fondaparinux are discussed by individual agent.

**Lepirudin**

Lepirudin is indicated in the United States as anticoagulation for patients having HIT with associated thromboembolic disease to prevent further thromboembolic complications.46,47 The recommended dose is a 0.4-mg/kg initial bolus followed by a 0.15-mg/kg per hour infusion, adjusted to aPTT ratios of 1.5 to 2.5. Lepirudin has also been evaluated at a lower dose (0.1 mg/kg per hour, without a bolus; aPTT adjusted to 1.5 to 2.5 times baseline) in HIT patients without thrombosis, although it is not labeled for such use.79 Relative overdose can occur with lepirudin at standard doses in patients with renal impairment. Hence, lepirudin requires reduced doses, with careful monitoring, in patients with serum creatinine values >1.6 mg/dL and must be avoided in patients on hemodialysis or with acute renal failure.80 Approximately 50% of patients exposed to lepirudin form anti-hirudin...
antibodies that can alter the drug’s pharmacokinetics, leading to increased plasma lepirudin concentrations and the need for close monitoring to reduce bleeding risk. 

Anaphylaxis, including anaphylactic death, occurs in an estimated 0.2% of patients reexposed to lepirudin. The severity of anaphylaxis may be reduced by omitting the bolus during lepirudin administration. Because of the severity of this adverse reaction, nonhirudin anticoagulants should be considered for use in patients with previous lepirudin exposure.

Three multicenter, prospective, similarly designed studies, known respectively as Heparin-Associated Thrombocytopenia (HAT)-1, HAT-2, and HAT-3, evaluated the safety and efficacy of lepirudin in patients with serologically confirmed HIT. Across the 3 studies, a total of 214 HIT patients with thrombosis received a 0.4-mg/kg bolus followed by a 0.15-mg/kg per hour infusion, and 145 HIT patients without thrombosis received a 0.1-mg/kg per hour infusion. The dose was adjusted to achieve aPTTs of 1.5 to 2.5 or 1.5 to 3.0 times the baseline value, depending on the reagent used. Treatment duration was typically 11 to 14 days. Median infusion rates in HAT-2 were 0.13 mg/kg per hour in HIT patients with thrombosis and 0.08 mg/kg per hour in HIT patients without thrombosis. Comparisons were made with 120 historical control patients. Lepirudin therapy significantly decreased the combined end point of death, new thromboembolic complications, and amputation at 35 days in 2 studies (25.4% in HAT-1 and 26.2% in HAT-3 versus 52.1% in control, P<0.014) (Figure 2). In HAT-2, the combined end point was 30.9% (P=0.12 versus control). There were no significant between-group differences in the individual components of the combined end point, with the exception that lepirudin therapy significantly reduced new thromboembolic complications in HAT-3 (9.9% versus 32.1%, P<0.001). aPTTs increased rapidly to target values and generally remained there during lepirudin therapy. Platelet counts were >100×10^9/L within 10 days in 89% to 93% of the lepirudin-treated patients. There was an excess of bleeding in the lepirudin group, compared with control, in HAT-2 (45% versus 27%, P<0.001). Major bleeding rates in the respective studies were 13.4%, 17.0%, and 19.5% (not reported for controls). In combined-study analyses for HIT patients with or without thrombosis, lepirudin therapy, compared with historical controls, significantly reduced the time to event for the combined end point (P<0.03) irrespective of the HIT presentation, primarily due to reductions in new thromboembolic complications. In HIT patients with thrombosis, lepirudin significantly increased bleeding that required transfusion (18.8% versus 7.1% in controls, P=0.02). Lepirudin therapy has also been compared with danaparoid therapy in a retrospective study, the details of which are described subsequently in the danaparoid section.

**Argatroban**

Argatroban is indicated in the United States as an anticoagulant for prophylaxis or treatment of thrombosis in patients with HIT. The recommended initial dose is 2 µg/kg per minute adjusted to achieve aPTTs 1.5 to 3 times the baseline value. Reduced doses are required in patients with hepatic impairment. There is no evidence of antibody generation to argatroban on prolonged or repeated administration, and no anaphylactic deaths have been reported. Direct thrombin inhibitors as a class prolong the prothrombin time and international normalized ratio (INR); however, this effect is particularly pronounced with argatroban. Although argatroban is routinely monitored with the aPTT, guidelines for monitoring the transition from argatroban to coumarins, including warfarin, with the INR have been published.

The clinical efficacy and safety of argatroban therapy in HIT patients have been demonstrated in the multicenter, prospective studies known as Argatroban-911 and Argatroban-915. In each study, patients having clinically diagnosed HIT received intravenous argatroban starting at 2 µg/kg per minute (or lower, in the presence of hepatic impairment), adjusted to maintain aPTTs 1.5 to 3.0 times the baseline value. Mean doses of 1.7 to 2.0 µg/kg per minute were infused for 5 to 7 days, on average, to 304 patients in Argatroban-911 and to 418 patients in Argatroban-915. Comparisons were made with historical control patients treated typically by heparin discontinuation and/or oral anticoagulation. Patients were stratified by their HIT presentation (ie, with or without thrombosis) for analyses. In both studies, argatroban therapy significantly reduced the composite end point (all-cause death, all-cause amputation, or new thrombosis) in HIT patients without thrombosis (25.6% and 28.0%, respectively, versus 38.8% in controls, P<0.04) (Figure 3). The composite incidence among argatroban-treated patients with HIT and thrombosis was 43.8% and 41.5% in the respective studies, compared with 56.5% in controls (P<0.13). Time-to-event analysis of the composite end point significantly favored argatroban in both presentations of HIT and in both studies (P<0.02). All-cause death and amputation rates were not different between groups, yet new thrombosis and death due to thrombosis were significantly reduced by argatroban therapy in each study (P<0.05). Combined-study analysis also revealed that argatroban therapy, versus control, significantly reduced new stroke (odds ratio, 0.31; P=0.04) and stroke-associated mortality (odds ratio, 0.18; P=0.039). aPTTs were generally therapeutic within 4 to 5 hours of starting therapy, and platelet counts...
recovered more rapidly in argatroban-treated patients than controls. Major bleeding in argatroban-treated patients (6.9% and 5.7% in the respective studies) was similar to that in controls (7%).

**Bivalirudin**

Bivalirudin, which is not approved for HIT, is a 20–amino acid polypeptide with sequence homology to hirudin. It is cleared by a combination of renal mechanisms and proteolytic cleavage, which may offer a pharmacological benefit for anticoagulation of patients with comorbid hepatic and renal disease. However, its clearance is reduced in renal dysfunction, up to 80% in dialysis-dependent patients, and decreased doses are required in moderate or severe renal impairment. Preliminary data are available on bivalirudin use in a limited number of HIT patients. One abstract described 45 patients who received bivalirudin at an average infusion dose of 0.17 mg/kg per hour, adjusted to aPTTs of 1.5 to 2.5 times the baseline value; 6 patients died, 1 patient had new thrombosis, and no patient experienced major bleeding. Another abstract described 15 patients treated with a mean initial dose of 0.16 mg/kg per hour; 6 patients died, and bivalirudin was stopped in 1 patient because of bleeding. Approximately 51% of anti-hirudin antibodies occurring in lepirudin-treated patients cross-react with bivalirudin in vitro, raising the theoretical concern that anaphylactic reactions may occur in patients treated with bivalirudin who have been previously exposed to lepirudin.

**Danaparoid**

Danaparoid is approved as an alternative anticoagulant for HIT in many countries (unavailable in the United States). It is contraindicated in patients with a history of thrombocytopenia with danaparoid or in whom an in vitro platelet aggregation test is positive in the presence of danaparoid. Danaparoid cross-reacts with 10% to 50% of HIT sera, depending on the assay. Although used in many patients, including >750 patients treated in a compassionate-use program, and often with success, danaparoid has also been associated with unfortunate treatment failures from clinically significant cross-reactivity. Danaparoid is renalley cleared, and doses should be reduced in patients with renal impairment.

In the compassionate-use program, the recommended danaparoid dose for thromboprophylaxis in HIT patients without thrombosis was 750 U administered subcutaneously twice or thrice daily. The recommended treatment of HIT patients with thrombosis was a 1500- to 3750-U bolus (depending on body weight) followed by a 400-U/h infusion for 4 hours, then a 300-U/h infusion for 4 hours, then a 150- to 200-U/h infusion for at least 5 days, with a target of 0.5 to 0.8 anti–factor Xa U/mL in plasma. In one report, 15 (6.5%) of 230 patients in the program experienced the appearance or persistence of thrombocytopenia (9 patients), new thromboembolism (4 patients), or bleeding (2 patients) during or within 2 days after treatment, and 59 (25.7%) patients died within 3 months. In a multicenter, randomized, open-label trial in HIT patients with thrombosis, danaparoid (n = 25), compared with dextran 70 (n = 17), each combined with warfarin, significantly increased the proportion of thromboembolic events resolved at hospital discharge (56% versus 14%, P = 0.02). However, consensus guidelines now recommend against warfarin use in HIT before resolution of thrombocytopenia. A retrospective study of 175 lepirudin-treated HIT patients from HAT-1 and -2 and 126 danaparoid-treated HIT patients from the same time period found no significant between-group difference in the 42-day combined end point of death, new thromboembolic complications, or amputation (21.5% versus 18.5%, P = 0.53) (Figure 3). Danaparoid therapy caused less bleeding requiring transfusion (2.5% versus 10.4%, P = 0.02). In a subgroup analysis of HIT patients without thrombosis, the cumulative risk of the combined end point was significantly higher with danaparoid than with lepirudin therapy (P = 0.02), suggesting that the recommended prophylaxis dose for danaparoid in HIT may be suboptimal.

**Fondaparinux**

Fondaparinux, a synthetic pentasaccharide that is structurally related to the anti-thrombin–binding site of heparin, is not approved for patients with HIT. The generation of HIT-related antigen depends on the polysaccharide chain length, with an optimum of 14 to 16 saccharides. In theory, because fondaparinux has 5 saccharides and is smaller than LMWH, it is expected to be less likely to induce HIT. In the single case series reported in full on fondaparinux use in HIT, 6 patients with a history of HIT and 2 patients with LMWH-induced HIT received fondaparinux 2.5 mg subcutaneously daily for 14 days, without bleeding or thromboembolic complications. Preliminary data are available for HIT patients administered fondaparinux 2.5 mg for at least 5 days as an initial treatment (n = 10) or after direct thrombin inhibition therapy (n = 10); no continued or recurrent thrombocytopenia and no thrombotic complications occurred.

**Additional Treatment Considerations**

Platelet transfusions should not be used for prophylaxis of bleeding in HIT because they may exacerbate the hypercoagulable state, leading to additional thrombosis. Surgical thromboembolectomy or systemic or local thrombolysis, as adjunctive therapy to alternative parenteral anticoagulation, may be appropriate for selected patients with large-vessel arterial thromboembolism or severe pulmonary embolism, respectively.

Platelet glycoprotein IIb/IIIa inhibitors, which have been used successfully with alternative anticoagulants during PCI, reduce thrombin generation indirectly and inhibit platelet aggregation. However, these agents lack direct anticoagulant effects and do not inhibit Fc receptor–mediated activation of platelets by HIT antibody. Hence, glycoprotein IIb/IIIa inhibitors should not be used as a sole therapy for treating HIT.

For patients needing long-term anticoagulation for an underlying medical condition or because of HIT-associated thrombosis, initiation of warfarin must be delayed until adequate alternative parenteral anticoagulation has been provided and platelet counts have recovered substantially (to at least 100 × 10^9/L or preferably 150 × 10^9/L). Warfarin should be started at the expected maintenance dose and not at a loading dose. Parenteral anticoagulation should be overlapped with warfarin for minimum of 5 days. When transi-
tioning from a direct thrombin inhibitor, careful monitoring may be needed. Direct thrombin inhibitors prolong the INR, the extent of which depends on the drug and its concentration, the residual vitamin K–dependent protein activity, and the assay reagent. Previously established relations with regard to bleeding risk and INRs during warfarin therapy are not fully applicable during direct thrombin inhibition. INRs >5 commonly occur during argatroban therapy and argatroban-warfarin cotherapy in HIT, without bleeding complications. Guidelines for monitoring the transition from lepirudin or argatroban to oral anticoagulation have been published. The chromogenic factor Xa assay is an alternative means to monitor warfarin during the transition period. Warfarin therapy is appropriate for a minimum of 3 to 6 months after an episode of HIT-associated thrombosis.

Bleeding is a safety concern with any anticoagulant therapy. Direct thrombin inhibitors lack a specific antidote, and protamine sulfate only negligibly neutralizes danaparoid. In case of excessive levels of anticoagulation, with or without bleeding, the anticoagulant should be stopped or its dose decreased. With the direct thrombin inhibitors, anticoagulant effects decrease to baseline, typically within hours, in accordance with the drug’s elimination half-life and the patient’s organ function. Specifically, the half-life of argatroban (39 to 51 minutes) is increased with hepatic impairment, and the half-lives of lepirudin (1.7 hours) and bivalirudin (36 minutes) are increased with renal impairment. Because of a prolonged half-life, rapid reversal after drug discontinuation is not an option with danaparoid (half-life of 25 hours) or fondaparinux (half-life of 15 hours). Hemodialysis or hemofiltration can sometimes reduce levels of lepirudin or bivalirudin; however, drug filtration characteristics vary considerably by filter type. Dialytic clearance of argatroban by high-flux membranes is clinically insignificant. Limited data exist on the use of recombinant factor VIIa as a nonspecific antidote for treating severe bleeding in patients with HIT. Symptomatic and supportive care should be given.

**Special Clinical Needs**

**Patients With a History of HIT**

Patients with a history of HIT may not invariably have recurrent HIT on heparin reexposure. In addition, heparin has been tolerated for a brief period, such as during cardiac surgery, in patients in whom heparin-PF4 antibodies have fully waned. However, until the risk of recurrent HIT in patients with a history of HIT is better defined, and because the consequences of recurrent HIT may be devastating, it is generally considered prudent to use an alternative anticoagulant to avoid reexposing these “at-risk” patients to heparin, when possible. In special circumstances in which planned heparin exposure may occur, such as cardiac surgery when HIT antibodies are undetectable (see following discussion), an alternative agent should be used for preoperative and postoperative anticoagulation to limit heparin exposure. In a prospective study of acute alternative anticoagulation in patients with a history of HIT, argatroban 2 μg/kg per minute, adjusted to aPTTs of 1.5 to 3.0 times baseline, provided adequate anticoagulation for venous or arterial thrombosis in 36 patients, without major bleeding or thrombotic complications.

**Cardiovascular Surgery**

In patients with HIT or with a history of HIT and lingering HIT antibodies, cardiovascular surgery should be delayed until HIT is fully resolved and antibodies are undetectable by a sensitive assay. If delay is impossible or the urgency of the situation precludes assessment of HIT antibody status in a patient with a history of HIT, alternative anticoagulation should preferably be used during the surgery. Limited experience exists with lepirudin, argatroban, bivalirudin, and danaparoid, sometimes together with antiplatelet agents, in this setting. It should be emphasized that safe, effective doses of alternative anticoagulants during cardiovascular surgery have not been established in clinical trials, and hence, potential concerns about bleeding or thrombotic complications remain. Other concerns include the lack of specific antidotes for these alternative anticoagulants as well as the potential need for monitoring by assays often not readily available, such as the ECT or anti–factor Xa level. Prospective studies are now ongoing in the United States to evaluate bivalirudin anticoagulation in HIT patients undergoing on- or off-pump cardiac surgery. In addition, the intraoperative use of heparin with one or more antiplatelet agents has been described in HIT patients. Heparin with oral dipyridamole preoperatively and intravenous prostacyclin (alprostadil) intraoperatively has been used at Massachusetts General Hospital for many years as an alternative; heparin is used only during the surgery to limit exposure.

In the special circumstance of patients with a history of HIT who lack detectable HIT antibodies and require cardiac surgery, heparin is currently recommended over alternative anticoagulants owing to the limited experience with the latter agents in cardiovascular surgery and their universal lack of an antidote. Again, care must be taken to minimize heparin exposure, using it only during surgery and administering alternative anticoagulation, when needed, before and after surgery.

**Percutaneous Coronary Intervention**

Argatroban is the only alternative anticoagulant approved in the United States for use in patients with or at risk for HIT who are undergoing PCI. The safety and efficacy of argatroban in this setting was evaluated in 3 similarly designed, multicenter, prospective studies, and the combined-study data are reported (Table 5). Patients with clinically significant hepatic dysfunction were excluded. Overall, 91 patients with HIT or a history of HIT underwent 112 PCIs while receiving intravenous argatroban 25 μg/kg per minute (350-μg/kg initial bolus), adjusted to achieve ACTs of 300 to 450 seconds. Among the 91 patients undergoing their first PCI on argatroban, subjective assessments of the satisfactory outcome of the procedure and adequate anticoagulation during PCI occurred in 94.5% and 97.8%, respectively; 7 (7.7%) patients experienced the composite of death (no patient), myocardial infarction (4 patients), or revascularization (4 patients) within 24 hours of PCI, and 1 (1.1%) patient had peri procedural major bleeding. No unsatisfactory outcomes occurred in 21 patients who underwent repeated PCI on...
argatroban at a mean of 150 days later. Findings from a multicenter, prospective study evaluating argatroban and glycoprotein IIb/IIIa inhibition therapy in patients undergoing PCI,\(^{78}\) while not conducted specifically in HIT patients, suggest that a reduced dose of argatroban (perhaps a 300-μg/kg bolus, followed by a 15-μg/kg per minute infusion) provides adequate anticoagulation in combination with glycoprotein IIb/IIIa inhibition during PCI.

Bivalirudin has been evaluated in a prospective, open-label study of 52 patients with HIT undergoing PCI (Table 5).\(^{4,72}\) Patients with severe renal impairment were excluded. Bivalirudin was administered as a 0.75- or 1.0-mg/kg bolus followed by a 1.75- or 2.5-mg/kg per hour infusion for 4 hours. The primary end point—major bleeding 48 hours after discontinuation or until discharge—occurred in 1 (1.9%) patient. Procedural success (TIMI grade 3 flow and <50% stenosis) and clinical success (absence of death, emergency bypass surgery, or Q-wave infarction) occurred in 98% and 96% of patients, respectively. Furthermore, bivalirudin is indicated in the United States as an anticoagulant in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty,\(^{102}\) and many interventional cardiologists have considerable experience with this agent in patients without HIT undergoing PCI.

Experience with lepirudin in patients with HIT undergoing PCI is limited to case reports and small, retrospective case series.\(^{91,103}\) In the largest retrospective series,\(^{91}\) 9 patients with a history of HIT or current HIT underwent 10 interventional procedures with lepirudin anticoagulation and glycoprotein IIb/IIIa blockade. Drug doses were not reported. Procedural success (<30% residual stenosis with TIMI 3 flow without death, myocardial infarction, or emergent revascularization within 30 days) occurred in 7 procedures, and bleeding requiring transfusion occurred in 1 patient.

There are anecdotal reports of successful danaparoid use in HIT patients undergoing PCI. A preprocedural intravenous 2250-U bolus (or greater for body weight >75 kg) followed by a 150- to 200-U/h infusion for 1 to 2 days postprocedurally has been suggested.\(^{67}\) A reduced bolus (1500 U) may be adequate if glycoprotein IIb/IIIa inhibition is used concurrently.\(^{104}\)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Argatroban (Lewis et al(^{39}))</th>
<th>Lepirudin (Mahaffey et al(^{42}))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial PCI Group</td>
<td>Repeated PCI Group†</td>
</tr>
<tr>
<td>Absence of death, emergency bypass surgery, or Q-wave infarction</td>
<td>89/91 (97.8%)</td>
<td>21/21 (100%)</td>
</tr>
<tr>
<td>Postprocedural stenosis &lt;50%*</td>
<td>80/88 (97.7%)</td>
<td>20/20 (100%)</td>
</tr>
<tr>
<td>Major bleeding†</td>
<td>1/91 (1.1%)</td>
<td>0/21 (0%)</td>
</tr>
</tbody>
</table>

*With TIMI grade 3 flow in the lepirudin study.
†Within 24 hours (argatroban) or 48 hours (lepirudin) of drug administration or until hospital discharge, whichever came first.
‡Mean separation of 150 days from initial PCI.

Published cases found that death or limb amputation occurred in 42% of pediatric HIT patients without therapy, compared with 18% treated with lepirudin, argatroban, or danaparoid.\(^{39}\) Although not systematically studied, neonates and children, in whom drugs often have different pharmacokinetics than in adults, appear to require greater doses of the alternative anticoagulants than do adults.\(^{24,67}\) A study is ongoing in the United States to evaluate argatroban anticoagulation, including its pharmacokinetics, in pediatric patients in whom heparin use is problematic.

**Future Directions**

Considerable progress has been made in the past decade to elucidate the pathogenesis of HIT, establish the frequency of HIT (and HIT antibody) in different patient populations, and identify and validate treatment options. Refinements in these areas are expected as the awareness of HIT increases and diagnostic approaches continue to improve. Fewer patients may be placed at risk for HIT in the future because it is anticipated that there will be relative increases in the use of LMWH compared with unfractionated heparin and, where approved, in alternative anticoagulants compared with heparins. In addition, more patients with HIT, whether or not complicated by thrombosis when suspected, will avoid catastrophic thromboembolic outcomes when they receive prompt, appropriate treatment, ie, immediate cessation of heparin and initiation of alternative anticoagulation. Ongoing clinical studies in HIT evaluating alternative anticoagulation in pediatrics and in cardiac surgery are expected to provide improved dosing guidance in these special clinical circumstances. The role of adjunctive therapies, perhaps antiplatelet therapy, with alternative anticoagulation for treating HIT remains to be investigated.

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**References**


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