Heparin-Induced Thrombocytopenia: Recognition, Treatment, and Prevention

The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy

Theodore E. Warkentin, MD, Chair; and Andreas Greinacher, MD

This chapter about the recognition, treatment, and prevention of heparin-induced thrombocytopenia (HIT) is part of the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy: Evidence Based Guidelines. Grade 1 recommendations are strong and indicate that the benefits do, or do not, outweigh risks, burden, and costs. Grade 2 suggests that individual patients’ values may lead to different choices (for a full understanding of the grading, see Guyatt et al, CHEST 2004; 126:179S–187S). Among the key recommendations in this chapter are the following: For patients in whom the risk of HIT is considered to be > 0.1%, we recommend platelet count monitoring (Grade 1C). For patients who are receiving therapeutic-dose unfractionated heparin (UFH), we suggest at least every-other-day platelet count monitoring until day 14, or until UFH is stopped, whichever occurs first (Grade 2C). For patients who are receiving postoperative antithrombotic prophylaxis with UFH (HIT risk > 1%), we suggest at least every-other-day platelet count monitoring between postoperative days 4 to 14 (or until UFH is stopped, whichever occurs first) [Grade 2C]. For medical/obstetric patients who are receiving prophylactic-dose UFH, postoperative patients receiving prophylactic-dose low molecular weight heparin (LMWH), postoperative patients receiving intravascular catheter UFH “flushes,” or medical/obstetrical patients receiving LMWH after first receiving UFH (risk, 0.1 to 1%), we suggest platelet count monitoring every 2 days or 3 days from day 4 to day 14, or until heparin is stopped, whichever occurs first (Grade 2C). For medical/obstetrical patients who are only receiving LMWH, or medical patients who are receiving only intravascular catheter UFH flushes (risk < 0.1%), we suggest clinicians do not use routine platelet count monitoring (Grade 2C). For patients with strongly suspected (or confirmed) HIT, whether or not complicated by thrombosis, we recommend use of an alternative anticoagulant, such as lepirudin (Grade 1C+), argatroban (Grade 1C), bivalirudin (Grade 2C), or danaparoid (Grade 1B). For patients with strongly suspected (or confirmed) HIT, we recommend routine ultrasonography of the lower-limb veins for investigation of deep venous thrombosis (Grade 1C); against the use of vitamin K antagonist (VKA) [coumarin] therapy until after the platelet count has substantially recovered; that the VKA antagonist be administered only during overlapping alternative anticoagulation (minimum 5-day overlap); and begun with low, maintenance doses (all Grade 2C). For patients receiving VKAs at the time of diagnosis of HIT, we recommend use of vitamin K (Grade 1C). For patients with a history of HIT who are HIT antibody negative and require cardiac surgery, we recommend use of UFH (Grade 1C). (CHEST 2004; 126:311S–337S)

Key words: antithrombotic; heparin; prophylaxis; thrombocytopenia

Abbreviations: ACT = activated clotting time; APTT = activated partial thromboplastin time; CBP = cardiopulmonary bypass; DTI = direct thrombin inhibitor; DVT = deep venous thrombosis; ECT = ecarin clotting time; EIA = enzyme immunoassay; FDA = US Food and Drug Administration; HAT = heparin-associated thrombocytopenia; INR = international normalized ratio; LMWH = low molecular weight heparin; HIT = heparin-induced thrombocytopenia; PCI = percutaneous coronary intervention; PF4 = platelet factor 4; RCT = randomized controlled trial; RRR = relative risk reduction; SRA = serotonin release assay; UFH = unfractionated heparin; SC = subcutaneous; VKA = vitamin K antagonist

Heparin-induced thrombocytopenia (HIT) is an antibody-mediated, adverse effect of heparin that is important because of its strong association with venous and arterial thrombosis.1–4 Patients treated with heparin who acquire HIT constitute a cohort with substantially increased thrombotic risk, both in relative (odds ratio for thrombosis, 20 to 40)1–5 and absolute (thrombosis risk, 30 to 75%)1–10 terms, depending on the patient population affected.

HIT should be considered a clinicopathologic syndrome because the diagnosis is based on both clinical and serologic grounds.11–14 Thus, HIT antibody seroconversion without thrombocytopenia or other clinical sequelae is not considered HIT, whereas a diagnosis of HIT is made when HIT antibody formation is accompanied by an otherwise unexplained platelet count fall (usually ≥ 50% fall, even if the platelet count nadir remains > 150 × 10⁹/L),2 or by skin lesions at heparin injection sites15 or acute systemic reactions (eg, chills, cardiopulmonary distress) after IV heparin bolus administration.7 Diagnostic specificity can be further increased by use of a sensitive washed platelet activation assay, as a positive platelet activation assay is more specific for clinical HIT than a positive antigen assay.16,17

The neoepitopes recognized by HIT antibodies are located on platelet factor 4 (PF4), and are formed when PF4 binds to heparin.18 PF4 is a member of the C-X-C
antibodies activate platelets,16,21 however, which probably explains the greater diagnostic specificity of certain platelet activation assays (e.g., platelet serotonin release assay [SRA]) for HIT compared with PF4-dependent enzyme immunoassay (EIA).16,22

Our chapter is organized into recognition, treatment, and prevention of HIT. The scope of our recommendations include both platelet count monitoring for HIT, as well as management of HIT, both in patients detected by thrombocytopenia alone (“isolated HIT”) and patients who present with HIT-associated thrombosis. The interrelatedness of platelet count monitoring and treatment recommendations is clear, when one considers that isolated HIT (a patient population with substantial risk of thrombosis) by definition can only be detected by platelet count monitoring. Table 1 lists the inclusion and exclusion criteria for the studies used to formulate our recommendations.

1.0 Recognition of HIT

1.1 Platelet count monitoring for HIT

HIT is a common adverse event in certain patient populations who receive standard, unfractionated heparin (UFH) for ≥1 week.10 The frequency of an adverse reaction can be described as “common” (or “frequent”) if its incidence is >1%.23 As described later, there is evidence that isolated HIT has a substantial risk of symptomatic and fatal thrombosis. Further, prospective cohort studies (with historical controls) suggest that antithrombotic therapy reduces the risk of thrombosis in patients with isolated HIT. In other clinical settings, the risk of HIT can be described as “in frequent” (or “uncommon”; 0.1 to 1%) or even “rare” (<0.1%).23 These considerations suggest that routine platelet count monitoring for HIT is appropriate in at least some clinical situations, and that it is reasonable to stratify the intensity of and/or need for platelet count monitoring in relation to the risk of HIT in a given patient population.

Another consideration that supports a role for platelet count monitoring in some clinical settings is that HIT antibody seroconversion and clinical HIT (thrombocytopenia) usually occur during specific time periods following initiation of heparin, namely days 5 to 10 (seroconversion and initial platelet count fall) and days 7 to 14 (reaching a threshold defining thrombocytopenia).1,2,6,7,24,25 Further, “rapid-onset HIT” (in which the platelet count fall begins within 24 h of starting heparin) is strongly associated with recent heparin exposure (within the past 100 days).24,25

The frequency of HIT among patients exposed to heparin is highly variable, and is influenced by the heparin preparation (bovine UFH > porcine UFH > low molecular weight heparin [LMWH])1,2,6,16,26–30 and the exposed patient population (after surgery > medical > pregnancy).1,2,4,6,19,31–34 Thus, whether to perform platelet count monitoring, and the intensity of such monitoring, depends on these considerations. Therefore, it is appropriate to perform platelet count monitoring in certain clinical situations, and to focus platelet count monitoring during those times when HIT usually occurs.

Recommendation

1.1.1 Platelet count monitoring of patients recently treated with heparin

Rapid-onset HIT refers to patients who have a large platelet count fall attributable to HIT antibodies within 24 h of starting heparin.24,25 Contrary to popular assumption, this phenomenon is not caused by an anamnestic immune response, but rather results from the administration of heparin to a patient who has already-circulating HIT antibodies that resulted from a recent heparin exposure.24,25 As a general rule, exposure within the past 100 days (and especially within the last month) is associated with the phenomenon of rapid-onset HIT.

Recommendation

1.1.1.1 For patients receiving heparin in whom the risk of HIT is considered to be >0.1%, we recommend platelet count monitoring over no platelet count monitoring (Grade 1C).

Underlying values and preferences. This recommendation places a high value on diagnosis and early treatment of HIT to prevent sequelae, and a lower value on the burden and cost of monitoring platelet counts.

1.1.2 Acute systemic reactions after IV UFH bolus

Rarely, patients acquire acute inflammatory (e.g., fever, chills) or cardiorespiratory (e.g., hypertension, tachycardia, dyspnea, chest pain, cardiorespiratory arrest) symptoms and signs within 30 min following an IV heparin bolus.7,35 These reactions can mimic acute pulmonary embolism (“pseudo-pulmonary embolism”36) and strongly suggest acute in vivo platelet activation secondary to HIT. The platelet count should be promptly measured, as an abrupt platelet count fall in this clinical context supports the diagnosis of HIT. Further, the platelet count drop is frequently transient,2 and thus a delay in determining the platelet count, especially if heparin is stopped, may lead to missing the diagnosis.

Recommendation

1.1.2.1 For patients who acquire acute inflammatory, cardiorespiratory, neurologic, or other unusual symptoms...
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and signs within 30 min following an IV UFH bolus, we recommend performing an immediate platelet count measurement, and comparing this value to recent prior platelet counts, in comparison with not performing a platelet count measure (Grade 1C).

1.1.3 Platelet count monitoring in patients receiving therapeutic-dose UFH

For patients receiving porcine UFH in therapeutic doses, either by IV or subcutaneous (SC), for the treatment of venous or arterial thrombosis, the risk of HIT has been estimated at approximately 1%, based on a review of several studies of the frequency of HIT in patients receiving porcine UFH for venous thromboembolism.

**Recommendation**

1.3. For patients who are receiving therapeutic-dose UFH, we suggest at least every-other-day platelet count monitoring until day 14, or until UFH is stopped, whichever occurs first (Grade 2C).

**Underlying values and preferences.** This recommendation places a high value on diagnosis and early treatment of HIT to prevent sequelae, and a lower value on the burden and cost of monitoring platelet counts.

1.1.4 Platelet count monitoring in postoperative patients receiving UFH antithrombotic prophylaxis

Patient groups at the highest risk of HIT (1 to 5%) include postoperative orthopedic, cardiac, and vascular surgery patients who are receiving UFH for 1 to 2 weeks. Data are not available for general surgery patients. However, we have included this patient population in this section, because patients undergoing major abdominal surgery might be at similar risk as the other major surgical procedures discussed. Thus, this section includes all “Postoperative Patients Receiving UFH Antithrombotic Prophylaxis.”

Our recommendation for platelet count monitoring in this and other patient populations (see also recommendations 1.1.4 to 1.1.6, inclusive) have been given a weak (Grade 2) recommendation because no study exists comparing outcomes using any particular platelet count monitoring strategy. Our suggestion to perform every-other-day monitoring takes into account the observation that platelet count declines in HIT, when they occur, are relatively rapid (median of 3 days from baseline [postoperative peak] to ≥50% platelet count decline).12

**Recommendation**

1.4. For patients who are receiving postoperative antithrombotic prophylaxis with UFH (HIT risk >1%), we suggest at least every-other-day platelet count monitoring between postoperative days 4 to 14, or until UFH is stopped, whichever occurs first (Grade 2C).

Underlying values and preferences. This recommendation places a high value on diagnosis and early treatment of HIT to prevent sequelae, and a lower value on the burden and cost of monitoring platelet counts.

1.1.5 Platelet count monitoring in patients in whom HIT is infrequent (0.1 to 1%)

There are several patient groups in which the risk of HIT can be classified as “infrequent,” i.e., 0.1 to 1%. These include medical or obstetric patients receiving prophylactic-dose UFH, postoperative patients receiving LMWH, postoperative/critical care patients receiving UFH flushes; and, theoretically, medical patients receiving LMWH after having received one or more preceding doses of UFH. In some settings, it may not be practical to obtain platelet counts, eg, patients receiving outpatient LMWH. Thus, less frequent platelet count monitoring may be appropriate in these patients, especially if the risk is thought to be closer to 0.1% than 1% (eg, postoperative patients receiving LMWH), and if the patient is instructed to contact the physician promptly if symptoms of venous thromboembolism occur (the most common complication of HIT).

**Recommendation**

1.5. For medical/obstetric patients who are receiving prophylactic-dose UFH, postoperative patients receiving prophylactic-dose LMWH, postoperative patients receiving intravascular catheter UFH flushes, or medical/obstetric patients receiving LMWH after first receiving UFH (HIT risk 0.1 to 1%), we suggest platelet count monitoring every 2 to 3 days from day 4 to day 14, or until heparin is stopped, whichever occurs first, when practical (Grade 2C).

**Underlying values and preferences.** This recommendation places a high value on diagnosis and early treatment of HIT to prevent sequelae, and a lower value on the burden and cost of monitoring platelet counts.

1.1.6 Platelet count monitoring when HIT is rare (<0.1%)

In medical and obstetric patients receiving LMWH, the risk of HIT appears to be rare (<0.1%). For example, only one possible case of HIT was observed among 1,167 pregnancies treated with LMWH in three studies. Although fewer data exist with respect to medical patients receiving LMWH or UFH as “flushes” (eg, oncology patients with indwelling catheters), the experience of the authors is that HIT is rare in this setting.

**Recommendation**

1.6. For medical/obstetric patients who are only receiving LMWH, or medical patients who are receiving only intravascular catheter UFH flushes (HIT risk <0.1%), we suggest clinicians do not use routine platelet count monitoring (Grade 2C).
Underlying values and preferences. This recommendation places a lower value on the rare diagnosis and early treatment of HIT to prevent sequelae, and a higher value on the burden and cost of monitoring platelet counts.

1.1.7 Screening for subclinical HIT antibody seroconversion

Prospective studies of HIT and HIT antibody formation\textsuperscript{1,2,6,16,28–30,62} indicate that HIT occurs in a minority of patients who form HIT antibodies. The typical serologic finding in the patient with clinical HIT (> 95% of patients) is positive testing in both of two sensitive and complementary assays: (1) platelet activation (or “functional”) assay using washed platelets (eg, \textsuperscript{14}C-SRA, heparin-induced platelet activation assay), or (2) PF4-dependent EIA.\textsuperscript{16} However, even though one (or both) assays are sensitive in detecting HIT antibodies, neither is completely specific for the HIT syndrome (although the functional assays are more specific than the EIA) [Table 2].\textsuperscript{13} Consequently, it is easier using serology to rule out a tentative diagnosis of HIT than to confirm the diagnosis, ie, the tests have a high negative predictive value but only a moderate positive predictive value. However, the “strength” of a positive test result provides useful diagnostic information regarding the likelihood of HIT. For example, a strong positive test result (eg, > 90% serotonin release or > 2.0 absorbance units) is associated with a high likelihood ratio for HIT in patients after orthopedic surgery (approximately 100), whereas a weak positive test result (eg, 20 to 50% serotonin release or 0.50 to 0.75 absorbance units) is associated with lower likelihood ratios for HIT in this patient population (approximately 30 to 40 and 15 to 20, respectively).\textsuperscript{16,17} For patients after cardiac surgery, the corresponding likelihood ratios for “strong” and “weak” serologic results are approximately 20 and 2 to 6, respectively.\textsuperscript{17} The diagnostic interpretation of these laboratory tests must be made in the context of the clinical estimation of the pretest probability of HIT.\textsuperscript{13,17,63}

Further, prospective data indicate that an increased risk of thrombosis occurs in the group of patients whose platelet count has fallen in relation to HIT antibody formation (ie, those with clinical HIT) rather than in patients who acquire HIT antibodies without a significant platelet count decline.\textsuperscript{1,2} In our view, it is not useful to perform HIT antibody testing in the absence of clinical indication of HIT, either by an unexpected fall in the platelet count, or an unexpected clinical event. Thus, routine platelet count monitoring, rather than routine HIT antibody studies, is most useful (and most practical) to identify patients who are at risk for thrombosis because of immunization triggered by heparin therapy.

**Recommendation**

1.1.7. In patients who receive heparin, we recommend against routine HIT antibody testing in the absence of

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*Reprinted with permission from Warkentin.\textsuperscript{13}

† “Early” refers to a fall in the platelet count that begins within the first 4 d of starting heparin; “late” refers to a fall that begins on day 5 or later.

The data range for the late platelet count fall indicates cardiac patients receiving UFH and orthopedic patients receiving LMWH, respectively.\textsuperscript{16}

The specificity varies because late thrombocytopenia due to a reason other than HIT may nevertheless show a false-positive HIT antibody result because of subclinical HIT antibody seroconversion (see § below).

‡Sensitivity defined in relation to those patients in prospective studies who had a positive test result when the platelet count fell by ≥ 50% after ≥ 5 days of heparin therapy, and in whom the available clinical information (particularly, evidence for alternative explanations for thrombocytopenia and the effect of stopping or continuing heparin) supported the diagnosis of HIT.\textsuperscript{1,16} Also, for SRA and heparin-induced platelet aggregation assay, assumes use of certain quality control maneuvers, including use of weak positive control sera, selected and/or multiple platelet donors. Also, in about 5% of heat-inactivated serum, heparin-independent platelet activation is observed. If a new serum aliquot is heat inactivated, and the test repeated, an interpretable result is achieved in at least half the cases. However, about 30 to 40% of samples (approximately 2% overall) give a repeated “indeterminate” result, and the activation assay is nondiagnostic.

¶Assumes that the heparin-induced platelet aggregation assay test and SRA have similar sensitivity and specificity profiles; other platelet activation end points that may also give acceptable results using washed platelets include detection of platelet-derived microparticles by flow cytometry.

§Assumes that a 90% specificity in early thrombocytopenia attributable to non-HIT disorders (eg, nonspecific platelet activation related to acute inflammatory proteins) declines to an 82% specificity in late thrombocytopenia that may be attributable to subclinical HIT antibody seroconversion.

¶Clinicopathologic definition assumes that at least one sensitive test result must be positive for diagnosis of HIT; specificity of the activation assay is indicated.
thrombocytopenia, thrombosis, heparin-induced skin lesions, or other sequelae of HIT (Grade 1C).

1.1.8 When should HIT be suspected?

Retrospective and prospective studies suggest that > 90% of patients with clinical HIT have a platelet count fall > 50% during their heparin treatment. In those patients who are recognized with lesser degrees of platelet count decline, almost all are identified because of thrombotic complications or other sequelae, such as heparin-induced skin lesions or acute systemic reactions following IV bolus UFH. The pretest probability of HIT should also be influenced by the temporal features of the platelet count fall and by the likelihood of other possible alternative diagnoses to explain the thrombocytopenia.

A diagnosis of HIT should be considered when thrombocytopenia (defined subsequently) occurs with a temporal pattern consistent with heparin-induced immunization, ie, platelet count fall that begins 5 to 10 days (or thrombocytopenia that occurs 7 to 14 days) after starting a course of heparin therapy (first day of heparin = day zero), or when thrombosis or other sequelae of HIT occur in patients treated (or recently treated) with heparin. The pretest estimation of the probability of HIT is also influenced by the pattern of the platelet count fall and by the likelihood of other possible alternative diagnoses to explain the thrombocytopenia. The strong association between HIT and thrombosis indicates that HIT should be suspected, and a platelet count drawn (and compared with previous values), in a patient who acquires symptomatic venous or arterial thrombosis during or within several days after receiving heparin treatment.

Approximately two thirds of HIT patients evince typical-onset HIT, ie, the platelet count begins to fall 5 to 10 days after starting heparin, although thrombocytopenic levels (eg, ≥ 50% fall or to < 150 x 10^9/L) are usually not reached until a few days later (approximately 7 to 14 days after beginning heparin). In approximately 25 to 30% of patients, the platelet count falls abruptly on beginning a course of heparin. Such rapid-onset HIT occurs in patients who have recently been exposed to heparin (within the previous 100 days), and represents abrupt-onset of platelet activation in a patient who has residual circulating HIT antibodies related to the recent prior heparin exposure.

In at most 3 to 5% of patients, the onset of thrombocytopenia begins several days after heparin has been stopped (delayed-onset HIT). This last syndrome, which was reported in late 2001, is consistent with a transient autoimmune nature of HIT, as it has been shown that such patients have PF4/heparin-reactive antibodies that can activate platelets even in the absence of heparin.

Definition of Thrombocytopenia in HIT

The majority of postoperative patients who acquire HIT sustain an otherwise unexplained ≥ 50% fall in the platelet count from the postoperative peak during the second week following surgery. This reduction occurs on a background of the normal pattern of a rising platelet count expected between postoperative days 4 to 14 (transient postoperative thrombocytosis). Thus, in postoperative HIT, the serial platelet counts form an “inverted v” as the initial platelet count recovery that begins about 2 to 3 days following surgery transforms unexpectedly to a falling platelet count a few days later. In contrast, in medical patients, the platelet count fall begins or accelerates from day 5 onwards, usually without a preceding profile of a rising platelet count. On occasion, the platelet count declines by < 50% even though the clinical and serologic findings otherwise strongly suggest HIT-associated thrombosis.

Although there are less data on an appropriate definition of HIT applicable to medical patients, it appears that a proportional (50%) fall in platelet count beginning between days 4 to 14 of heparin therapy is appropriate. In our opinion, such a threshold avoids trivial platelet count declines that might be detected if an absolute threshold, such as 150 x 10^9/L, is used to define thrombocytopenia, especially as transient thrombocytosis does not often occur in medical patients.

We are making a strong recommendation regarding thrombocytopenia in HIT because there is good evidence that a proportional fall in platelet count of ≥ 50% is superior to an absolute threshold of 150 x 10^9/L for the detection of HIT, at least in postoperative patients (improved sensitivity for HIT without loss of diagnostic specificity). However, no single definition of thrombocytopenia is appropriate in all clinical situations.

Recommendation

1.1.8 For patients receiving heparin, or who have received heparin within the previous 2 weeks, we recommend excluding a diagnosis of HIT if the platelet count falls by ≥ 50%, and/or a thrombotic event occurs, between days 4 to 14 following initiation of heparin, even if the patient is no longer receiving heparin therapy when thrombosis or thrombocytopenia have occurred (Grade 1C).

1.1.9 Special situation: anticoagulant prophylaxis and platelet count monitoring after cardiac surgery

The risk of symptomatic venous thrombosis is relatively low in patients after cardiac surgery, even when no antithrombotic prophylaxis is administered (although subclinical deep venous thrombosis [DVT] can be detected in 20% of patients). To our knowledge, there are no formal studies proving that routine anticoagulant prophylaxis either with UFH or LMWH is safe and effective following cardiac surgery. Many cardiac surgery centers give antithrombotic prophylaxis with UFH (North America more than Europe) or LMWH (Europe more than North America). Even if anticoagulant prophylaxis is not routinely administered, individual patients after cardiac surgery may receive anticoagulants
because of a prosthetic valve or unexpected complications such as atrial fibrillation, thrombotic stroke, or prolonged immobilization.

The risk of HIT antibody formation is especially high in the population after cardiac surgery, ranging from 35 to 65% by days 7 to 10, even when postoperative anticoagulant prophylaxis with heparin is not administered. More importantly, the absolute risk of clinical HIT in such patients who receive UFH following surgery ranges from 1 to 3%, 6,53–55,69 Finally, this patient population has a relatively high burden of atherosclerosis, and appears to be at a disproportionately higher risk for life- and limb-threatening arterial complications, compared with other patient populations. 7

A nonrandomized trial 54,55 reported a lower frequency of HIT with LMWH use, compared with UFH use, following cardiac surgery. However, there were differences in the patient population that led to one or the other drug being administered. Further, HIT antibodies resulting from UFH therapy frequently cross-react with LMWH, and since patients after cardiac surgery receiving LMWH have invariably received UFH during cardiac surgery, there is the potential for HIT to occur more frequently with LMWH in this patient population than in other clinical settings.

Thus, given the known high risk of HIT in this patient population, we believe that monitoring for HIT is especially important if UFH or LMWH is used. A practical problem in monitoring for HIT after postcardiac surgery is that major hemodilution occurs both during, and in the first several days following, cardiac surgery. This perioperative platelet count decrease typically attains its nadir 2 days following surgery. However, HIT is rare in the first 4 days following cardiac surgery, even in patients who have received heparin during the precardiac surgery period. This is because HIT resulting from heparin exposure during angiography or for treatment of acute coronary syndrome is infrequent (<1%), whereas postoperative dilutional thrombocytopenia occurs universally. Thus, it is difficult on clinical grounds to distinguish the occasional case of HIT beginning soon after cardiac surgery (in which immunization resulted from preoperative heparin exposure). In contrast, HIT is a relatively likely explanation for a platelet count fall ≥50% that begins from postoperative day 5 onwards. This is because the circumstances of cardiac surgery are a frequent stimulus for HIT antibody generation, and because the typical onset of HIT (beginning 5 to 10 days after cardiac surgery) coincides with the time period in which the platelet count typically is rising to thrombocytocytic levels following perioperative hemodilution. Accordingly, in patients after cardiac surgery, a fall in the platelet count of ≥50% from the highest postoperative value that occurs between postoperative days 4 to 14 should be considered HIT unless proven otherwise (day of cardiac surgery = day zero). 5,54

**Recommendation**

1.1.9. For postoperative cardiac surgery patients, we recommend excluding a diagnosis of HIT if the platelet count falls by ≥50% (and/or a thrombotic event occurs) between postoperative days 4 to 14 (day of cardiac surgery = day zero) [Grade 1C].

### 2.0 Treatment of HIT

HIT is a prothrombotic condition that is associated with increased in vivo thrombin generation (as evidenced by the presence of elevated levels of thrombin-antithrombin complexes 70) and thus can be considered an acquired, hypercoagulability syndrome. However, unlike other acquired hypercoagulability syndromes (eg, antiphospholipid antibody syndrome, malignancy-associated thrombosis), HIT is transient, with recovery of platelet counts to normal levels within days or weeks, and disappearance of the pathogenic HIT antibodies within weeks or a few months. Thus, there is important potential benefit (over the risk) of optimal antithrombotic management over the relatively brief period of the patient’s life in which this paradoxical adverse event has occurred.

The mechanism of this hypercoagulability state is multifactorial, and includes the following: (1) in vivo platelet activation, 72 with formation of procoagulant, platelet-derived microparticles 72–74 caused by occupancy and cross-linking of platelet Fc receptors 73 by in situ formation of PF4/heparin/IgG immune complexes; 76 (2) expression of tissue factor on endothelial cells that have become activated because HIT antibodies recognize PF4 bound to endothelial heparan sulfate; 77,78 and (3) expression of tissue factor by monocytes activated by HIT antibodies. 79,80 Neutralization of the anticoagulant effects of heparin by PF4 released from activated platelets may explain “heparin resistance” that is commonly observed in HIT.

Marked in vivo thrombin generation helps explain several clinical aspects of HIT, including its association with venous and arterial thrombosis, the occurrence of decompensated (hypofibrinogenemic) disseminated intravascular coagulation in 5 to 10% of HIT patients, and the risk for progression of DVT to venous limb gangrene (or, less often, “classic” nonacral coumarin-induced skin necrosis) in some patients with HIT who are treated with warfarin or other vitamin K antagonists (VKAs). 81–86 These coumarin-induced necrosis syndromes result from a disturbance in procoagulant-anticoagulant balance during VKA therapy: warfarin treatment results in severe acquired reduction in protein C, while at the same time it fails to control thrombin generation. 81,82 Finally, recognition of the role for in vivo thrombin generation in HIT provides a rationale for current therapies that emphasize reduction of thrombin generation, 11,70 either via direct inhibition of thrombin (eg, argatroban, lepirudin, bivalirudin) or by inhibiting factor Xa (eg, danaparoid, fondaparinux).

In making recommendations for the management of HIT, we have chosen to combine the approach to patients with “isolated HIT” and HIT-associated thrombosis. There are three reasons for this approach. First, from the point of view of pathophysiology, patients with isolated HIT and HIT-associated thrombosis have similar disease processes, as shown by platelet count nadirs (median, approximately 50 to 60 × 10^9/L, for each group), and
similar elevations of thrombin-antithrombin complexes. Second, the time course of thrombosis in HIT is a continuum, with approximately equal numbers of patients being recognized with symptomatic thrombosis (1) during the initial period of a falling platelet count, (2) after crossing a threshold defining thrombocytopenia but while heparin treatment remains ongoing, and (3) after discontinuation of heparin because of thrombocytopenia. Third, and most importantly, among patients who are recognized as having isolated HIT (subsequently confirmed serologically), and who are managed by simple discontinuation of heparin, or substitution of heparin by warfarin, the risk of symptomatic thrombosis ranges from 25 to 50%, including an overall risk of fatal thrombosis of approximately 5%. These event rates resemble those in other clinical situations in which antithrombotic management is generally considered mandatory (eg, after hip fracture).

Unlike hip fractures, however, the diagnosis of HIT may not be initially clear, especially since HIT might not be the only potential explanation for thrombocytopenia and/or thrombosis in patients receiving heparin. Thus, it is important to emphasize that the recommendations we have made are appropriate for patients in whom the diagnosis of HIT is strongly suspected (or “confirmed” by strong positive test results for HIT antibodies). In clinical settings in which HIT is considered unlikely, it may be appropriate to continue heparin or (in settings of antithrombotic prophylaxis) to administer usual prophylactic doses of an alternative anticoagulant, eg, prophylactic-dose recombinant hirudin (15 mg bid SC), fondaparinux (2.5 mg qd SC), or danaparoid (750 U bid or tid SC, where available). Scoring systems to help physicians estimate the pretest probability of HIT have been developed.

2.1 Nonheparin anticoagulants for HIT

Table 3 lists five agents that can be considered for treatment or prevention of HIT-associated thrombosis. Pharmacokinetic information, including site of organ clearance for these anticoagulants, is also listed. Of these drugs, only two (argatroban, lepirudin) are approved for treatment of HIT in the United States. Another agent, bivalirudin, which is approved for anticoagulation during percutaneous coronary interventions (PCIs), has been used off-label to a limited extent in HIT. Among these pro-

2.1.1.1 Treatment of HIT-associated thrombosis. Table 4 summarizes the results of the efficacy and major bleeding end points for the lepirudin and argatroban prospective cohort groups of patients with HIT complicated by thrombosis, including their respective historical control data. The initial prospective studies utilizing the DTIs, lepirudin and argatroban, showed that new thrombosis occurred in 10.1% and 19.4% of patients receiving lepirudin and argatroban, respectively, and the composite end point occurred in 21.3% and 43.8% of patients receiving lepirudin and argatroban, respectively. Compared with their respective historical controls, these results corresponded to relative risk reductions (RRRs) of 63% and 44% for lepirudin and argatroban, respectively. Later trials showed better outcomes with both agents: the reported thrombosis rate declined from 10.1 to 6.1% with lepirudin, and from 19.4 to 13.1% with argatroban. A large postmarketing study with lepirudin showed an even lower incidence of thrombosis (5.2%). Significant differences in the entry criteria and conduct of the trials occurred. For example, patients entered into the lepirudin trials needed to be positive for HIT antibodies, whereas argatroban patients were entered based on a clinical diagnosis (only 65% of patients were shown to have HIT antibodies in the Arg-911 study, and the data for the Arg-915 study are not reported). Moreover, patients received lepirudin for 12.1, 13.5, and 14 days (mean values of three lepirudin trials for HIT-associated thrombosis), but argatroban only for 5.9 to 7.1 days (means of the Arg-911 and Arg-915 trials, respectively). A greater percentage of patients in the lepirudin trials were transitioned to a VKA, compared with patients in the argatroban trials (at least 83% vs 62%). Particularly as observation periods...
## Table 3—Nonheparin Anticoagulants for Use in HIT

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Therapeutic Dosing</th>
<th>Elimination (Half-Life)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DTIs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lepirudin92</td>
<td>(With or without bolus, 0.4 mg/kg); initial infusion rate, 0.15 mg/kg/h IV (target, 1.5–2.5 times patient’s baseline or mean of laboratory normal range)*</td>
<td>Renal (80 min)</td>
<td>Approved in the United States for treatment of thrombosis complicating HIT; half-life rises greatly in renal failure; lower target APTT range (1.5–2.0 times baseline) has similar efficacy and less bleeding risk (Andreas Greinacher, MD; unpublished data; January 2004); high rate of antihirudin antibodies (40–60%) that are usually not clinically significant; risk of anaphylaxis (rare); avoiding the initial bolus may reduce risk of drug accumulation in patients with unrecognized mild renal failure, and may reduce the risk or severity of anaphylaxis.</td>
</tr>
<tr>
<td>Argatroban93</td>
<td>Initial infusion rate, 2 μg/kg/min (no initial bolus) for patients with HIT</td>
<td>Hepatobiliary (40–50 min)</td>
<td>Approved in the United States for both prevention and treatment of HIT-associated thrombosis, and for anticoagulation during angioplasty when heparin is contraindicated; argatroban increases the INR, and thus a higher INR therapeutic range may be required during overlapping argatroban/warfarin therapy. For patients with HIT undergoing PCI, initial infusion is 25 μg/kg/min with an initial bolus of 350 μg/kg</td>
</tr>
<tr>
<td>Bivalirudin94</td>
<td>Initial infusion rate, 0.15–0.20 mg/kg/h IV (target, 1.5–2.5 times patient’s baseline or mean of laboratory normal range (no initial bolus)</td>
<td>Both enzymic (80%) and renal (20%) metabolism (25 min) administered over 3–5 min</td>
<td>Approved in the United States for anticoagulation during PCI; favorable anecdotal experience in HIT; shorter half-life and minor renal excretion (20% component) suggests theoretical advantages over lepirudin, particularly for cardiac surgery (currently under study).</td>
</tr>
<tr>
<td><strong>Factor Xa inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Danaparoid95</td>
<td>Bolus: 2,250 U; infusion, 400 U/h for 4 h, then 300 U/h for 4 h, then 200 U/h, adjusted by anti-Xa levels</td>
<td>Renal (24 h, anti-Xa activity)</td>
<td>Withdrawn from US market in April 2002, but remains approved/available for treatment/prevention of HIT-thrombosis in Canada, continental Europe, New Zealand; potential in vitro cross-reactivity (rare) is not predictable by in vitro testing; thus, cross-reactivity testing not recommended prior to use.</td>
</tr>
<tr>
<td>Fondaparinux96</td>
<td>Not established for HIT</td>
<td>Renal (17–20 h)</td>
<td>Approved for DVT prophylaxis after orthopedic surgery; theoretically, lack of in vitro cross-reactivity with HIT antibodies suggests it may be useful in HIT (minimal data).</td>
</tr>
</tbody>
</table>

*Dosing in patients with isolated thrombocytopenia: no bolus, 0.1 mg/kg/h, aPTT adjusted to 1.5–2.0X mean laboratory normal range; marked dose-reduction is required in renal insufficiency.

†Adjust IV danaparoid bolus for body weight, as follows: < 60 kg, 1,500 U; 60–75 kg, 2,250 U; 75–90 kg, 3,000 U; > 90 kg, 3,750 U.
<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Dosing (Duration of DTI Treatment, Mean Days)</th>
<th>Patients, No.†</th>
<th>Study Design (Control Group)</th>
<th>% New Thrombosis (Control Subjects)</th>
<th>% Limb Amputation (Control Subjects)</th>
<th>% Composite End Point‡ (Control Subjects)</th>
<th>% Major Bleeds (Control Subjects)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lepirudin111</td>
<td>Bolus, 0.4 mg/kg; 0.15 mg/kg/h§ (13.3)</td>
<td>113</td>
<td>Prospective (historical controls)</td>
<td>10.1% (27.2%][[RRR = 63%]</td>
<td>6.5% (10.4%) [RRR = 38%]</td>
<td>21.3% (47.8%][[RRR = 53%]</td>
<td>18.8% (7.1%][[RRR = 55%]</td>
<td>Meta-analysis of two prospective (historical control) studies (HAT-1,110 HAT-2110); all patients tested positive for HIT antibodies.</td>
</tr>
<tr>
<td>Lepirudin112</td>
<td>See above (14.0)</td>
<td>98</td>
<td>Prospective (historical controls)</td>
<td>6.1% [RRR = 78%]</td>
<td>5.1% [RRR = 51%]</td>
<td>21.5% [RRR = 55%]</td>
<td>20.4%</td>
<td>Extension study (HAT-3) performed awaiting regulatory approval; all patients tested positive for HIT antibodies.</td>
</tr>
<tr>
<td>Lepirudin113</td>
<td>See above (12.1)</td>
<td>496</td>
<td>Postmarketing study</td>
<td>5.2%</td>
<td>5.8%</td>
<td>21.9%¶</td>
<td>5.4%</td>
<td>77% of patients tested positive for HIT antibodies; thrombotic death rate = 1.8%</td>
</tr>
<tr>
<td>Argatroban114</td>
<td>2 μg/kg/min# (no bolus) (5.9)</td>
<td>144</td>
<td>Prospective (historical controls)</td>
<td>19.4% (34.8%)][RRR = 44%]</td>
<td>11.8% (10.9%)[RRR = −8%]</td>
<td>43.8%†† (56.5%)[RRR = 22%]</td>
<td>11.1% (2.2%)</td>
<td>Positive testing for HIT antibodies not required for study entry (65% of patients shown to have HIT antibodies)</td>
</tr>
<tr>
<td>Argatroban115</td>
<td>See above (7.1)</td>
<td>229</td>
<td>Prospective (historical controls)</td>
<td>13.1%[RRR = 62%]</td>
<td>14.8%[RRR = −36%]</td>
<td>41.5%††[RRR = 27%]</td>
<td>6.1%</td>
<td>Positive testing for HIT antibodies not required for study entry (number testing positive not reported)</td>
</tr>
</tbody>
</table>

*The end points shown represent time-to-event analysis (day 35) for lepirudin, and categorical analysis (day 37) for argatroban.
†Number of patients treated with the DTI (control subjects numbered 75 for lepirudin and 46 for argatroban). 
‡Composite end point: all-cause mortality, all-cause limb amputation, and new thrombosis (each patient counted only once), unless otherwise indicated. 
§APTT adjusted to 1.5–2.5 times baseline APTT (or the mean laboratory normal range if the baseline APTT was unavailable); indicated dosing given to 105 of 113 patients (remaining 8 patients received 0.2 mg/kg bolus in conjunction with thrombolytic therapy). 
¶Composite end point likely overestimated, as some patients may have had more than one end point. 
[APTT adjusted to 1.5–3.0 times baseline APTT. 
**One additional patient each is included in the DTI and control group (compared with original publication114), as these two patients died and sustained limb amputation (personal communication; Dr. Marcie Hursting, PhD; February 2004). 
††p values not significant by categorical analysis, but p = 0.014 (hazard ratio = 0.57) and p = 0.008 (hazard ratio = 0.56) for Arg-911 and Arg-915 studies, respectively, using time-to-event analysis.
in the studies were relatively long (35 days and 37 days for lepirudin and argatroban, respectively), the longer duration of lepirudin therapy, and the greater likelihood of transition to VKA, could explain its greater apparent efficacy.

Limb amputation represents a relatively “hard” end point. Comparing limb amputation rates among the trials, there is a lower amputation rate among patients who received lepirudin, compared with argatroban (12 of 214 patients [5.6%] vs 51 of 373 patients [13.7%]) when comparing the three combined Heparin-Associated Thrombocytopenia (HAT) studies and Arg-911/915 study event rates shown in Table 4. Further, the RRR values for limb amputation were 38 to 51% for lepirudin (compared with historical controls), but were 8 to 36% for argatroban, ie, the limb amputation rates were higher than the corresponding historical controls. The explanation for this difference in limb amputation rates between the lepirudin and argatroban studies is not known. However, one plausible reason is that the combination of shorter treatment duration in the argatroban trials, compared with the lepirudin studies (5.9 to 7.1 days vs 12.1 to 14 days), combined with the greater potential of argatroban and VKA to prolong the international normalized ratio (INR), may have led to early cessation of argatroban, with the potential for progression of limb thrombosis (and venous limb ischemia and gangrene) in patients with active HIT. Our recommendations for managing DTI-VKA overlap are discussed later in section 2.2.

Recombinant hirudin (including lepirudin) has been shown to be superior to UFH in randomized clinical trials (RCTs) of acute coronary syndrome and angioplasty. In contrast, similar evidence for efficacy of univalent DTIs, such as argatroban, in similar patient populations is not available.

Although bivalirudin appears to be promising as a treatment for HIT, based on case series, the absence of historical or contemporaneous control data, and the uncertainty regarding the numbers of patients who had clinical HIT in some of the studies, we provide weak recommendation (grade 2C). Compared with lepirudin and argatroban, bivalirudin offers some significant pharmacologic advantages (short half-life, enzymatic metabolism, low immunogenicity, minimal effect on INR prolongation).

Danaparoid

Table 5 shows studies that have evaluated danaparoid as treatment of HIT complicated by thrombosis. Danaparoid was studied in a randomized open-label study that compared danaparoid (plus warfarin) against dextran-70 (plus warfarin). Patients received danaparoid without prior testing for in vitro cross-reactivity against HIT antibodies. This study showed a significantly lower progression of thrombosis rate (12.0% vs 52.9%) among the 25 patients who received danaparoid, compared with the 17 control patients. No patients had major bleeding.

Additional corroborating evidence for the efficacy of danaparoid in HIT includes a comparison between lepirudin and danaparoid for treatment of HIT-associated thrombosis that used identical inclusion/exclusion criteria, and that analyzed patients with HIT diagnosed in the same laboratory during the identical time period. Thus, unlike the prospective cohort studies of lepirudin and argatroban that utilized historical controls, this evaluation included contemporaneous controls. The study suggested that danaparoid and lepirudin have similar efficacy for treatment of HIT-associated thrombosis (9.4% thrombosis rate with danaparoid, 7.9% thrombosis rate with lepirudin), but with significantly less major bleeding observed with danaparoid (2.5% vs 10.4%, respectively, p < 0.05).

A retrospective evaluation of danaparoid vs abciximab showed a significantly lower thrombotic event rate in patients treated with danaparoid. (Danaparoid has been removed from the market.)

Certain of the pharmacokinetic features of danaparoid, such as its long half-life, lack of effect on the INR, and its potential for SC administration make it an appropriate choice for an otherwise uncomplicated patient with venous thromboembolism in whom eventual overlap with oral anticoagulants is required. Danaparoid does not cross the placenta, and thus should be safe for management of pregnant patients with HIT.

Fondaparinux

Fondaparinux has some pharmacologic similarities with danaparoid. Both have anti-factor Xa activity, either exclusively (fondaparinux, anti-Xa/anti-IIa ratio > 100) or predominantly (danaparoid, anti-Xa/anti-IIa ratio = 22). Both fondaparinux and danaparoid have long half-lives for their anti-factor Xa activities (17 h and 25 h, respectively), and both show either absent (fondaparinux) or generally negligible (danaparoid) in vitro cross-reactivity with HIT antibodies. All of these features of fondaparinux indicate that at least theoretically it should be useful for treating patients with HIT. As fondaparinux is marketed in a prophylactic-dose regimen (2.5 mg qd SC) for prevention of thrombosis after orthopedic surgery, this suggests that it also may be appropriate for prevention of thrombosis in its low-dose regimen in non-HIT situations in which the physician would prefer not to administer heparin, eg, a thrombocytopenic patient in whom HIT is nevertheless judged to be unlikely. However, the minimal data supporting the efficacy of fondaparinux in HIT and other thrombocytopenic situations precludes us from making any recommendation.

Definition and natural history of HIT

2.1.1.2 Treatment of isolated HIT. Isolated HIT is defined as “the initial recognition of HIT because of thrombocytopenia alone, rather than because symptoms or signs of thrombosis draw attention to the possibility of underlying HIT.” Previously, it was believed that simple discontinuation of heparin might avoid subsequent thrombosis in these patients. However, seven
### Table 5—Treatment of Thrombosis Complicating HIT: Danaparoid

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Dosing</th>
<th>Patients, No.*</th>
<th>Study Design (Control Group)</th>
<th>New Thrombosis† (Control Subjects)</th>
<th>Composite End Point† (Control Subjects)</th>
<th>Major Bleeds‡ (Control Subjects)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danaparoid104</td>
<td>Bolus 2,400 U plus 200 U/h for 5 d‡</td>
<td>25</td>
<td>Randomized trial (dextran 70 control subjects)</td>
<td>12.0% (52.9%)/</td>
<td></td>
<td></td>
<td>20.0% (52.9%)/¶</td>
</tr>
<tr>
<td>Danaparoid105</td>
<td>Bolus 2,500 U plus 200 U/h‡</td>
<td>53#</td>
<td>Retrospective (lepirudin prospective cohort)</td>
<td>9.4%# (7.9%)</td>
<td>Approximately 20% (Approximately 20%)**</td>
<td>2.5% (10.4%)/¶</td>
<td>Bleeding rate may have been underestimated with danaparoid since this value includes other patients who received low-dose danaparoid regimen.</td>
</tr>
<tr>
<td>Danaparoid106</td>
<td>Various</td>
<td>35</td>
<td>Retrospective (ancrod, warfarin control subjects)</td>
<td>5.7% (24.5%)/¶</td>
<td></td>
<td></td>
<td>Control group received ancord (snake venom no longer recommended for treatment of HIT).</td>
</tr>
<tr>
<td>Danaparoid107</td>
<td>Various</td>
<td>122</td>
<td>Retrospective</td>
<td>6.6%‡ †</td>
<td>&gt; 25.7%‡ †</td>
<td></td>
<td>Compassionate release program.</td>
</tr>
</tbody>
</table>

*Number of patients treated with the study drug (excludes control subjects).
†Composite end point: all-cause mortality, all-cause limb amputation, and new thrombosis (each patient counted only once).
‡No anticoagulant monitoring was performed; after initial 2,400-U bolus, patients received 400 U/h for 2 h, then 300 U/h for 2 h, then 200 U/h for 5 d.
§Statistically significant difference (p < 0.05).
‖End point indicates: “no improvement/deterioration” and “slight improvement” groups, as response of existing thrombi, rather than frequency of new thrombosis, was analyzed; 17 control patients received dextran 70.
¶Includes four deaths in each arm of study; limb amputation status not given.
#Indicates 53 patients who received therapeutic-dose danaparoid; the lepirudin controls include 114 patients.
**The composite end point data are based upon all 86 patients who had thrombosis at baseline and who received danaparoid in any dose (lepirudin controls, n = 124); the outcome (approximately 20%) indicates the estimated cumulative event rate at 42 d, as read from Figure 2 in Farner et al.105
††New thrombosis was listed as “failure” in 8 of 122 evaluable patients treated for thrombosis complicating HIT.
†‡Indicates all-cause mortality in entire 230 patient population (thus, composite end point is underestimated as other end points not included).
observational studies\textsuperscript{1, 9, 10, 105, 111, 114, 115, 122, 123} suggest that there is a substantial risk for symptomatic thrombosis among patients with isolated HIT (Table 6). The three largest retrospective studies\textsuperscript{9, 10, 114} observed the frequency of symptomatic, objectively confirmed thrombosis to range from 23 to 52%; thrombotic death rates in two studies were 4.3% and 4.8%, respectively. In a large prospective cohort (n = 113),\textsuperscript{111} 10.4% acquired new thrombosis or death over a mean period of 1.7 days (time period prior to entry into the lepirudin treatment trial). Systematic duplex ultrasonography applied to 16 consecutive patients with isolated HIT showed a 50% frequency of subclinical DVT in one retrospective study.\textsuperscript{123} A large retrospective study by Wallis et al\textsuperscript{10}

<table>
<thead>
<tr>
<th>Study Design (Follow-Up)</th>
<th>n</th>
<th>Frequency of Thrombosis, No. (%)</th>
<th>Comment</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective (to hospital discharge)</td>
<td>4</td>
<td>(75.0)</td>
<td>Nine patients identified with HIT (platelet count &lt; 150 x 10^9/L) in a clinical trial; five patients presented with HIT-associated thrombosis; of the four remaining patients with isolated HIT, symptomatic DVT occurred in three patients (75%) after stopping heparin.</td>
<td>1</td>
</tr>
<tr>
<td>Retrospective (30 d)</td>
<td>62</td>
<td>(51.6)</td>
<td>Patients\textsuperscript{1} tested positive for HIT antibodies (SRA); 65 patients with HIT-associated thrombosis were excluded; composite end point = 61.3%; thrombotic death rate, 4.8%; Patients: after trauma/orthopedic/general surgery (40%), after cardiac surgery (8%), medical (45%), other (7%).</td>
<td>9, 122</td>
</tr>
<tr>
<td>Retrospective (not stated)</td>
<td>16</td>
<td>50.0</td>
<td>Patients with any thrombosis prior to HIT were excluded; patients tested positive for HIT antibodies (platelet aggregation test); all patients underwent duplex venography, with asymptomatic DVT identified in 8 of 16 patients (50.0%).</td>
<td>123</td>
</tr>
<tr>
<td>Retrospective (to hospital discharge)</td>
<td>113</td>
<td>38.1 (23.1)</td>
<td>Patients tested positive for HIT antibodies (platelet aggregation test); all-cause mortality, 27.4%; all-cause mortality; Patients: after trauma/orthopedic/general surgery (21%), after cardiac surgery (59%), medical patients (12%), other (8%).</td>
<td>10</td>
</tr>
<tr>
<td>Prospective (1.7 d [mean])</td>
<td>113</td>
<td>10.4 (first 1.7 d)</td>
<td>Patient cohort awaiting entry into prospective lepirudin trials; 6.1% per day composite end point event rate = 10.4% over 1.7 (mean) d.</td>
<td>111</td>
</tr>
<tr>
<td>Retrospective (42 d)</td>
<td>35</td>
<td>20.0</td>
<td>83% of patients received low-dose danaparoid; composite end point = 31.4% (categorical analysis) and 53% (time-to-event analysis)</td>
<td>105</td>
</tr>
<tr>
<td>Retrospective cohort (37 d)</td>
<td>139</td>
<td>23.0</td>
<td>Historical control group (argatroban studies; thrombosis rate may have been underestimated [only 81% tested positive for HIT antibodies]); composite end point = 38.8%; thrombotic death rate, 4.3%.</td>
<td>114, 115</td>
</tr>
</tbody>
</table>

\textsuperscript{*}Composite end point in all-cause mortality, limb amputation, new thrombosis.

\textsuperscript{1}Definition of “isolated HIT” did not exclude patients with thrombosis prior to onset of HIT: 19 of 62 patients (30.6%) had thrombosis before HIT (myocardial infarction, n = 8; thrombotic stroke, n = 2; pulmonary embolism, n = 4; DVT, n = 5); however, the risk of subsequent HIT-associated thrombosis following heparin cessation was similar whether or not thrombosis had occurred prior to HIT (11 of 19 vs 21 of 43; p = 0.70).

\textsuperscript{2}A more conservative approach is to include only those patients in whom thrombosis occurred \(> 24\) h after stopping heparin; in this analysis, 22 patients with earlier thrombosis (including patients presenting with HIT-associated thrombosis) are excluded from both the numerator and denominator, to give the value 21 of 91 patients (23.1%); of these patients, early heparin cessation was associated with higher thrombosis rate than late heparin cessation (11 of 33 patients [33.3%] vs 10 of 58 patients [17.2%]; p = 0.12 by two-sided Fisher exact test).
provided information as to whether early cessation of heparin (within 48 h of occurrence of HIT, defined as the day the platelet count fell by ≥ 50% during heparin treatment) was associated with improved outcomes. Overall, these investigators found that HIT-associated thrombosis occurred in 43 of 113 patients (38.1%). Interestingly, early cessation of heparin was not associated with a decreased thrombotic event rate, compared with later heparin cessation (45% vs 34%; p = 0.24). However, since heparin cessation could have been prompted by attention drawn to HIT by a complicating thrombosis itself, a more conservative estimate of the risk of thrombosis in isolated HIT in this study can be obtained by excluding from analysis the 22 patients who acquired thrombosis within 24 h of stopping heparin. If the data are analyzed excluding these 22 patients, then of the remaining 91 patients, early heparin cessation was associated with a trend to higher thrombosis than late heparin cessation: 11 of 33 patients (33.3%) vs 10 of 58 patients (17.2%) [p = 0.04].

**Anticoagulation in isolated HIT**

The optimal management strategy for isolated HIT remains uncertain. A retrospective study found that low-dose (prophylactic-dose) danaparoid was associated with a high failure rate when administered for isolated HIT (composite end point, 53% by time-to-event analysis). Routine screening by ultrasonography for lower-limb DVT was not performed in this study, and so whether low-dose danaparoid might still be appropriate for patients in whom lower-limb DVT has been ruled out is uncertain. Second, the recommended lepirudin regimen in these patients was associated with low risk of new thrombosis (2.7% and 2.1%, respectively) in two large studies (meta-analysis of three prospective studies of 111 patients, and postmarketing observational study of 612 patients), with the composite end point being observed in 10 of 111 patients (9.0%) in the prospective studies. Although this lepirudin dosing regimen omits the initial lepirudin bolus, and begins with a 33% lower initial infusion rate compared with the therapeutic regimen (0.1 instead of 0.15 mg/kg/h), it includes dose adjustments according to the activated partial thromboplastin time (APTT), and thus effectively achieves “therapeutic” dosing within 24 h. Third, the argatroban trials used the same (therapeutic-dose) regimen whether patients had thrombosis complicating HIT or isolated HIT; for the latter group of patients, argatroban (compared with historical controls) was associated with lower rate of thrombosis (8.1% vs 22.4%, p < 0.001; and 5.8% vs 23.0%, p < 0.001) and a lower frequency of the composite end point of new thrombosis, all-cause mortality, and limb amputation being reached (25.6% vs 38.8%, p = 0.014; and 28.0% vs 38.8%, p = 0.04). Major bleeding in these studies of DTIs for isolated HIT ranged from 3.1 to 5.3%, to 5.9 to 14.4% of patients receiving argatroban and lepirudin, respectively. Finally, as HIT is a hypercoagulability state associated with much greater levels of thrombin generation than in other high-risk settings for venous thrombosis (eg, after orthopedic surgery), it is biologically plausible that prophylactic-dose anticoagulation may be relatively ineffective in HIT patients. In individual situations, factors that would mitigate against use of therapeutic-dose alternative anticoagulation include low confidence in the clinical diagnosis of HIT (especially prior to obtaining HIT antibody test results), evidence of impaired hemostasis on physical examination, and very severe thrombocytopenia (platelet count < 10 × 10^9/L).

In patients with strongly suspected isolated HIT, or when the diagnosis is supported by serologic studies, we recommend continuing the alternative anticoagulant until the platelet count has recovered to a stable plateau. Whether adding a short course of warfarin anticoagulation (following platelet count recovery) provides additional protection against late HIT-associated thrombosis is unresolved. The high frequency of subclinical DVT in this patient setting suggests that routine ultrasonography is appropriate in these patients, since if silent venous thrombosis is identified, it could influence the duration of anticoagulant therapy.

The study by Farner and colleagues also provided insights into dosing issues of patients with isolated thrombocytopenia. Patients treated with danaparoid for isolated HIT suffered from a high thrombotic-event rate, compared with patients received lepirudin. However, the danaparoid-treated patients generally received only prophylactic-dose therapy, whereas APTT-adjusted dosing was performed in patients receiving lepirudin (ie, therapeutic-dose therapy). Thus, these data support the use of therapeutic-dose danaparoid (Table 3) in patients strongly suspected (or confirmed) to have isolated HIT or HIT complicated by thrombosis.

In summary, in the absence of any prospective clinical trials comparing one antithrombotic agent with another for management of HIT, selection of a particular anticoagulant agent should be based on patient-specific factors, relevant drug pharmacology and pharmacokinetics, jurisdictional availability/approval, and prior physician experience and confidence in the use of any particular agent. None of the agents used to treat HIT has an antidote, and thus careful drug selection for the appropriate patient is a relevant issue.

**Recommendations**

2.1.1. For patients with strongly suspected (or confirmed) HIT, whether or not complicated by thrombosis, we recommend use of an alternative, nonheparin anticoagulant in therapeutic doses, such as lepirudin (Grade 1C+), argatroban (Grade 1C), bivalirudin (Grade 2C), or danaparoid (Grade 1B), over further UFH or LMWH therapy, and over no further anticoagulation (with or without vena caval filter).

2.1.2. For patients with strongly suspected (or confirmed) HIT, whether or not there is clinical evidence of lower-limb DVT, we recommend routine ultrasonography of the lower-limb veins for investigation of DVT, over not performing routine ultrasonography (Grade 1C).
2.2 VKAs

Treatment of HIT-associated DVT with warfarin or phenprocoumon alone can contribute to venous limb gangrene.\textsuperscript{82–86} Affected patients characteristically have had their heparin (or alternative anticoagulant) discontinued, and typically have a high INR (usually $>3.5$); the explanation for this characteristic laboratory feature is a severe reduction in factor VII that parallels the reduction in protein C.\textsuperscript{82,125} Studies of plasma from affected patients has shown persisting thrombin generation (marked elevation in thrombin-antithrombin complexes) and marked reduction in protein C levels, compared with unaffected control subjects.\textsuperscript{82} In theory, patients with hereditary abnormalities of the protein C natural anticoagulant pathway, or who have severe acquired natural anticoagulant depletion secondary to severe HIT, could acquire venous limb gangrene in the absence of VKA therapy, but this occurs rarely.\textsuperscript{7,82}

Venous limb gangrene occurred in 8 of 66 patients (12.1%; 95% confidence interval [CI], 5.4 to 22.5%) with HIT-associated DVT who were treated with warfarin (with or without ancrod) in a study of 158 consecutive patients with antibody-positive HIT identified during 15 years in one medical community.\textsuperscript{82} Venous limb gangrene also occurred in 1 of 21 patients (4.8%; 95% CI, 0.12 to 23.8%) treated with phenprocoumon (patients identified from the historical control group for the lepirudin treatment trial).\textsuperscript{111} In contrast, a large retrospective cohort study\textsuperscript{126} did not identify any patients with venous limb gangrene among 51 HIT patients who received warfarin. However, only 16 of these patients had active DVT when warfarin was started (upper 95% CI for venous limb gangrene for 0 of 16 patients, 20.6%). These three studies\textsuperscript{82,111,126} have overlapping CIs that indicate the actual risk of warfarin-induced venous limb gangrene could be from 5 to 20%. Since ancrod (defibrinogenating snake venom) increases thrombin generation in HIT,\textsuperscript{127} the use of this agent may have contributed to increased risk of venous gangrene in the study reporting the highest frequency of this complication. In addition, a number of case reports also describe patients whose clinical course is consistent with warfarin-induced venous limb gangrene.\textsuperscript{128–130}

2.2.1 Management of DTI-VKA overlap

The transition period of anticoagulation with a DTI (lepirudin, argatroban) and warfarin in patients with HIT-associated DVT can be problematic if the warfarin is started too soon and/or the DTI discontinued too soon. Indeed, there are reported cases of venous gangrene in patients with HIT\textsuperscript{91,92} when the DTI had been discontinued during persisting thrombocytopenia. Given the relatively short half-lives of the available DTIs, it is likely that venous limb gangrene occurs because of persistent HIT-associated hypercoagulability (due to continuing thrombin generation and concomitant depletion of protein C natural anticoagulant related to warfarin) after the thrombin inhibitor cleared from the circulation. Prolongation of the INR by argatroban\textsuperscript{131–133} also makes the conversion to warfarin anticoagulation more complex. Whereas lepirudin,\textsuperscript{111,133} and bivalirudin\textsuperscript{98,133} cause minimal prolongation of the prothrombin time/INR, a substantial influence on the INR has been observed in patients receiving overlapping argatroban and warfarin (mean INR of 3.7 on argatroban alone that rose to 4.9 during overlapping therapy before declining to 3.4 when argatroban was stopped and warfarin continued alone).\textsuperscript{132} These clinical observations and theoretical considerations lead to our recommendation to avoid warfarin therapy until there has been substantial recovery of HIT-associated thrombocytopenia, and to ensure that the alternative anticoagulant is continued until the platelet count has returned to normal levels.

Recommendation

2.2.1. For patients with strongly suspected or confirmed HIT, we recommend against the use of VKA (coumarin) therapy until after the platelet count has substantially recovered (eg, to at least $100 \times 10^9/L$, and preferably, $150 \times 10^9/L$); that the VKA be administered only during overlapping alternative anticoagulation (minimum 5-day overlap), and begun with low, maintenance doses (maximum, 5 mg of warfarin, and 6 mg of phenprocoumon); that the alternative anticoagulant not be stopped until the platelet count has reached a stable plateau, and with at least the last 2 days the INR within the target therapeutic range (Grade 1C).

2.2.2 Reversal of VKA anticoagulation

Sometimes, the VKA has already been started when HIT is recognized. In this situation, we recommend reversing vitamin K antagonism by administering vitamin K, either by oral or IV route (5 to 10 mg). There are two reasons for this recommendation. First, coumarin-induced microvascular thrombosis can begin abruptly, and evolve quickly to skin necrosis. And second, prolongation of the APTT by VKA therapy can lead to underdosing of DTI therapy used to manage the HIT. Thus, there is the potential for protein C depletion secondary to VKA therapy, and subtherapeutic dosing by DTI, resulting in the circumstances that favor progression to microvascular thrombosis.

Recommendation

2.2.2. For patients receiving VKAs at the time of diagnosis of HIT, we recommend use of vitamin K (Grade 2C).

2.3 LMWH for HIT

Although LMWH is less likely to cause HIT antibody formation,\textsuperscript{1,2,6,30} and less likely to cause HIT in patients who have formed HIT antibodies,\textsuperscript{1,2,6} compared with UFH, LMWH is equally reactive as UFH in activation assays of HIT sera using washed platelets.\textsuperscript{1,114} Further, there is a substantial risk for persisting/recurrent thrombocytopenia and/or new thrombosis during treatment of
HIT with LMWH. These investigators performed a retrospective cohort study of 89 patients who received at least 2 days of therapeutic-dose anticoagulation following diagnosis of HIT with either LMWH (n = 36), VKA (n = 27), danaparoid (n = 9), or no anticoagulation (n = 17). Platelet count recovery occurred significantly less often (p < 0.001) with LMWH (13 of 36 patients; 36.1%) compared with the other approaches (81.1%; p < 0.001). New thrombosis occurred in 47.2% of patients who received LMWH, which was similar to that seen using VKA (33.3%; p = 0.27) or no anticoagulation (23.5%; p = 0.10), but which was significantly higher than observed with danaparoid (0.0%; p = 0.001). Given the availability of nonheparin anticoagulants to treat HIT, LMWH should be considered contraindicated for treatment of acute HIT.

Recommendation

2.3.1. For patients with strongly suspected HIT, whether or not complicated by thrombosis, we recommend against use of LMWH (Grade 1C+).

2.4 Prophylactic platelet transfusions for HIT

Platelet transfusions are generally considered as being relatively contraindicated for the prevention of bleeding in patients with acute HIT. This is because petechiae and other mucocutaneous bleeding typical of thrombocytopenia are not clinical features of HIT, despite even severe thrombocytopenia, and platelet transfusions have been linked with thrombotic events, albeit only in anecdotal reports. However, this issue has not been investigated systematically. In situations of diagnostic uncertainty or high bleeding risk (as judged by the clinician), or if overt bleeding occurs, platelet transfusions in the setting of possible or probable HIT may be appropriate, particularly if the heparin has been stopped for several hours.

Recommendation

2.4.1. For patients with strongly suspected or confirmed HIT who do not have active bleeding, we suggest that prophylactic platelet transfusions not be administered (Grade 2C).

3.0 Special Patient Populations

3.1 Patients with previous HIT undergoing cardiac or vascular surgery

In general, one is reluctant to expose a patient with a history of known (or strongly suspected) drug hypersensitivity to the drug in question. However, there are several reasons why HIT is an important exception to this general rule. First, among patients with typical-onset HIT, there is no relation between day of onset and a history of previous heparin exposure. This observation suggests that no anamnestic immune response occurs in HIT. Second, among patients with rapid-onset HIT, there is a strong association with recent (< 100 days), rather than remote (> 100 days) prior heparin exposure. Moreover, HIT antibodies have been shown to be transient, with the median time to negative activation and antigen assays of 50 days and 80 days, respectively. Third, in situations when heparin has been accidentally or deliberately readministered in situations when HIT antibodies were no longer present, recurrence of HIT antibodies usually did not occur. And, in those situations when HIT antibodies were regenerated, they did not occur sooner, or at stronger levels, than in the previous seroconversion episode that had led to clinical HIT.

Three reports include five or more patients who have undergone heparin rechallenge in the setting of previous HIT (although seropositivity was not established for all patients for the suspected previous episode of HIT in one study). Other studies describe single-case anecdotes in similar circumstances. In most instances, the heparin rechallenge was performed to permit cardiac or vascular surgery. None of the patients had rapid-onset HIT or rapid regeneration of HIT antibodies. HIT antibodies formed in two patients that were weaker (and occurred later) than those that developed during the prior episode of HIT, and did not present a clinical problem as heparin was not used in the postoperative period. Since there is limited information on whether the overall risk of clinical HIT is greater (or less) than in patients without a previous history of HIT, planned heparin reexposure should be restricted to the surgical procedure itself, and alternative anticoagulants should be used for preoperative or postoperative anticoagulation, if required.

The limited experience with alternative anticoagulants for cardiac surgery, and the inability to readily reverse their anticoagulant effects following surgery, are important considerations that makes this a strong recommendation. On balance, we consider the risk resulting from a potential boosting of HIT antibodies (especially occurring well into the postoperative period) to be much lower than the risk of (peri)operative complications, especially major bleeding, associated with the nonheparin anticoagulants.

Recommendation

3.1.1. For patients with a history of HIT who are HIT antibody negative and require cardiac surgery, we recommend the use of UFH over a nonheparin anticoagulant (Grade 1C).

Remark: Preoperative and postoperative anticoagulation, if indicated, should be administered with a nonheparin anticoagulant.

3.2 Patients with acute or subacute HIT undergoing cardiac surgery

Table lists various options for cardiac surgery in patients with acute or previous HIT. Repeat heparin exposure is an option for a patient with a previous history of HIT, especially if HIT occurred > 100 days prior. This is because HIT antibodies are gen-
erally undetectable (or weak) by this time, and are usually not regenerated during the brief heparin re-exposure required to permit cardiac surgery. Ideally, it should be demonstrated that HIT antibodies are no longer detectable serologically before planning heparin re-exposure. Although the risk of regenerating pathogenic antibodies and developing HIT once more appears to be low, it is prudent to restrict heparin use to the period of cardiopulmonary bypass (CPB), and use alternative anticoagulants for preoperative and postoperative anticoagulation. Patients with recent HIT whose platelet count has recovered, but who still have detectable HIT antibodies ("subacute HIT"), should be considered at risk for rapid-onset HIT on heparin re-exposure, unless the activation assay is negative and the antigen assay is only weakly positive. In patients with acute or subacute HIT who require cardiac surgery, there are anecdotal reports describing various strategies (Table 7). No comparative studies exist, and so the actual treatment selected should be based on site-dependent considerations, such as availability of drug and laboratory monitoring, previous physician experience, patient-dependent factors (eg, renal or hepatic insufficiency), and so forth. Anecdotal success has been observed using bivalirudin.

### Table 7—Anticoagulant Protocols Used for Cardiac Surgery

<table>
<thead>
<tr>
<th>Anticoagulant Approach</th>
<th>Protocol</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Give heparin when HIT antibodies no longer detectable</td>
<td>Standard UFH dosing for CPB; avoid UFH before and after cardiac surgery</td>
<td>Demonstrate absence of HIT antibodies before surgery, if possible; 0 of 15 patients regenerated HIT antibodies in one study, even if antibodies are regenerated, this is unlikely to occur before day 5.</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>Off-pump: bolus, 0.75 mg/kg, then 1.75 mg/kg/h infusion to maintain activated clotting time &gt; 300 s; CPB: detailed protocol (under investigation) available from the manufacturer (The Medicines Company; Parsippany, NJ)</td>
<td>Shorter half-life (25 min) and minor renal excretion (20%) are advantageous for cardiac surgery; anecdotal experience during off-pump cardiac surgery; recent pilot study during CPB has led to FDA-approved protocol under current study; special considerations: avoid using patient blood for testing graft patency or for cardioplegia solution (as clots can form in stagnant, bivalirudin-anticoagulated blood); special maneuvers needed to prevent cloting of CPB circuit after surgery.</td>
</tr>
<tr>
<td>Lepirudin</td>
<td>Detailed protocol published elsewhere</td>
<td>ECT monitoring recommended; risk for drug accumulation if postoperative renal failure occurs; no antidote; special maneuvers needed to prevent clotting of CPB after surgery.</td>
</tr>
<tr>
<td>Heparin plus prostacyclin analogue (epoprostenol or iloprost)</td>
<td>Standard UFH dosing for CPB; eproprostenol: step-wise increments of 5 ng/kg/min, beginning at 5 ng/kg/min, until target rate of 30 ng/kg/min reached.</td>
<td>Epoprostenol: half-life = 3–6 min; platelet aggregation monitoring was not performed in one study; can cause severe hypotension (managed with norepinephrine); successful outcomes reported in two studies of nine patients; eproprostenol (but not iloprost) is available in the United States (approval: primary pulmonary hypertension).</td>
</tr>
<tr>
<td>Heparin plus tirofiban</td>
<td>Standard UFH dosing for CPB; tirofiban: 10 μg/kg bolus, then 0.15 μg/kg/min until 1 h before anticipated conclusion of CPB</td>
<td>47 patients reported: 44 of 47 patients discharged on schedule from hospital (two deaths, one prolonged ICU stay); HIT antibodies detectable in 35 of 47 patients (remaining patients had HIT diagnosed previously); however, manufacturer of tirofiban does not recommend this approach, as fatal bleeds have been reported.</td>
</tr>
<tr>
<td>Danaparoid</td>
<td>Detailed protocols for CPB are published elsewhere</td>
<td>High bleeding risk (no antidote and long half-life); anti-Xa monitoring recommended; severe bleeding is frequent; lower doses of danaparoid may be appropriate for off-pump cardiac surgery.</td>
</tr>
<tr>
<td>Argatroban</td>
<td>Off-pump experience reported</td>
<td>Minimal experience.</td>
</tr>
</tbody>
</table>
during CPB, whereas larger case series have been reported using lepirudin. Target drug levels appropriate for CPB have been established (lepirudin, 3.5 to 4 μg/mL; bivalirudin, 10 to 15 μg/mL), with intraoperative monitoring best performed using the ecarin clotting time (ECT), rather than the activated clotting time (ACT). Both agents also require special action by the cardiac anesthesiologist and/or perfusionist, eg, adding the DTI to the circuit following surgery to prevent pump clotting, ensuring that any remaining pump volume contents intended for reinfusion to the patient should first be processed using a cell saver, thus washing away most of the DTI, etc. The largest study of lepirudin for CPB in patients with acute or previous HIT reported survival without thrombosis in 54 of 57 patients (95%). Bivalirudin has several important advantages over lepirudin for use in CPB, including a shorter half-life and predominantly nonrenal metabolism.

Coadministration of UFH with either epoprostenol (prostacyclin analog) or tirofiban (platelet glycoprotein IIb/IIIa antagonist) has been used with success for CPB surgery in patients with acute or previous HIT. Two reports describing epoprostenol use in nine patients observed successful outcomes in all, with one study (five patients) performing no intraoperative laboratory monitoring (the other study employed platelet aggregometry). Vasopressors are required to manage potentially severe intraoperative hypotension caused by epoprostenol. Tirofiban was used in 47 patients with acute or previous HIT, with successful outcomes in 44 patients. However, the manufacturer discourages use of tirofiban for cardiac surgery because fatal bleeding outcomes have occurred.

Despite its long half-life, danaparoid has been used for heart surgery, including a series of 53 patients undergoing CPB, most of whom received a fixed-dose regimen without laboratory monitoring. Severe postoperative bleeding (>20 U of blood product required) occurred in 21% of patients, and clots in the operative field were observed in 34% of patients. Subsequently, use of intraoperative monitoring has been advocated, but it remains uncertain whether this reduces bleeding.

Significantly lower doses of anticoagulation (about one half to one third) are required for off-pump cardiac surgery, and this option should be considered in appropriate patients. Anticoagulant agents for which off-pump experience has been reported include bivalirudin, lepirudin, argatroban, and danaparoid. Recently, bivalirudin was compared in a randomized trial against heparin (with protamine reversal) for off-pump cardiac surgery in non-HIT patients. Bleeding was similar between the patient groups. A possible advantage of bivalirudin was a significantly reduced rate of early graft occlusion, compared with the heparin study arm.

**Recommendations**

3.2.1. For patients with acute HIT (thrombocytopenic, HIT antibody positive) who require cardiac surgery, we recommend one of the following alternative anticoagulant approaches (in descending order of preference): delaying surgery (if possible) until HIT antibodies are negative (see recommendation 3.1.1.) [Grade 1C]; using bivalirudin for intraoperative anticoagulation during CPB (if ECT available) [Grade 1C] or during off-pump cardiac surgery (Grade 1C+); using lepirudin for intraoperative anticoagulation (if ECT available and patient has normal renal function) [Grade 1C]; using UFH plus the antiplatelet agent, epoprostenol (if ECT monitoring not available or renal insufficiency precludes lepirudin use) [Grade 2C]; using UFH plus the antiplatelet agent, tirofiban (Grade 2C); or using danaparoid for intraoperative anticoagulation (if anti-factor Xa levels are available) [Grade 2C].

3.2.2. For patients with subacute HIT (platelet count recovery, but continuing HIT antibody positive), we recommend delaying surgery (if possible) until HIT antibodies are negative, then using heparin (see recommendation 3.1.1.) [Grade 1C]. Alternatively, we suggest the use of a nonheparin anticoagulant (see recommendation 3.2.1.) [Grade 2C].

3.3 PCIs

Invasive cardiologic procedures such as angioplasty and stent insertion are generally performed with heparin therapy. For patients with acute or recent HIT, alternative agents include argatroban (US Food and Drug Administration [FDA] approved in 2002 for PCI when heparin is contraindicated), bivalirudin (FDA-approved anticoagulant for PCI and non-HIT patients), and lepirudin or desirudin (studies in HIT and non-HIT patients undergoing PCI). An experience using argatroban for PCI in patients with acute or previous HIT was published, with patients receiving standard dosing (bolus, 350 μg/kg followed by infusion at 25 μg/kg/min, with adjustments to achieve and maintain ACTs of 300 to 450 s). A total of 112 PCIs were performed on 91 patients (14 with platelet counts < 100 x 10^9/L during their first PCI). The primary outcome was a satisfactory PCI (subjective assessment of the investigator), which occurred in 86 of 91 (94.5%) patients undergoing initial PCI, and in all 21 patients undergoing repeat PCI. Major acute complications (death, emergent coronary bypass surgery) occurred in only two patients, and major bleeding in only 1 patient in the first group.

Bivalirudin has also been studied prospectively for use during PCI in patients with acute or previous HIT. The primary end point was major bleeding within 48 h after completion of the bivalirudin infusion (or by discharge, if that occurred sooner). Clinical success was defined as procedural success without death, emergency bypass surgery, or q-wave infarction. Early in the trial, patients received bivalirudin as a 1.0 mg/kg IV bolus, followed by 2.5 mg/kg/h by IV infusion for 4 h (with adjustments to maintain the ACT at > 300 s). Later, the bolus was lowered to 0.75 mg/kg, followed by a 1.75 mg/kg/h infusion for 4 h. Among the 52 patients studied, procedural success (Thrombolysis in Myocardial Infarction trial grade 3 flow and < 50% stenosis) and clinical success were achieved in 98% and 96%, respectively. Only one patient (1.9%) had major bleeding. There were no
abrupt closures, nor was thrombus formation reported during or after PCI. One patient died of cardiac arrest 46 h after successful PCI.

Danaparoid has also been used to provide antithrombotic therapy during cardiac catheterization, with or without stenting or other maneuvers, with anecdotal reports of success. Recommendations regarding use of alternative anticoagulants in PCI also are given in the Chapter in this Supplement by Popma et al.

**Recommendation**

3.3.1. For patients with acute or previous HIT who require cardiac catheterization or PCI, we recommend use of an alternative anticoagulant, such as argatroban (Grade 1C), bivalirudin (Grade 1C), lepirudin (Grade 1C), or danaparoid (Grade 2C), over the use of heparin.

3.4 Hemodialysis

Only anecdotal reports are available on the subject of anticoagulation in hemodialysis. Alternatives (where available) include saline solution flushing, citrate, danaparoid, lepirudin, and argatroban. We have not made any specific recommendations for anticoagulation of this patient population.

**4.0 Prevention of HIT**

4.1 Reducing HIT antibody formation and clinical HIT

4.1.1 UFH vs LMWH

An RCT that compared UFH (obtained from porcine mucosa) with LMWH (enoxaparin) found a significantly reduced frequency of HIT in the patients receiving LMWH following hip replacement surgery; using the definition of a ≥50% fall in the platelet count between day 4 and day 14 (while receiving heparin therapy), the frequency of HIT was 16 of 332 patients (4.8%) with UFH, but only 2 of 333 patients (0.6%) with LMWH (p = 0.00062). The frequency of HIT-associated thrombosis was also greater with UFH in this study: 12 of 332 cases (3.6%) vs 1 of 333 cases (0.3%) [p = 0.00165]. This study also showed a lower frequency of HIT antibody formation with LMWH, whether measured by platelet serotonin release assay or PF4-dependent EIA. A nonrandomized comparison between UFH and LMWH (enoxaparin) administered after orthopedic surgery also found a higher frequency of HIT antibody formation with UFH, as well as a higher frequency of HIT-associated thrombosis (3.3% vs 0.6%, respectively).

Two randomized studies comparing another LMWH preparation (reviparin) with UFH have also shown a significantly lower frequency of HIT antibody formation with the LMWH, whether administered following orthopedic surgery or for treatment of DVT. The orthopedic trial did not report the frequency of HIT, and in the DVT trial, only one patient (who received UFH) acquired antibody-positive HIT. A nonrandomized comparison of UFH and LMWH (dalteparin) after cardiac surgery also showed a higher frequency of HIT with UFH: 9 of 263 cases (3.4%) vs 1 of 370 cases (0.3%); however, duration and route of administration of anticoagulation differed, as well as the composition of the patient groups.

The American College of Chest Physicians conference members examined the question of whether they should make a general recommendation favoring LMWH over UFH for the prevention of HIT. The participants—in the view of lack of sufficient evidence for all patient groups—agreed about making this recommendation. Some participants believed that prevention of HIT was an important primary goal, sufficiently dominant to determine the decision regarding choice of LMWH and UFH. Other participants believed that the question of whether LMWH is safer in terms of HIT prevention in nonorthopedic surgery settings is unproven, and that HIT risk should only be one among a number of considerations in the choice. Moreover, this latter group of participants noted that such a general recommendation would have considerable economic consequences, particularly in North America where costs of LMWH exceed those in Europe. Thus, we have not provided a recommendation on this question, except in post-orthopedic surgery patients in whom randomized controlled trial evidence is available indicating a difference in both risk of HIT and HIT-associated thrombosis between LMWH and UFH.

**Recommendation**

4.1.1. For postoperative orthopedic surgery patients, we recommend the use of LMWH over UFH (Grade 1A).

4.2 Bovine vs porcine UFH

There is also evidence that UFH derived from bovine lung is more likely to cause HIT and HIT antibody formation than UFH obtained from porcine gut. A meta-analysis of four randomized clinical trials that compared these two heparin preparations for treatment of venous thromboembolism found a significantly lower frequency of HIT in patients receiving porcine UFH.

Two groups studied the frequency of HIT antibody formation following cardiac surgery in patients randomized to receive UFH from either bovine lung or porcine intestinal mucosa. However, one study utilized patient serum obtained only 5 days following surgery (ie, too soon to exclude formation of HIT antibodies). Recently, in the second study, Francis and colleagues observed a significantly lower frequency of HIT antibody formation in cardiac surgery patients who received porcine UFH, compared with bovine UFH. This study used the surrogate outcome of HIT antibody formation, rather than clinical HIT, as their primary study endpoint. The biological basis for a difference in immunogenicity between animal sources of heparin could relate to the greater polysaccharide chain length and degree of sulfation in bovine lung heparin, which could facilitate immunogenicity by enhanced reactions with PF4.
Recommendations

4.2.1. For the treatment of patients with thrombosis, we recommend against the use of bovine UFH, in comparison with porcine UFH or LMWH (Grade 1A).

4.2.2. For patients undergoing cardiac surgery, we recommend the use of porcine UFH for intraoperative anticoagulation, in comparison with bovine UFH (Grade 1B).

Summary of Recommendations

1.0 Recognition of HIT

1.1 Platelet count monitoring for HIT

1.1.1 Platelet count monitoring of patients recently treated with heparin

1.1.1.1 For patients who are starting UFH or LMWH treatment and who have received UFH within the past 100 days, or those patients in whom exposure history is uncertain, we suggest obtaining a baseline platelet count and then a repeat platelet count within 24 h of starting heparin (Grade 2C).

1.1.2 Acute systemic reactions after IV UFH bolus

1.1.2. For patients who acquire acute inflammatory, cardiorespiratory, neurologic, or other unusual symptoms and signs within 30 min following an IV UFH bolus, we recommend performing an immediate platelet count measurement, and comparing this value to recent prior platelet counts, in comparison with not performing a platelet count measure (Grade 1C).

1.1.3 Platelet count monitoring in patients receiving therapeutic-dose UFH

1.1.3. For patients who are receiving therapeutic-dose UFH, we suggest at least every-other-day platelet count monitoring until day 14, or until UFH is stopped, whichever occurs first (Grade 2C).

Underlying values and preferences. This recommendation places a high value on diagnosis and early treatment of HIT to prevent sequelae, and a lower value on the burden and cost of monitoring platelet counts.

1.1.4 Platelet count monitoring in postoperative patients receiving UFH antithrombotic prophylaxis

1.1.4. For patients who are receiving postoperative antithrombotic prophylaxis with UFH (HIT risk > 1%), we suggest at least every-other-day platelet count monitoring between postoperative days 4 to 14, or until UFH is stopped, whichever occurs first (Grade 2C).

Underlying values and preferences. This recommendation places a high value on diagnosis and early treatment of HIT to prevent sequelae and a lower value on the burden and cost of monitoring platelet counts.

1.1.5 Platelet count monitoring in patients in whom HIT is infrequent (0.1 to 1%)

1.1.5. For medical/obstetrical patients who are receiving prophylactic-dose UFH, postoperative patients receiving prophylactic-dose LMWH, postoperative patients receiving intravascular catheter UFH “flushes,” or medical/obstetric patients receiving LMWH after first receiving UFH (HIT risk, 0.1 to 1%), we suggest platelet count monitoring every 2 or 3 days from day 4 to day 14 (or until heparin is stopped, whichever occurs first), when practical (Grade 2C).

Underlying values and preferences. This recommendation places a high value on diagnosis and early treatment of HIT to prevent sequelae and a lower value on the burden and cost of monitoring platelet counts.

1.1.6 Platelet count monitoring when HIT is rare (< 0.1%)

1.1.6. For medical/obstetric patients who are only receiving LMWH, or medical patients who are receiving only intravascular catheter UFH flushes (HIT risk < 0.1%), we suggest clinicians do not use routine platelet count monitoring (Grade 2C).

Underlying values and preferences. This recommendation places a lower value on the rare diagnosis and early treatment of HIT to prevent sequelae, and a higher value on the burden and cost of monitoring platelet counts.

1.1.7 Screening for subclinical HIT antibody seroconversion

1.1.7. In patients who receive heparin, we recommend against routine HIT antibody testing in the absence of thrombocytopenia, thrombosis, heparin-induced skin lesions, or other sequelae of HIT (Grade 1C).

1.1.8 When should HIT be suspected?

1.1.8. For patients receiving heparin, or who have received heparin within the previous 2 weeks, we...
recommend excluding a diagnosis of HIT if the platelet count falls by ≥ 50%, and/or a thrombotic event occurs, between days 4 to 14 following initiation of heparin, even if the patient is no longer receiving heparin therapy when thrombosis or thrombocytopenia have occurred (Grade 1C).

1.1.9 Special situation: anticoagulant prophylaxis and platelet count monitoring after cardiac surgery

1.1.9. For postoperative cardiac surgery patients, we recommend excluding a diagnosis of HIT if the platelet count falls by ≥ 50% (and/or a thrombotic event occurs) between postoperative days 4 to day 14 (day of cardiac surgery = day zero) (Grade 1C).

2.0 Treatment of HIT

2.1 Nonheparin anticoagulants for HIT

2.1.1. For patients with strongly suspected (or confirmed) HIT, whether or not complicated by thrombosis, we recommend use of an alternative, nonheparin anticoagulant, such as lepirudin (Grade 1C+), argatroban (Grade 1C), bivalirudin (Grade 2C), or danaparoid (Grade 1B), over further UFH or LMWH therapy, and over no further anticoagulation (with or without vena caval filter).

2.1.2. For patients with strongly suspected (or confirmed) HIT, whether or not there is clinical evidence of lower-limb DVT, we recommend routine ultrasonography of the lower-limb veins for investigation of DVT, over not performing routine ultrasonography (Grade 1C).

2.2 VKAs

2.2.1 Management of DTI-VKA overlap

2.2.1. For patients with strongly suspected or confirmed HIT, we recommend against the use of vitamin K antagonist (coumarin) therapy until after the platelet count has substantially recovered (eg, to at least 100 x 10^9/L, and preferably, 150 x 10^9/L); that the VKA be administered only during overlapping alternative anticoagulation (minimum 5-day overlap), and begun with low, maintenance doses (maximum, 5 mg, warfarin; 6 mg, phenprocoumon); that the alternative anticoagulant not be stopped until the platelet count has reached a stable plateau, and with at least the last 2 days the INR within the target therapeutic range (all Grade 1C).

2.2.2 Reversal of VKA anticoagulation

2.2.2. For patients receiving VKAs at the time of diagnosis of HIT, we recommend use of vitamin K (Grade 2C).

2.3 LMWH for HIT

2.3. For patients with strongly suspected HIT, whether or not complicated by thrombosis, we recommend against use of LMWH (Grade 1C+).

2.4 Prophylactic platelet transfusions for HIT

2.4. For patients with strongly-suspected or confirmed HIT who do not have active bleeding, we suggest that prophylactic platelet transfusions not be administered (Grade 2C).

3.0 Special Patient Populations

3.1 Patients with previous HIT undergoing cardiac or vascular surgery

3.1.1. For patients with a history of HIT who are HIT antibody negative and require cardiac surgery, we recommend the use of UFH over a nonheparin anticoagulant (Grade 1C).

Remark: Preoperative and postoperative anticoagulation, if indicated, should be administered with a nonheparin anticoagulant.

3.2 Patients with acute or subacute HIT undergoing cardiac surgery

3.2.1. For patients with acute HIT (thrombocytopenic, HIT antibody positive) who require cardiac surgery, we recommend one of the following alternative anticoagulant approaches (in descending order of preference): delaying surgery (if possible) until HIT antibodies are negative (see recommendation 3.1.1.) [Grade 1C]; using bivalirudin for intraoperative anticoagulation during cardiopulmonary bypass (if ecarin clotting time [ECT] available) [Grade 1C] or during off-pump cardiac surgery (Grade 1C+); using lepirudin for intraoperative anticoagulation (if ecarin clotting time available and patient has normal renal function) [Grade 1C]; using UFH plus the antiplatelet agent, epoprostenol (if ECT monitoring not available or renal insufficiency precludes lepirudin use) [Grade 2C]; using UFH plus the antiplatelet agent, tirofiban (Grade 2C); or using danaparoid for intraoperative anticoagulation (if anti-factor Xa levels are available) [Grade 2C].

3.2.2. For patients with subacute HIT (platelet count recovery, but continuing HIT antibody-positive), we recommend delaying surgery (if possible) until HIT antibodies are negative, then using heparin (see recommendation 3.1.1.) [Grade 1C]. Alternatively, we suggest the use of a nonheparin anticoagulant (see recommendation 3.2.1.) [Grade 2C].

3.3 PCIs

3.3. For patients with acute or previous HIT who require cardiac catheterization or PCI, we recommend use
of an alternative anticoagulant, such as argatroban (Grade 1C), bivalirudin (Grade 1C), lepirudin (Grade 1C), or danaparoid (Grade 2C), over the use of heparin.

4.0 Prevention of HIT

4.1 Reducing HIT antibody formation and clinical HIT

4.1.1 UFH vs LMWH

4.1.1. For postoperative orthopedic surgery patients, we recommend the use of LMWH over UFH (Grade 1A).

4.2 Bovine vs porcine UFH

4.2.1. For the treatment of patients with thrombosis, we recommend against the use of bovine UFH, in comparison with porcine UFH or LMWH (Grade 1A).

4.2.2. For patients undergoing cardiac surgery, we recommend the use of porcine UFH for intraoperative anticoagulation, in comparison with bovine UFH (Grade 1B).

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