An unexpected decrease in the platelet count to a value <100,000/mm$^3$ is a situation frequently faced that demands immediate explanation or evaluation. Many underlying conditions such as bone marrow disorders, disseminated intravascular coagulation, sepsis, thrombotic thrombocytopenic purpura, hypersplenism, and immune disorders are well-known causes of thrombocytopenia. Drugs that may cause thrombocytopenia include quinine, antibiotics, histamine$_2$-blockers, sulfa drugs, unfractionated heparin (UFH), and low-molecular-weight heparin (LMWH). The evaluation and proper management of patients who develop thrombocytopenia during treatment with heparin is critically important. Failure to properly diagnose and treat thrombocytopenia can lead to a paradoxical effect, widespread thrombosis, and death.¹

There are 2 causes of thrombocytopenia in heparin-treated patients. The first is heparin-associated thrombocytopenia (or HAT, previously also known as HIT I). HAT is defined as mild thrombocytopenia (platelets 100,000–130,000/mm$^3$) occurring 1–4 days after the start of heparin. The incidence of this nonthrombogenic, nonimmune-mediated thrombocytopenia is approximately 25%. HAT is caused by a direct interaction between heparin and platelets; antibodies play no role. Patients with HAT usually have no complications, and the thrombocytopenia resolves as soon as heparin is discontinued.¹

Heparin-induced thrombocytopenia (HIT or HIT II) is a less common but much more serious condition associated with immune destruction and activation of platelets from antibodies that bind to heparin–platelet factor 4 (PF4) complexes, leading to platelet aggregation and thrombocytopenia. The incidence of HIT varies from 1% to 3% of patients receiving UFH.² It has been suggested that HIT oc-
curs more frequently after large intravenous doses of UFH than after smaller subcutaneous injections, but it has also been observed after one-time low-dose intravenous line flushes.\textsuperscript{1,3} Formation of antibody, which occurs in approximately 3–20% of patients who receive heparin, does not define the presence of HIT. However, thrombosis is rare in the absence of thrombocytopenia.\textsuperscript{3} Typically, patients with HIT have a decrease in their platelet count 5–10 days after the initial exposure to heparin therapy. The platelet count usually, but not always, declines to <100,000/mm\textsuperscript{3}, or >50% of the baseline preheparin value. In rare cases, values <20,000/mm\textsuperscript{3} are seen.\textsuperscript{1} The platelet count can drop more precipitously if the patient has been exposed to heparin during the previous 3 months.\textsuperscript{4}

A review of the available literature from the National Library of Medicine from 1992 through June 2001 and selected references from the reviewed literature was undertaken to describe the syndrome and various management approaches depending on the clinical situation. Recent advances in recognition and newly available pharmacologic management are included for this commonly unrecognized or mistreated syndrome. Even though the incidence of HIT is rare, use of UFH is very common, especially in the acute-care setting. LMWH use is increasing as well, sometimes with long-term courses used in selected situations (i.e., thrombosis or adverse events in the presence of therapeutic warfarin). Thus, the possibility of HIT becomes frequent in situations where UFH or LMWH is commonly used.

**Pathophysiology**

Circulating heparin or heparin-like compounds (LMWHs) have a high affinity for PF4, which is normally found in the platelet α-granules. This leads to formation of antigenic heparin–PF4 complexes. Unlike the ≥18 saccharide units required to bind heparin to thrombin and antithrombin, only 12–14 saccharide units are needed to form the antigenic PF4 complex. Because of this, larger LMWH preparations (>4000 Da) can cause HIT.\textsuperscript{5,6} The risk of antibody formation and clinical HIT is considered to be lower than that of UFH. Once the antigenic complex has formed, in vitro cross-reactivity with LMWH has been reported\textsuperscript{7} to be >80%.

Altered PF4 configuration after binding to heparin exposes several antigenic sites that can trigger an immune reaction, most notably by immunoglobulin (Ig) G, but occasionally by IgA and IgM.\textsuperscript{14} The circulating IgG–heparin–PF4 complexes bind to the platelet FcγRIa receptor, resulting in platelet aggregation and further release of PF4 that perpetuates the cycle. As a result of platelet activation, platelet clumping occurs, leading to rapid clearance and thrombocytopenia. In addition, vesicular platelet-membrane microparticles are released from the platelet. These microparticles are highly thrombogenic and activate the coagulation system. As a result, one sees elevated d-dimer and thrombin–antithrombin complexes as well as a decrease in antithrombin, protein C, and heparin cofactor II concentrations.\textsuperscript{5–11}

Endothelial injury due to mechanical injury such as surgery or angioplasty can cause further release of additional PF4. This excess PF4 then binds to heparin-like molecules on the surface of endothelial cells. The circulating HIT antibody then binds to the complex on the epithelial surface, causing further platelet activation.\textsuperscript{2,11}

**CLINICAL MANIFESTATIONS**

HIT is associated with a high incidence of clinically manifested thromboembolism (venous or arterial), with the HIT thrombotic syndrome (HITTS) occurring in 25–50% of patients with HIT.\textsuperscript{13} HITTS is strongly associated with the presence of both HIT antibodies and thrombocytopenia, but not to the magnitude of the platelet nadir.\textsuperscript{14} Venous thrombosis occurs approximately 4 times more often than arterial thrombosis (Table 1).\textsuperscript{5} Arterial thrombosis consists primarily of platelets, which can yield a white appearance to the clot on pathology; hence, the term “white-clot syndrome” is used. Patients who have undergone recent surgery in whom endothelial wall disruption occurs are at increased risk because of the release of PF4, platelet activation, and resultant hypercoagulable state.\textsuperscript{15}

The increased postsurgical risk of HITTS may also depend on the type of surgery performed. Patients undergoing cardiac bypass graft (CABG) surgery requiring UFH are postulated to have a higher incidence of positive HIT activation detected using both activation and antigen assays, but a lower incidence of HITTS compared with patients undergoing orthopedic surgical procedures.\textsuperscript{16} However, patients recently undergoing cardiac procedures are not routinely reevaluated for thrombosis formation since it requires an invasive procedure. This is in contrast to orthopedic procedures, where postprocedure ultrasound testing can identify a venous thrombosis, potentially increasing the reported incidence of HITTS. The incidence of HIT-positive assays and HITTS in orthopedic surgery patients receiving an LMWH is lower than in patients receiving

**Table 1. Clinical Manifestations of HIT**

| Thromboembolism | arterial
<table>
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<tr>
<td>stroke</td>
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<tr>
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<td>deep-vein thrombosis</td>
</tr>
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<td>pulmonary embolism</td>
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<td>localized skin reactions</td>
</tr>
<tr>
<td></td>
<td>acute systemic reactions</td>
</tr>
<tr>
<td></td>
<td>global transient amnesia</td>
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</tbody>
</table>

HIT = heparin-induced thrombocytopenia.
One prospective, randomized trial in 665 patients receiving subcutaneous UFH or LMWH for thromboprophylaxis after hip surgery showed a HIT rate of 2.7% versus <1%, respectively. Hemorrhage during HIT is rare. Diagnosis is usually based on the time between initial heparin exposure and the subsequent fall in the platelet count, clinical manifestations, and in vitro laboratory testing.

Acute HIT may develop in patients given an intravenous bolus of heparin if they were previously exposed to heparin, usually within a 3-month period. The clinical picture may include fever, chills, tachycardia, hypertension, flushing, chest pain, dyspnea, nausea, vomiting, or diarrhea within 5–30 minutes of UFH exposure. Common clinical sequelae of unrecognized HIT are acute venous and/or arterial thrombosis, and death from pulmonary embolism or stroke. Less common complications of HIT include warfarin-associated venous limb gangrene, bilateral adrenal hemorrhagic infarction, and DIC. Warfarin appears to have a detrimental effect if started alone at the time that HIT becomes manifest. The postulated cause of this warfarin effect is from decreasing vitamin K–dependent natural anticoagulants protein C and protein S concentrations shortly after initiation. The decrease in these proteins may lead to acute thrombotic events.

A skin reaction has been reported to be associated with a positive HIT antibody screen, but not necessarily a decrease in platelet count. It is a local skin reaction described as painful red plaques or necrotic skin lesions at the site of subcutaneous heparin injections ≥5 days after the initiation of treatment. Tissue pathology typically has revealed microvascular thrombi.

Global amnesia is an unusual and rare presentation of HIT described in 2 patients shortly after exposure to intravenous boluses of UFH. In these cases, the amnesia lasted less than a day, and computed tomography scans were negative.

**Laboratory Testing**

Early recognition and management of the HIT syndrome are critical in order to prevent unwanted thrombotic complications. In addition to baseline platelet count, a daily platelet count is suggested starting on day 1 of UFH therapy if the patient has a history of recent exposure to UFH, and on day 4 of UFH treatment in the absence of prior exposure. Confirmation of HIT antibody can be done using an antigen or an activation functional assay that suggests the presence of HIT antibodies based on the heparin-dependent, platelet-activating property. The platelet activation assay detects HIT IgG antibodies that are able to cross-link platelet FcyIIa receptors in the presence of heparin and PF4. Since platelet activation can be a nonspecific end point, it is important to separate the effects of HIT antibodies from other activators that might be present in the serum or plasma sample. Activation assays are performed using washed platelets or citrated plasma samples.

Several advantages exist for the use of washed platelets in HIT testing. These include the ability to run multiple assays at the same time to test various reaction conditions, and the ability to compare weak or strong HIT serum controls for quality control. Additional advantages include the use of various reaction conditions that test high and low heparin concentrations to rule out false-positive platelet activation. The major disadvantage is that this is a technically demanding procedure requiring highly trained personnel, expensive flow-cytometry equipment, and HIT antibody donors.

The more common citrated plasma assay methods differ among laboratories, but they usually assess aggregation response of platelets using a 1:1 mix of citrate-anticoagulated platelet-poor plasma obtained from the patient, and normal plasma in the presence of therapeutic heparin concentrations. Citrated plasma assays include flow cytometry and platelet aggregation to assess activation of platelets. A different assay, the serotonin-release assay, has a sensitivity and specificity of approximately 90%, but it is technically difficult to perform and requires radioactive substance. Citrated plasma assay methods are generally less sensitive than those using washed platelets. Platelet aggregation assays are widely available and can assess cross-reactivity to other heparin-like agents. Disadvantages of platelet aggregation include lower specificity and sensitivity, the requirement of screened donor plasma, and difficulty maintaining proficiency when test volume is low.

Another assay for HIT-associated antibodies is the enzyme-linked immunosorbent assay (ELISA), which detects the binding of antibodies to immobilized PF4–heparin complexes. The ELISA detects the presence of the IgG antibody and has sensitivity of approximately 90%. Disadvantages include the inability to assess cross-reactivity with other heparin-like compounds such as LMWHs and lower specificity (frequent false-positive determinations). A negative ELISA result coupled with low clinical suspicion essentially rules out HIT. However, the addition of a negative platelet aggregation assay provides even higher positive predictive value for ruling out HIT, especially in the presence of a weakly positive ELISA result or in the presence of other immune disorders that can cause false-positive ELISA results.

Unfortunately, the ideal assay for HIT — one that is easy to perform, inexpensive, very specific, and sensitive — does not yet exist. When HIT is suspected, the assay available with the shortest turnaround time should be used (usually an ELISA). A platelet aggregation assay should also be considered in all patients with a high clinical suspicion of HIT who have negative ELISA results, and in all situations where the test result will affect long-term anticoagulation management.

**Treatment**

Once HIT is strongly suspected or diagnosed, several anticoagulation treatment decisions need to be made. First, all sources of heparin must be removed, including use in arterial line bags, heparin-coated or -bathed catheters, or instruments and catheter flushes. The outside cover of the
medical chart should be clearly labeled “avoid all heparin.” Heparin cessation alone, however, may not be sufficient since the incidence of HIT-associated thrombosis remains high in the first week after stopping heparin, and thrombosis can occur for up to a month. The cumulative frequency of HIT-associated thrombosis in patients presenting with thrombocytopenia is approximately 50% at 30 days after cessation of heparin. Because of the high risk of thrombosis, alternative anticoagulant therapy must be considered until the platelet count has recovered.

Currently, the only recommended parenteral anticoagulant option is the use of the low-molecular-weight heparinoid danaparoid, or use of one of the immunologically distinct thrombin inhibitors, lepirudin, bivalirudin, or argatroban (Table 2). Even though the incidence of HIT is lower in patients initially treated with an LMWH, it should not be substituted for heparin since there is immunologic cross-reactivity between these agents and the HIT antibody. Initiating warfarin alone in presence of HIT should be avoided.

DANAPAROID

Danaparoid is composed of depolymerized glycosaminoglycans derived from porcine gut mucosa. It consists of heparan sulfate (84%), dermatan sulfate (12%), and chondroitin sulfate (4%). Similar to heparin, danaparoid inhibits factor Xa after promoting its binding with antithrombin. Danaparoid has been shown to have a lower (~10%) but measurable cross-reactivity with heparin for HIT antibody in vitro. There is, however, little clinical evidence that substitution of danaparoid for heparin leads to adverse outcomes in patients with HIT, such as progression or development of thrombosis. The number of days required for the platelet count to recover in patients with HIT has been shown to be similar, regardless of the presence or absence of antibodies that cross-react with danaparoid. The usual route of administration is subcutaneous, with limited data available for intravenous infusions. The intensity of anticoagulation can only be assessed using a functional anti-Xa activity test. Use of a chromogenic peptide substrate is available test to monitor its anticoagulant effects, and no rapid means of reversing the anticoagulant effect if bleeding occurs. Nonhemorrhagic adverse effects reported for danaparoid include skin rash, fever, nausea, constipation, in-jection site pain, ischemic headache, and urinary tract infection. The incidence of major bleeding during danaparoid treatment of HIT is reported to be 3.1%. The dose depends on the medical indication for anticoagulation and, in some cases, the patient’s weight.

For acute thrombosis, treatment can be initiated with an intravenous bolus dose of 1250–3700 units followed by 400 units/h for 4 hours, 300 units/h for 4 more hours, then 150–200 units/h. If thrombosis developed more than 5 days before, a bolus of 1250 units followed by 750–1250 units subcutaneously every 8–12 hours can be used. For postsurgical prophylaxis of deep-vein thrombosis or use in patients with a history of deep-vein thrombosis but no active thromboembolism, a dose of 750 units (for patients weighing <90 kg) or 1250 (>90 kg) is suggested every 8 hours in acute HIT, or every 12 hours in patients with a recent history of HIT. Danaparoid is only approved for prophylaxis of postoperative deep-vein thrombosis following hip surgery. It is not presently approved by the Food and Drug Administration for use in patients with HIT.

ARGATROBAN

Argatroban is a small, synthetic, direct thrombin inhibitor derived from the amino acid argi-
nine. It inhibits thrombin by reversibly binding at the catalytic site independent of antithrombin or other cofactors. Serum concentrations are not affected in renal failure, making the drug potentially useful in patients who have HIT and renal insufficiency or failure. The dose response of the drug is linear, and is monitored using the aPTT or activated clotting time (ACT).

Lewis et al. compared the efficacy and safety of intravenous argatroban 2 µg/kg/min adjusted to an aPTT 1.5–3 times the control in patients with either HIT (n = 160) or HITTS (n = 114). Treatment was maintained for 5.3 ± 0.3 and 5.9 ± 0.2 days, respectively, with corresponding mean ± SE infusion rates of 2.0 ± 0.1 and 1.9 ± 0.1 µg/kg/min, respectively, in the 2 groups. Clinical outcomes at 37 days were compared with HIT historical controls (n = 193) (Table 3). In both groups, once therapy was initiated, there was a rapid increase in the platelet count and significant improvement compared with the control group.

Since no antagonist is currently available to reverse the effects of argatroban, the occurrence of major bleeding during treatment is a serious problem. Nonhemorrhagic adverse effects reported for argatroban include headaches, dizziness, cardiac arrhythmias, cardiac arrest, hypotension, airway reactions, diarrhea, nausea, abdominal pain, and, rarely, anorexia or increased serum transaminases. Rebound angina has been noted after stopping the argatroban infusion in patients with unstable angina. Neutralizing antibodies have not been observed following use of argatroban.

A primary disadvantage to argatroban is that it prolongs the international normalized ratio (INR). The magnitude of the effect may, in part, be thromboplastin dependent, with potentially greater variability when reagents with a higher international sensitivity index are used. The rise in the measured INR is linear with the argatroban dose. To assess the degree of warfarin anticoagulation during therapy with both warfarin and argatroban, the argatroban infusion must be stopped for 4–6 hours (longer in patients with cardiac or hepatic insufficiency) and the INR remeasured. This INR determination should accurately reflect the warfarin response. Because combination therapy using argatroban and warfarin increases the aPTT in a linear, dose-dependent fashion, measurement of the aPTT when argatroban is not being infused may be useful in documenting the absence of an argatroban effect (keeping in mind that warfarin may moderately increase the aPTT). Patients receiving argatroban should not be tested for coagulation defects using routine (clot-based) assays because argatroban inhibits these assays, causing a false decrease in fibrinogen and factor concentrations, and a false increase in the level of protein C. This interference is not seen with chromogenic assays.

Argatroban is labeled for use in patients who have or are at high risk for developing HIT.

LEPIRUDIN

Lepirudin (r-hirudin) is an rDNA derivative of natural hirudin, a direct thrombin inhibitor produced from leech

<table>
<thead>
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<th>Trial</th>
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<th>Outcome</th>
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<td>major bleeding (%)</td>
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</table>

HIT = heparin-induced thrombocytopenia; HITTS = HIT with thrombosis syndrome; IC = intracranial bleeding; TEC = thromboembolic complication. *Historical control of HIT prior to availability of direct antithrombin. *Day of outcome assessment after initiation of therapy. 4Primary efficacy composite end points of death, amputation, or new thrombosis.
salivary glands. Lepirudin selectively and irreversibly binds to thrombin at both substrate recognition and enzyme catalytic sites. This lepirudin–thrombin complex can be detected up to 18 hours after a dose. Lepirudin blocks thrombin activity independent of antithrombin and heparin cofactor II, and effectively inhibits fibrin-bound thrombin, thereby blocking the activation of platelets and factors V, VIII, and XIII. It is immunologically distinct and has a no cross-reactivity with HIT antibodies. Lepirudin is not affected by PF4 or protamine, and appears to be a weak immunogen. Antihirudin antibodies have been observed in patients with HIT who were treated ≤5 days with lepirudin. The presence of these antibodies has not been associated with any adverse effects or clinical resistance to lepirudin.

The effectiveness of lepirudin in HIT was evaluated in 2 prospective, multicenter studies that used historical controls, HAT-1 (n = 82) and HAT-2 (n = 112). Enrollment criteria included confirmation of HIT antibodies at a single central laboratory prior to initiating therapy. This may have resulted in a delay in onset of treatment. Results showed a reduction in new thromboembolism, amputation, and death in patients receiving lepirudin compared with the placebo control (Table 3). The cumulative incidence of bleeding at 35 days was significantly higher in the lepirudin-treated versus control groups (42% vs. 23.6%; p = 0.001). Similarly, more lepirudin-treated patients required transfusions (18.8% vs. 7.1%; p = 0.02). No fatal or intracranial bleeds were noted in the lepirudin-treated patients. In general use, major hemorrhagic adverse reactions reported include intracranial bleeding (0–2%), to approximately 14% for more common minor bleeding.

An advantage with the intravenous delivery of lepirudin is the ability to monitor its anticoagulation activity using the aPTT, which increases in a dose-dependent manner. Correlation between the aPTT and lepirudin concentrations declines above aPTT values >70 seconds. The recommended target aPTT in patients with HIT is 1.5–2.5 times the control value. For treatment of venous thrombosis, one randomized, dose-ranging study compared 3 different regimens of subcutaneously administered lepirudin, 0.75, 1.25, and 2 mg/kg every 12 hours, with UFH (5000 units bolus; 1250 units/h titrated) in patients with deep-vein thrombosis (n = 121). Lepirudin 1.25 mg/kg every 12 hours was just as effective as adjusted-dose UFH. The group receiving lepirudin 2 mg/kg had an increased incidence of complications.

Lepirudin is predominantly eliminated by the kidneys. In patients with creatinine clearance (Cl_{cre}) values >60 mL/min, the recommended dose for acute thromboembolism is a bolus of 0.4 mg/kg (up to 110 kg) followed by an infusion of 0.15 mg/kg/h. The dose is reduced to a bolus of 0.2 mg/kg followed by a constant infusion of 0.1 mg/kg/h when concurrent thrombolysis has been used. For prophylaxis or patients with a history of deep-vein thrombosis (but no acute thromboembolism), an infusion (no bolus) of 0.1–0.15 mg/kg/h is suggested. Dosing reductions of 50% are recommended when Cl_{cre} values are 45–60 mL/min, and 30% of the normal dose for Cl_{cre} values of 30–44 mL/min. For Cl_{cre} 15–29 mL/min, 15% of the normal dose is suggested. Use in patients with Cl_{cre} <15 mL/min is discussed in the renal failure section. Lepirudin, marketed under the trade name Refludan (Berlex), has a labeled indication for anticoagulation in patients with HIT and associated thromboembolism in order to prevent further thrombotic complications.

**DESIRUDIN**

Desirudin is another direct thrombin inhibitor that is a recombinant form of hirudin. The C-terminal amino acid sequence of hirudin is linked with a peptide derived from the fibrinogen cleavage region. The greatest clinical use of this agent has been in patients undergoing angioplasty or for deep-vein thrombosis prophylaxis after orthopedic hip and knee replacement surgery. Given as a subcutaneous injection or by intravenous bolus and infusion, the dose–response relationship correlates with the aPTT and thrombin time. Excretion is primarily renal (40–60% removed unchanged), with a half-life of 2–3 hours. An incidence of serious bleeding of 5–7% and minor bleeding of 11–15% has been reported in connection with intravenous or subcutaneous desirudin. Desirudin is not recommended for use in patients with severe hepatic or renal impairment and is contraindicated in pregnancy because birth defects were detected in animal experiments. Presently, desirudin is not approved for use in the US, and information for its use in HIT is limited.

**BIVALIRUDIN**

Bivalirudin is another direct thrombin inhibitor that is a synthetic analog of r-hirudin. As with other direct thrombin inhibitors, it does not depend on antithrombin as a cofactor. Binding of bivalirudin is reversible at the enzymatic catalytic site and at the anion binding site of thrombin. It has been shown to effectively inhibit clot-bound thrombin and is not affected by components of platelet-release reactions. Intravenous bivalirudin produces a dose-dependent prolongation of the aPTT, ACT, and thrombin time. Unlike some other direct thrombin inhibitors, bivalirudin has the potential advantage of producing only transient thrombin inhibition, which may allow a wider therapeutic window and permit the use of higher doses.

Most data concerning the use of bivalirudin regard patients with unstable angina, coronary angioplasty, and patients treated with streptokinase for acute myocardial infarction. One-dose ranging study has suggested that it is effective when given in a dose of 1 mg/kg every 8 hours subcutaneously to prevent deep-vein thrombosis in orthopedic surgery patients. For other indications, additional studies are needed to determine bivalirudin’s potential as an anticoagulant. Unlike lepirudin, no antibodies to bivalirudin have been detected during therapy. Bivalirudin therapy has been associated with a significantly lower incidence of major bleeding compared with UFH.
these studies, the incidence of adverse hemorrhagic events with bivalirudin was 3.8%, with <0.5% of the patients having serious intracranial bleeding and <0.2% having retroperitoneal bleeding. Nonhemorrhagic adverse effects include occasional headaches and diarrhea. Partial-dose reductions may be necessary in the presence of renal insufficiency, since 20% of the drug is eliminated unchanged in the urine. Data on its use in HIT are limited. Presently, bivalirudin is approved for use in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA).

**MELAGATRAN**

Melagatran is a direct antithrombin that is the active metabolite of the investigational oral prodrug ximelagatran (H376/95 AstraZeneca). Approximately 20% of ximegalatran is metabolized to melagatran by the liver. Melagatran has no significant protein binding, a small volume of distribution (0.2 L/kg), with peak plasma concentration achieved 1.6–1.9 hours after oral administration. Melagatran is primarily eliminated via the kidneys, with a half-life of 4–5 hours. The AUC increases linearly with increased doses. As with the other direct antithrombins, it may be a possible option in HIT, especially when the oral route is desired. Data supporting the safe and effective use of ximegalatran in HIT are presently not available.

**FONDAPARINUX**

Fondaparinux (Org31540/SR90107A), commonly known as pentasaccharide, is a synthetic compound that contains the precise saccharide sequence found in UFH that binds and accelerates antithrombin activity. It directly accelerates antithrombin-mediated Xa inactivation in a linear and dose-dependent manner. Given by subcutaneous injection, fondaparinux is almost exclusively bound to antithrombin, with a peak plasma concentration achieved at 2.2–2.6 hours and a plasma half-life of approximately 15–18 hours. Fondaparinux was compared using a serotonin-release assay with UFH and enoxaparin in the sera of 30 patients with HIT. Unlike UFH and enoxaparin, fondaparinux did not demonstrate any cross-reactivity with the heparin–PF4 antibodies. Fondaparinux, marketed as Arixtra (Sanofi-Synthelabo), has been approved by the Food and Drug Administration for prophylaxis of deep-vein thrombosis in patients undergoing hip and knee surgery. It is in Phase III clinical trials for treatment of venous thrombosis and acute coronary syndromes. Fondaparinux may be a potential option for subcutaneous routes in the presence of HIT with deep-vein thrombosis prophylaxis concerns. No data, however, are presently available on its safe or effective use in patients with HIT.

**WARFARIN**

In the setting of HIT, warfarin therapy alone should not be used to replace heparin since inhibition of the synthesis of the vitamin K–dependent protein C and protein S may actually accelerate the underlying procoagulant condition. Warfarin-induced skin necrosis and venous limb gangrene have been reported in patients with HIT treated with warfarin. This is characterized clinically by necrosis complicating deep-venous thrombosis in the absence of large-vessel arterial occlusion. Thus, use of an anticoagulant that directly inhibits thrombin is necessary before starting warfarin therapy in a patient with active HIT. Even though not a suggested approach, modest doses of warfarin alone have not been shown to be associated with adverse outcomes in patients with HIT. If anticoagulation is desired for an extended period of time, warfarin can be initiated after antithrombin therapy has been established. When an INR value of 2.0 has been reached (and reflects factor II inhibition), then the thrombin inhibitor can be discontinued.

**ANECDOtal TREATMENT APPROACHES**

Other therapies that have been attempted to treat HIT include the use of prostacycline, glycoprotein IIb/IIIa inhibitors, ancord, dextran, IgG agents, and plasmapheresis. Prostacycline is thought to decrease platelet activation, but is associated with a high incidence of hypotension. Early studies of combined use of antithrombins and IIb/IIIa inhibitors suggest that they are beneficial, but more studies are needed. Ancrod has a slow onset of action over 12–24 hours, no direct antithrombin activity, and a high incidence of bleeding. Plasmapheresis is thought to remove heparin-associated IgG. High-dose, intravenous IgG prevents platelet aggregation by competitively inhibiting binding of the HIT–IgG complex to the Fc receptor. Limited reports of patients have shown reversal of platelet aggregation and the stabilization of thrombosis with plasmapheresis or high-dose IgG. Plasmapheresis is an invasive procedure, and intravenous Ig is in short supply and very expensive.

**Treatment of HIT in Special Situations**

**RENAL FAILURE/HEMODIALYSIS**

Heparin is frequently used in hemodialysis patients to prevent thrombosis of the dialysis circuit. In the presence of HIT, bathing dialyzers in heparin must be avoided in addition to any heparin flushes. Several options including citrate or saline solutions have been used to prevent clotting of the dialyzer circuit.

The manufacturer of lepirudin presently does not recommend its use when Cr<15 mL/min. Experience with lepirudin in azotemia has previously been investigated for the prevention of clotting in the dialysis circuit and in case reports describing treatment against systemic thrombosis.

Elimination rates and resultant aPTT values for r-hirudin have been reported in hemodialysis patients with various degrees of renal function (0–12.18 mL/min). The calculated half-life of lepirudin is 15–316 hours, with a
significant inverse correlation with the Cl\textsubscript{cr}. Measured aPTT values were above baseline for 2–3 days, with the exception of 2 nephrectomized patients in whom the return took 8 and 30 days.\textsuperscript{65} Another study\textsuperscript{66} showed a median clearance ± SD of 19.2 ± 4.9 mL/min (Cl\textsubscript{cr} 12.1–27.2 mL/min) compared with 165 ± 32 mL/min (Cl\textsubscript{cr} 93–126 mL/min). Vanholder et al.\textsuperscript{67} reported the half-life of lepirudin was more than 30 times longer among patients with renal failure (51.8 ± 15.6, compared with 1.7 ± 1.5 hours in healthy controls; p < 0.001) and AUC 60 times higher. Distribution volumes were slightly lower among patients with renal failure.

Treatment approaches depend on the presence or absence of an active thrombotic event and the need for prophylaxis to prevent clotting of the dialyzer. For prophylaxis in patients undergoing dialysis, a bolus dose of lepirudin 0.1 mg/kg before dialysis has been suggested.\textsuperscript{68} The same authors suggested, with continuous veno-veno hemofiltration, a continuous intravenous infusion of 0.005 mg/kg/h immediately before the filter, adjusting the aPTT to 1.5–2.5 times control. Fisher et al.\textsuperscript{69} studied lepirudin in critically ill patients with suspected HIT receiving continuous veno-venous hemodialysis using a polysulfone high-flux dialyzer. Infusion doses ranged from 0.006 to 0.009 mg/kg/h (total body weight; n = 2), depending on urine output.

Use of lepirudin for treatment of systemic thrombosis in patients with renal failure has been described. In one case report,\textsuperscript{70} a lepirudin bolus dose of 0.2 mg/kg, followed by lower bolus doses (0.05 mg/kg) on days 7 and 13 (no constant infusion), was used to prevent thromboembolism in a HIT patient. The aPTT after the initial bolus was greater than the aPTT goal of 85 seconds for 2 days, eventually decreasing to <50 seconds on day 7 when the next bolus was administered. The patient died from cardiopulmonary arrest shortly after the third dose. In a separate report,\textsuperscript{71} 2 patients with renal failure who required hemodialysis were safely managed with a constant infusion of lepirudin ranging from 0.005 to 0.01 mg/kg/h depending on the degree of residual renal function. Adjustments were successfully made using aPTT values determined 8 hours after any infusion rate change. Depending on renal function changes, dosing adjustments were required to maintain adequate anticoagulation. Unfortunately, the anticoagulation effects of lepirudin in renal insufficiency can last for days and lead to an increased risk of unwanted bleeding complications. Since prolonged anticoagulation effects after stopping lepirudin still pose a significant concern, use of this agent in azotemia should be avoided.

The pharmacokinetics of bivalirudin have been studied in patients with various degrees of renal insufficiency. Patients with moderate to severe renal insufficiencies experienced a 45% and 68% reduction, respectively, in drug clearance.\textsuperscript{72} An interesting finding was a lower incidence of bleeding as renal function deteriorated when compared with heparin, which showed a higher bleeding occurrence as renal function declined. Presently, there is no clear dosing guideline for bivalirudin use in significant renal insufficiency.

Danaparoid has been used in patients undergoing hemodialysis, in doses of 2250–3750 units intravenously or subcutaneously every 12 hours, targeting plasma anti-Xa concentrations of <0.3 U/mL prior to dialysis and 0.5–1.0 U/mL during dialysis.\textsuperscript{73} A long half-life is one disadvantage of danaparoid use in this population with a high risk for bleeding.

Argatroban’s favorable pharmacokinetic profile makes this agent the preferred thrombin inhibitor when renal function is compromised. Argatroban is readily metabolized into a major derivative, M1, which has pharmacologic characteristics distinct from its parent compound. Clot-based assays such as the aPTT measure the cumulative anticoagulant effects of both argatroban and its active M1 metabolite.\textsuperscript{74} In a small cohort of 30 HIT patients,\textsuperscript{74} the M1-metabolite concentrations correlated well with the results of global clotting assays. The pharmacokinetics and pharmacodynamics of argatroban in brief infusions have been studied in a small number of patients with renal failure.\textsuperscript{75} In 6 patients with normal renal function and in 5 with Cl\textsubscript{cr} <29 mL/min, no significant differences in plasma argatroban, aPTT, or whole-blood ACT were noted. Unfortunately, the continuous infusion used in this study lasted only 4 hours. Data on use of argatroban in hemodialysis is not presently available. Our own experience with 2 patients was that no change in aPTT occurred; thus, no change in dose was required during intermittent hemodialysis using conventional (Torry 2.0) and high-efficiency (Fresenius 70) dialyzers. Argatroban is likely to be preferred in patients with HIT and renal failure since dosing adjustments are not dependent on renal function. Use in hemodialysis needs further study to establish safety and efficacy.

**PREGNANCY**

Data on the treatment of HIT in pregnancy are scarce. Danaparoid, lepirudin, argatroban, and bivalirudin are classified as pregnancy category B, based on limited animal data.\textsuperscript{75,33,40} Experiments\textsuperscript{80} in pregnant rabbits showed lepirudin fetal plasma concentrations <2% of the maternal concentration. Large doses of 30 mg/kg were associated with embryotoxicity, but not with doses ≤10 mg/kg. In a single case,\textsuperscript{76} no drug was detected in the breast milk of a woman receiving lepirudin 50 mg every 12 hours. In another case report,\textsuperscript{77} lepirudin 15 mg given subcutaneously twice daily from week 25 to term was successful in preventing thrombosis in a pregnant woman with systemic lupus erythematosus and recurrent venous thrombotic events who developed HIT secondary to dalteparin. No bleeding or fetal toxicity was detected.

Danaparoid has been used successfully as a prophylactic and therapeutic agent during pregnancy.\textsuperscript{78} No evidence of anti-Xa activity was found in the placental blood, suggesting that danaparoid does not cross the placenta. Another option for patients whose pregnancy is beyond 12 weeks is to institute warfarin therapy until term, at which time an antithrombin, if needed, can be given.\textsuperscript{79}
PEDIATRICS

Documentation of HIT and use of antithrombins in children is limited. There is one case report of a 12-year-old child with HITTS who was managed using a bolus dose of lepirudin 0.2 mg/kg followed by an infusion ranging from 0.1 to 0.7 mg/kg/h to maintain the aPTT at 50–80 seconds for 8 days. Another case involved an 11-year-old child with thromboembolism. Lepirudin was infused at 0.15–0.22 mg/kg/h for 58 days. No serious adverse events occurred in either case.

Danaparoid has also been used successfully in children. For patients up to 17 years of age and weight of <55 kg, the manufacturer recommends 10 units/kg subcutaneously every 12 hours for prophylaxis, and a 30-unit/kg bolus followed by a 1.2- to 4.0-unit/kg infusion, targeting anti-Xa concentrations of 0.4–0.6 U/mL.

Use of argatroban was reported in 2 neonates on extracorporeal membrane oxygenation (ECMO) for 6 and 78 days, respectively. Continuous intravenous argatroban was administered at doses ranging from 0.5 to 10 µg/kg/min to maintain ACT values of approximately 200 seconds. There was no evidence of intracranial bleeding or cannula-site hemorrhage, or need to replace the oxygenator or ECMO circuit.

CARDIAC SURGERY

Lepirudin has been used safely in noncardiopulmonary bypass surgery with minimal blood loss or complications while preventing thrombotic events. In a report of 57 patients with HIT requiring CABG, lepirudin was safely and effectively infused using online monitoring of lepirudin concentrations. Dosing requirements per minute during cardiopulmonary bypass ranged from 0.016 to 0.035 µg/kg/min with concurrent 24-hour blood drainage of 50–2200 milliliters. Full recovery was seen in 54 patients, with 3 dying as a result of complications unrelated to the perioperative management. Four patients with impaired renal function showed prolonged lepirudin elimination and excessive bleeding requiring surgical reexploration.

One retrospective review of patients with HIT who underwent CABG reported a mean dose of lepirudin in 17 patients with normal renal function (group 1) of 0.81 mg/kg compared with 0.73 mg/kg in 4 renal impaired patients (group 2) who had serum creatinine values >1.5 mg/dL. The mean aPTT at 12 hours after CABG was 45 seconds for group 1 and >100 seconds with group 2. Twelve-hour postprocedure total blood loss averaged 150 and 1700 mL in groups 1 and 2, respectively. Renally impaired patients required more blood transfusions. Although exact dosing is not well established, it is important to consider using a bolus dose, followed by priming of the bypass circuit. Monitoring anticoagulant activity should be done using the ecarin clotting time, since it has been shown to be more accurate than the ACT in monitoring lepirudin’s anticoagulant effect. Since lepirudin has no known reversal agent, the timing of discontinuing the infusion prior to removing the bypass has to be carefully determined to avoid postoperative bleeding.

A separate, unique treatment approach was reported in 10 patients with HIT and renal impairment (Clcr <50 mL/min) undergoing cardiopulmonary bypass surgery. A baseline aPTT of 40–60 seconds was reached with a bolus of lepirudin 5 mg, followed by a continuous infusion at 2 mg/h. At the beginning of the surgery, lepirudin was stopped. Ten minutes before cannulation for cardiopulmonary bypass, a bolus of the IIb/IIIa platelet inhibitor tirofiban (Aggrastat) 10 µg/kg was given, followed by a continuous infusion at 0.15 µg/kg/min during surgery. Five minutes after the bolus of tirofiban, a bolus dose of UFH 400 IU/kg was given and cardiopulmonary bypass was started when the target ACT of 480 seconds was reached. Additional UFH was administered only when the ACT fell to <480 seconds. Postoperative anticoagulation therapy was started immediately after surgery, with a continuous infusion of lepirudin 5 mg/h, to achieve an aPTT of 40–60 seconds. Platelet concentrations were monitored every 4 hours over the first 12 hours, then twice daily thereafter until discharge. Results showed no need for additional heparin. Two patients required transfusion of platelet concentrates; 5 patients required blood transfusions and fresh frozen plasma. The immediate postoperative ACT ranged from 115 to 145 seconds. All patients were discharged from the intensive care unit within 24 hours, with no additional transfusions being required after surgery. Between 7 and 10 days after surgery, all patients were discharged from the hospital. No preoperative increase in D-dimers or postoperative decrease in platelets was noted.

Data on the use of argatroban in patients with HIT undergoing cardiopulmonary bypass are limited. Arnoletti and Whitman reported the use of argatroban in a 51-year-old man with severe 2-vessel coronary artery disease, congestive heart failure (ejection fraction 15%), and acute myocardial infarction who developed HIT after coronary angioplasty. A continuous infusion of argatroban infusion was initiated at 3 µg/kg/min for 2 days, with an aPTT targeted between 1.5 and 3 times the control value. He then underwent coronary bypass surgery using an “Octopus” tissue-stabilizing device without cardiopulmonary bypass 2 days later, with the argatroban infusion discontinued 30 minutes prior to surgery. No anticoagulants were administered during the surgery. The aPTT values measured at the start of anesthesia and 5 hours later were 50.2 and 35.6 seconds, respectively. Surgery was uneventful, and the patient was discharged 6 days after surgery.

The use of argatroban has been reported in adults undergoing a left-heart bypass. The dose of argatroban started 20–30 minutes before the bypass ranged from 0.5 to 5 µg/kg/min (common dose 2 µg/kg/min) or intravenous bolus dose of argatroban 200–300 µg to achieve rapid anticoagulant effect. ACT values gradually increased from a baseline level of 125 ± 8.9 to 177.1 ± 31.7 seconds and 241.5 ± 16.3 seconds at 10 minutes and 60 minutes after the start of bypass, respectively. The prolonged ACT spontaneously recovered to 143.9 ± 21.6 seconds within 1 hour.
after the end of argatroban administration. Bleeding complications and final outcomes were not reported. When comparing these results with those from patients receiving a UFH bolus of 100 units/kg, blood loss was significantly reduced for the argatroban-treated patients. Proper use of argatroban in patients undergoing open heart surgery is not established and should be approached with caution until further data are available.

The safest and most effective approach to anticoagulation in patients with HIT requiring open heart surgery is not clear. Unless emergent surgery is needed, one option is to wait for >100 days until the heparin antibodies have disappeared. In this situation, it has been suggested to avoid postoperative heparin if possible.88

**ACUTE CORONARY EVENTS**

Despite widespread use of UFH for treatment of arterial thrombosis, it does not effectively inhibit fibrin-bound thrombin and platelet-bound factor Xa, which may explain its relative ineffectiveness in the treatment of acute coronary syndromes. Direct thrombin inhibitors do inhibit clot-bound thrombin. Depending on the patients’ presentation, other nonheparin approaches can also be considered in patients with HIT including use of thrombolytics, glycoprotein IIb–IIIa inhibitors, and aspirin or clopidogrel. Several clinical trials have studied the short-term use of direct thrombin inhibitors in the use of acute coronary syndromes. These include in percutaneous coronary angioplasty, unstable angina, or acute myocardial infarction.89-99 The most optimal regimen in acute coronary syndromes depends on various patient-specific factors. The incidence of major bleeding was variable between the studies, but generally less than with heparin in comparison trials. Minor bleeding appeared to be slightly more common in the antithrombin arms of the trials (Table 4).52,53,89-93,95-101 Direct thrombin inhibitors provide one option in HIT with acute coronary syndromes, and current data indicate at least some short-term benefits in the first week, but long-term benefits compared with UFH at 1 month may not be sustained.

**Use of Anticoagulants in Patients with HIT**

Managing a patient with HIT may not be straightforward. Can heparin simply be stopped or should additional anticoagulants be added? If heparin is discontinued, which agent should be used and for how long? Unfortunately, for some clinical situations, there are no clear answers.

In patients with HIT who have an acute thrombotic event, heparin must be stopped and a direct thrombin inhibitor or danaparoid should be initiated. The choice of an agent should depend on presence of data supporting its use in specific clinical presentations, patient’s renal function, or whether initiating long-term warfarin therapy is planned. If the patient has a therapeutic INR at the time HIT is diagnosed, heparin can simply be discontinued and no additional antithrombic therapy started since warfarin should be sufficient. Warfarin can be started as long as another antithrombin agent is being used. Once the target INR is reached, the antithrombin can be discontinued. If, for some reason, warfarin is contraindicated, then a subcutaneous regimen with a longer-acting agent such as danaparoid should be considered. In these individuals, a functional assay testing for antibody that cross-reacts to danaparoid should be considered. Heparin or LMWHs should not be used during this time.

In patients who do not have an acute thrombotic event, it is not clear whether anticoagulant therapy is needed. In order to prevent HIT-associated thrombosis, patients at high risk for thrombosis such as those recovering from total hip or knee arthroplasty, or after CABG surgery, substitution of a different anticoagulant should be considered. Again, warfarin should not be started in these patients without the addition of an antithrombin agent.

Reexposing a patient to UFH several months after a documented HIT episode is always a concern to a clinician. Patients who have had HIT are frequently labeled as having an allergy to heparin. Many clinicians never rechallenge these patients with prior HIT. However, the risk of recurrent HIT appears to diminish as a function of time. In a review4 of 243 patients with serologically confirmed HIT using both the serotonin-release assay and ELISA, 70% of patients initially had a typical pattern of HIT onset (i.e., decrease in platelet count began ≥ 24 d after start of heparin therapy). Of these patients, 28% had definitely received previous heparin treatment, 29% had possible previous UFH treatment, and 44% had not previously been exposed to heparin. The remaining 30% had developed rapid onset of HIT (≤ 4 d, median 10.5 h). All the patients with rapid onset had received UFH within the previous 100 days. Blood samples collected during the 180 days after the initial positive serologic results were tested with both the serotonin-release assay and ELISA. During this time of recovery from HIT-associated thrombocytopenia, HIT antibodies in the serum fell to undetectable concentrations a median of 50 and 85 days, respectively. Seven patients with undetectable concentrations of heparin antibody were reexposed to heparin, and no new episode of HIT was noted. The authors concluded that HIT could begin rapidly in patients who have been exposed to heparin within 100 days, and that heparin antibodies do not invariably reappear with subsequent heparin use.

Thus, heparin therapy is still an option for patients with history of HIT, but only if they have not been treated with heparin for >3 months, allowing the disappearance of the heparin-dependent antibody. For any patient who has a history of HIT and for whom reexposure to heparin is planned, a baseline and daily platelet count should be performed.

**Summary**

Choice of anticoagulation agents and dosing for patients with documented HIT remains empiric. Careful clinical assessment of the patient’s medical presentation, and use of
### Table 4. Direct Thrombin Inhibitors in Acute Coronary Syndrome

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Reference</th>
<th>Trial</th>
<th>Pts. (n)</th>
<th>Drug/Dose</th>
<th>Heparin Dose</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>ACS</td>
<td>Oasis</td>
<td>OASIS 1</td>
<td>909</td>
<td>lepirudin</td>
<td>bolus: 5000 units infusion: 15 units/kg/h combined meta-analysis of both trials; lepirudin groups had significant RR reduction in cardiovascular death or AMI (19%; p = 0.039); cardiovascular death, AMI, or refractory angina (20%; p = 0.005); need for additional interventions (17%; p = 0.009) during the first 7 d; significantly higher incidence of major bleeding requiring transfusion in pts. receiving lepirudin compared with UFH (1.2% vs. 0.7%; p = 0.01)</td>
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<td></td>
<td>Investigators (1997)</td>
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<td>low dose bolus: 0.2 mg/kg infusion: 0.1 mg/kg/h or placebo control</td>
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<td></td>
<td>(1999)</td>
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<td>medium dose bolus: 0.4 mg/kg infusion: 0.15 mg/kg/h</td>
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<td></td>
<td>OASIS 2</td>
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<td>10 141</td>
<td>lepirudin</td>
<td>bolus: 5000 units infusion: 15 units/kg/h desirudin pts. showed initial benefit in the first 2 d; 11% reduction in end points at 30 d not significant</td>
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<td>bolus: 0.4 mg/kg infusion: 0.15 mg/kg/h</td>
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<tr>
<td>GUSTO Iib</td>
<td>Investigators</td>
<td>GUSTO Iib</td>
<td>12 142</td>
<td>desirudin</td>
<td>bolus: 5000 units infusion: 1000 units/h adjusted to aPTT 60-85 sec results showed dose-dependent reduction in postprocedure troponin T concentrations using lepirudin compared with UFH; lepirudin infusion reduced to 0.04 mg/kg/h after 24 h in both dosing regimens; long-term benefits not clear</td>
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<td></td>
<td>(1996)</td>
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<td></td>
<td>bolus: 0.1 mg/kg infusion: 0.1 mg/kg/h</td>
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<td>PTCA</td>
<td>Ruprecht et al. (1995)</td>
<td>PTCA</td>
<td>61</td>
<td>lepirudin</td>
<td>bolus: 150 units/kg infusion: 20 units/kg/h × 24 h, then 7 units/kg/h no significant difference in primary end points of death, AMI, abrupt vessel closure, or rapid deterioration of cardiac origin; pts. receiving bivalirudin with postinfarction angina had significantly lower incidence of the above end points vs. UFH (9.1% vs. 14.2%; p = 0.04)</td>
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<td>low dose bolus: 0.3 mg/kg infusion: 0.12 mg/kg/h</td>
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<td>high dose bolus: 0.5 mg/kg infusion: 0.24 mg/kg/h</td>
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<td></td>
<td>Bittl et al. (1995)</td>
<td>Bittl and Feit (1998)</td>
<td>4098</td>
<td>bivalirudin</td>
<td>bolus: 125 units/kg infusion: 15 units/kg/h adjusted to ACT &gt;350 sec bivalirudin associated with significant reduction in procedure failure (5.1% vs. 10.8% with UFH; p = 0.004) as well as death, AMI, and revascularization (p ≤ 0.05); major and minor bleeding lower in bivalirudin group; at 6 mo, no difference between groups for AMI, revascularization, ischemic events, clinical restenosis, or death</td>
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<td></td>
<td>(1998)</td>
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<td>bolus: 1 mg/kg infusion: 2.5 mg/kg/h × 4 h, then 0.2 mg/kg/h × 14–20 h</td>
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<td></td>
<td>HAS</td>
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<td>704</td>
<td>bivalirudin</td>
<td>bolus: 175 units/kg infusion: 15 units/kg/h adjusted to ACT &gt;350 sec</td>
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<td>bolus: 2.5 mg/kg/h × 4 h, then 0.2 mg/kg/h × 14–20 h</td>
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<td></td>
<td>Serruys et al. (1997)</td>
<td>HELVETICA</td>
<td>1141</td>
<td>desirudin</td>
<td>bolus: 10,000 units infusion: 15 units/kg/h or placebo control cardiac events rates at 96 h reduced in the combined desirudin groups (p = 0.023) vs. UFH; lowest in the sc desirudin group; at 7 mo, event-free survival no different between groups</td>
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<td>bolus: 40 mg infusion: 0.2 mg/kg/h or 40 mg sc bid × 48 h</td>
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</table>

ACS = acute coronary syndrome; ACT = activated clotting time; AMI = acute myocardial infarction; aPTT = activated partial thromboplastin time; GUSTO = Global Use of Strategies to Open Occluded Coronary Arteries; HAS = Hirulog Angioplasty Study; HELVETICA = Hirudin in a European Trial versus Heparin in the Prevention of Restinosis after PTCA Trial; OASIS = Organization to Assess Strategies for Ischemic Syndromes; PTCA = percutaneous coronary angioplasty; RR = relative risk; SKUFH = unfractionated heparin.

(continued on page 500)
HIT-specific assays serve as valuable tools in decisions on management. The selection of anticoagulant therapy depends primarily on efficacy of the agent in patient-specific situations, safety for its use, and absence of cross-reactivity to HIT antibodies.

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<table>
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<tr>
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<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMI</td>
<td>Neuhaus et al. (1994)</td>
<td>HIT III</td>
<td>302</td>
<td>lepirudin bolus: 0.4 mg/kg infusion: 0.15 mg/kg/h</td>
<td>bolus: 70 units/kg infusion: 15 units/kg/h</td>
<td>pts. with AMI receiving alteplase; trial stopped early due to higher rate of intracranial bleeding, increased stroke rate, major bleeding, ventricular rupture, and in-hospital deaths in lepirudin group as adjuncts to thrombolysis with streptokinase and aspirin within 6 h of AMI symptoms; at 30 d, no difference between groups in bleeding, total mortality, reinfarction rate, stroke, refractory angina, or rescue PTCA</td>
</tr>
<tr>
<td>AMI</td>
<td>Neuhaus et al. (1999)</td>
<td>HIT-IV</td>
<td>1208</td>
<td>lepirudin bolus: 0.2 mg/kg sc bid: 0.5 mg/kg for 5–7 d</td>
<td>12500 units sc bid for 5–7 d</td>
<td></td>
</tr>
<tr>
<td>AMI</td>
<td>Jang et al. (1999)</td>
<td>125 argatroban bolus: 100 units/kg infusion: 1.0 µg/kg/min or 3.0 µg/kg/min</td>
<td>bolus: 70 units/kg infusion: 15 units/kg/h</td>
<td>adjunct to thrombolysis with alteplase and aspirin in AMI (&lt;6 h); possible dose-dependent enhanced reperfusion with argatroban vs. UFH, especially if treated within the first 3 h of symptoms; no statistically significant difference in combined incidence of death, recurrent AMI, revascularization, and recurrent ischemia, or major bleeding</td>
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<tr>
<td>AMI</td>
<td>TIMI 9B Investigators (1996)</td>
<td>TIMI 9B</td>
<td>3002</td>
<td>desirudin bolus: 0.1 mg/kg infusion: 0.1 mg/kg/h for 96 h</td>
<td>bolus: 5000 units infusion: 1000 units/h</td>
<td>pts. within 12 h of AMI symptoms received alteplase or streptokinase; 30-d incidence of primary endpoints of death, recurrent AMI, heart failure, and/or cardiogenic shock not different between groups</td>
</tr>
<tr>
<td>AMI</td>
<td>HERO Investigators (1997)</td>
<td>HERO</td>
<td>412</td>
<td>bivalirudin low dose bolus: 0.125 mg/kg infusion: 0.25 mg/kg/h x 12 h, then 0.125 mg/kg/h high dose bolus: 0.25 mg/kg infusion: 0.5 mg/kg/h x 12 h, then 0.25 mg/kg/h</td>
<td>bolus: 5000 units infusion: 1000–1200 units/h</td>
<td>AMI pts. receiving streptokinase TIMI grade 3 flow showed slight dose-related improvement with bivalirudin at 90 and 120 min over UFH; incidence of death, AMI, and cardiogenic shock showed reduction of 20–30%, but was not significant</td>
</tr>
<tr>
<td>AMI</td>
<td>HERO-2 Investigators (2001)</td>
<td>HERO-2</td>
<td>17 073</td>
<td>bivalirudin bolus: 0.25 mg/kg infusion: 0.5 mg/kg/h x 12 h, then 0.25 mg/kg/h x 36 h</td>
<td>bolus: 5000 units infusion: &lt;80 kg, 800 units/h; &gt;80 kg, 1000 units/h</td>
<td>AMI with ST elevation plus 1.5 mu SK. Small increase in mild to moderate bleeding with 30% reduction in adjudicated reinfarction at 96 h. 30 days, no difference in mortality between groups</td>
</tr>
</tbody>
</table>

AMI = acute myocardial infarction; GUSTO = Global Use of Strategies to open Occluded Coronary Arteries; HERO = Hirulog and Early Reperfusion–Occlusion; HIT = Recombinant Hirudin for Improvement of Thrombolysis; MI = myocardial infarction; PTCA = percutaneous coronary angio-plasty; TIMI = Thrombolysis in Myocardial Infarction; UA = unstable angina; UFH = unfractionated heparin.


100. Bittl JA, Ahmed WH. Relation between abrupt vessel closure and the anticoagulation response to heparin or bivalirudin during coronary angioplasty. Am J Cardiol 1998;82:50P-6P.


EXTRACTO

OBJETIVO: Describir la trombocitopenia inducida por heparina (TIH), una reacción adversa inmune a heparina o heparina de bajo peso molecular. Las opciones de tratamiento disponibles y las consideraciones de terapias en investigación son discutidas.


SELECCIÓN DE ESTUDIOS: Los artículos relacionados a TIH, análisis de laboratorio y opciones de tratamiento que se incluyen con el uso de estos agentes en las condiciones clínicas seleccionadas fueron evaluadas e incluidas.

CONCLUSIONES: La TIH es una rara pero potencial reacción adversa severa y recientemente ésta fue entendida ligeramente. Esta reacción tenía limitadas opciones de tratamiento. Los avances recientes que describen el reconocimiento y las manifestaciones clínicas inmunes medias en la TIH, que incluyen las opciones de tratamientos antitrombóticos recientes, han cambiado dramaticamente los resultados para pacientes que tengan este síndrome.

Wilma M Guzman-Santos

RÉSUMÉ

OBJECTIF: Décrire le syndrome de thrombocytopénie induit par l’héparine (HIT ou HIT-2), une réaction indésirable à l’héparine ou aux héparines à faible poids moléculaire de nature immunologique. Les options et considérations thérapeutiques sont également présentées.


SÉLECTION DES ÉTUDES: Les articles traitant de la thrombocytopénie induite par l’héparine, les tests diagnostiques et les options thérapeutiques furent inclus dans cet article pour évaluation.

CONCLUSIONS: La HIT est une réaction indésirable de l’héparine rare mais potentiellement sévère. Jusqu’à récemment, peu était connu de ce syndrome et son traitement. Maintenant, le niveau de connaissance sur la détection de ce syndrome, sur ses manifestations clínicas et sur ses traitements a grandement augmenté de sorte qu’il est possible maintenant de modifier favorablement l’évolution de ce syndrome.

Marc M Perreault