Treatment and Prevention of Heparin-Induced Thrombocytopenia*

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)

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This chapter about the recognition, treatment, and prevention of heparin-induced thrombocytopenia (HIT) is part of the Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Grade 1 recommendations are strong and indicate that the benefits do, or do not, outweigh risks, burden, and costs. Grade 2 suggests that individual patient values may lead to different choices. Among the key recommendations in this chapter are the following: For patients receiving heparin in whom the clinician considers the risk of HIT to be > 1.0%, we recommend platelet count monitoring over no platelet count monitoring (Grade 1C). For patients who are receiving heparin or have received heparin within the previous 2 weeks, we recommend investigating for a diagnosis of HIT if the platelet count falls by ≥ 50%, and/or a thrombotic event occurs, between days 5 and 14 (inclusive) following initiation of heparin, even if the patient is no longer receiving heparin therapy when thrombosis or thrombocytopenia has occurred (Grade 1C). For patients with strongly suspected (or confirmed) HIT, whether or not complicated by thrombosis, we recommend use of an alternative, nonheparin anticoagulant (danaparoid [Grade 1B], lepirudin [Grade 1C], argatroban [Grade 1C], fondaparinux [Grade 2C], or bivalirudin [Grade 2C]) over the further use of unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) therapy or initiation/continuation of vitamin K antagonists (VKAs) [Grade 1B]. The guidelines include specific recommendations for nonheparin anticoagulant dosing that differ from the package inserts. For patients with strongly suspected or confirmed HIT, we recommend *against* the use of vitamin K antagonist (VKA) [coumarin] therapy until after the platelet count has substantially recovered (usually, to at least 150×10^9/L) over starting VKA therapy at a lower platelet count (Grade 1B); that VKA therapy be started only with low maintenance doses (maximum, 5 mg of warfarin or 6 mg of phenprocoumon) over higher initial doses (Grade 1B); and that the nonheparin anticoagulant (*eg*, lepirudin, argatroban, danaparoid) be continued until the platelet count has reached a stable plateau, the international normalized ratio (INR) has reached the intended target range, and after a minimum overlap of at least 5 days between nonheparin anticoagulation and VKA therapy rather than a shorter overlap (Grade 1B). For patients receiving VKAs at the time of diagnosis of HIT, we recommend use of vitamin K (10 mg po or 5 to 10 mg IV) [Grade 1C]. ***(CHEST 2008; 133:340S–380S)***

Key words: argatroban; bivalirudin; coumarin-induced necrosis; danaparoid; fondaparinux; heparin-induced thrombocytopenia; IgG; lepirudin; low-molecular-weight heparin; unfractionated heparin

Abbreviations: ACT = activated clotting time; APTT = activated partial thromboplastin time; CI = confidence interval; CPB = cardiopulmonary bypass; DIC = disseminated intravascular coagulation; DTI = direct thrombin inhibitor; DVT = deep venous thrombosis; ECT = ecarin clotting time; EIA = enzyme immunoassay; EMEA = European Agency for the Evaluation of Medicinal Products; FDA = Food and Drug Administration; HIPA = heparin-induced platelet activation assay; HIT = heparin-induced thrombocytopenia; INR = international normalized ratio; LMWH = low-molecular-weight heparin; OD = optical density; OR = odds ratio; PCI = percutaneous coronary intervention; PE = pulmonary embolism; PF4 = platelet factor 4; RCT = randomized controlled trial; RR = relative risk; SC = subcutaneous; SRA = serotonin release assay; UFH = unfractionated heparin; VKA = vitamin K antagonist

Summary of Recommendations

1.0 Recognition of HIT

1.1 Platelet Count Monitoring for HIT

1.1. For patients receiving heparin in whom the clinician considers the risk of HIT to be > 1.0%, we recommend platelet count monitoring over no platelet count monitoring (Grade 1C). **For patients receiving heparin who have an estimated risk of HIT of 0.1 to 1.0%, we suggest platelet count monitoring over no platelet count monitoring** (Grade 2C).

1.1.1 Platelet Count Monitoring of Patients Recently Treated With Heparin

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 recommend obtaining a baseline platelet count and then a repeat platelet count within 24 h of starting heparin over not obtaining a repeat platelet count (Grade 1C).

1.1.2 Anaphylactoid Reactions After IV UFH Bolus

1.1.2. For patients in whom acute inflammatory, cardiorespiratory, neurologic, or other unusual symptoms and signs develop 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, over not performing a platelet count (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 platelet count monitoring at least every 2 or 3 days from day 4 to day 14 (or until heparin is stopped, whichever occurs first) over less frequent platelet count monitoring (Grade 2C).

1.1.4 Platelet Count Monitoring in Postoperative Patients Receiving UFH Antithrombotic Prophylaxis (Highest Risk Group for HIT)

1.1.4. For patients who are receiving postoperative antithrombotic prophylaxis with UFH, *ie*, the patient population at highest risk for HIT (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) over less frequent platelet count monitoring (Grade 2C).

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/obstetrical patients receiving LMWH after first receiving UFH (estimated HIT risk, 0.1 to 1%), we suggest platelet count monitoring at least every 2 or 3 days from day 4 to day 14 (or until heparin is stopped, whichever occurs first), when practical, over less frequent platelet count monitoring (Grade 2C).

1.1.6 Platelet Count Monitoring When HIT is Rare (< 0.1%): UFH and LMWH

1.1.6. For medical/obstetrical patients who are receiving only 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).

1.1.7 Platelet Count Monitoring When HIT is Rare (< 0.1%): Fondaparinux

1.1.7. For patients who are receiving fondaparinux thromboprophylaxis or treatment, we recommend that clinicians do not use routine platelet count monitoring (Grade 1C).

1.1.8 Management of Patients in Whom Platelet Counts Are Not Monitored

1.1.8. In outpatients who will receive heparin prophylaxis or treatment, informed consent

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should include HIT and its typical sequelae (new thrombosis, skin lesions) and the patient should be advised to seek medical advice if these events occur (Grade 2C).

1.1.9 Screening for Subclinical HIT Antibody Seroconversion

1.1.9. In patients who receive heparin, or in whom heparin treatment is planned (*eg*, for cardiac or vascular surgery), we recommend against routine HIT antibody testing in the absence of thrombocytopenia, thrombosis, heparin-induced skin lesions, or other signs pointing to a potential diagnosis of HIT (Grade 1C).

1.1.10 When Should HIT Be Suspected?

1.1.10. For patients who are receiving heparin or have received heparin within the previous 2 weeks, we recommend investigating for a diagnosis of HIT if the platelet count falls by ≥ 50%, and/or a thrombotic event occurs, between days 5 and 14 (inclusive) following initiation of heparin, even if the patient is no longer receiving heparin therapy when thrombosis or thrombocytopenia has occurred (Grade 1C).

1.2 Special Situation: Anticoagulant Prophylaxis and Platelet Count Monitoring After Cardiac Surgery

1.2. For postoperative cardiac surgery patients, we recommend investigating for HIT antibodies if the platelet count falls by ≥ 50%, and/or a thrombotic event occurs, between postoperative days 5 and 14 (inclusive; day of cardiac surgery = day 0) [Grade 1C].

2.0 Treatment of HIT

2.1 Nonheparin Anticoagulants for Treating HIT (With or Without Thrombosis)

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 (danaparoid [Grade 1B], **lepirudin** [Grade 1C], **argatroban** [Grade 1C], **fondaparinux** [Grade 2C], **bivalirudin** [Grade 2C]) **over the further use of UFH or LMWH therapy or initiation/continuation of a VKA** (Grade 1B).

2.1.2. For patients receiving lepirudin, the initial lepirudin infusion rate should be no higher than 0.10 mg/kg/h (patients with creatinine < 90 μmol/L), with lower infusion rates for patients with higher serum creatinine levels (creatinine, 90 to 140 μmol/L: starting infusion rate, 0.05 mg/kg/h; creatinine, 140 to 400 μmol/L: starting infusion rate, 0.01 mg/kg/h; creatinine > 400 μmol/L: starting infusion rate, 0.005 mg/kg/h) [Grade 1C]. **Furthermore, we recommend that the initial IV bolus either be omitted or, in case of perceived life- or limb-threatening thrombosis, be given at a reduced dose (0.2 mg/kg)** [Grade 1C]. **Further, we recommend that APTT monitoring be performed at 4-h intervals until it is apparent that steady state within the therapeutic range (1.5- to 2.0-times patient baseline [or mean laboratory] APTT) is achieved** (Grade 1C).

2.1.3. When argatroban is used to treat patients who have heart failure, multiple organ system failure, or severe anasarca or who are postcardiac surgery, we suggest beginning the initial infusion at a rate between 0.5 and 1.2 μg/kg/min, with subsequent adjustments using the APTT, over the usual recommended starting dose of 2.0 μg/kg/min (Grade 2C).

2.1.4. When danaparoid is used to treat patients with strongly suspected (or confirmed) HIT, we recommend a therapeutic-dose regimen (see text) administered (at least initially) by the IV route over prophylactic-dose regimens or initial SC administration (Grade 1B).

2.1.5. 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 Direct Thrombin Inhibitor–VKA Overlap

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 (*ie*, usually to at least 150×10^9/L) over starting VKA therapy at a lower platelet count (Grade 1B); **that VKA therapy be started only with low, maintenance doses (maximum, 5 mg of warfarin or 6 mg of phenprocoumon) rather than with higher initial doses** (Grade 1B); **and that the nonheparin anticoagulant (*eg*, lepirudin, argatroban, danaparoid) be continued until the platelet count has reached a stable plateau, the INR has reached the intended target range, and after a minimum overlap of at least 5 days between nonheparin**

anticoagulation and VKA therapy rather than a shorter overlap (Grade 1B).

2.2.2 Reversal of VKA Anticoagulation

2.2.2. For patients receiving a VKA at the time of diagnosis of HIT, we recommend use of vitamin K (10 mg po or 5 to 10 mg IV) [Grade 1C].

2.3 LMWH for HIT

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

2.4 Prophylactic Platelet Transfusions for HIT

2.4.1. For patients with strongly suspected or confirmed HIT who do not have active bleeding, we suggest that prophylactic platelet transfusions should not be given (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 1B).

3.1.2. For patients with a history of HIT who are antibody positive by platelet factor 4 (PF4)-dependent enzyme immunoassay (EIA) but antibody negative by washed platelet activation assay, we recommend the use of UFH over a nonheparin anticoagulant (Grade 2C).

Remark: Preoperative and postoperative anticoagulation, if indicated, should be given 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 has resolved and antibodies are negative (then see Recommendation 3.1.1.) or weakly positive (then see Recommendation 3.1.2.) [Grade 1B]**; using bivalirudin for intraoperative anticoagulation during cardiopulmonary bypass (if techniques of cardiac surgery and anesthesiology have been adapted to the unique features of bivalirudin pharmacology)** [Grade 1B] **or during "off-pump" cardiac surgery** (Grade 1B)**; using lepirudin for intraoperative anticoagulation (if ECT is available and patient has normal renal function and is judged to be at low risk for postcardiac surgery renal dysfunction)** [Grade 2C]**; using UFH plus the antiplatelet agent epoprostenol (if ECT monitoring is 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 for off-pump coronary artery bypass surgery** (Grade 2C) **over performing the surgery with UFH when platelet-activating anti-PF4/heparin antibodies are known to be present in a patient with acute or recent HIT.**

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 (washed platelet activation assay) are negative, then using heparin (see Recommendation 3.1.1.) over using a nonheparin anticoagulant (Grade 1C)**. If surgery cannot be delayed, we suggest the use of a nonheparin anticoagulant (see Recommendation 3.2.1.) over the use of UFH** (Grade 2C).

3.3 Percutaneous Coronary Interventions

3.3.1. For patients with strongly suspected (or confirmed) acute HIT who require cardiac catheterization or percutaneous coronary intervention (PCI), we recommend a nonheparin anticoagulant (bivalirudin [Grade 1B]**, argatroban** [Grade 1C]**, lepirudin** [Grade 1C]**, or danaparoid** [Grade 1C]) **over UFH or LMWH** (Grade 1B).

3.3.2. For patients with previous HIT (who are antibody negative) who require cardiac catheterization or PCI, we suggest use of a nonheparin anticoagulant (see Recommendation 3.3.1.) over UFH or LMWH (Grade 2C).

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 in whom HIT develops constitute a cohort with substantially increased thrombotic risk, both in relative (odds ratio [OR] for thrombosis, 20 to 40[1–5]) and absolute (thrombosis risk, 30 to 75%[1–10]) terms, depending on the patient population affected.

Because the diagnosis is based on both clinical and serologic grounds, clinicians should consider HIT a *clinicopathologic syndrome*.[11–14] Thus, neither thrombocytopenia or thrombosis without the presence of heparin-dependent antibodies, nor the isolated presence of antibodies without thrombocytopenia, thrombosis, or other clinical sequelae, meet the criteria for HIT. Rather, clinicians make a diagnosis of HIT when any of the following events occurs in association with the presence of "HIT antibodies" detected by *in vitro* assays: (1) an otherwise unexplained platelet count fall (defined by various investigators as a minimum platelet count fall of 30%,[15,16] 40%,[17] or 50%[2]—even if the platelet count nadir remains $> 150 \times 10^9$/L (note: the "baseline" platelet count is not necessarily the preheparin platelet count, but rather the highest platelet count during the 2-week period that follows initiation of heparin therapy and that immediately precedes the platelet count decline indicating HIT); (2) venous or arterial thrombosis (most often, deep venous thrombosis [DVT], pulmonary embolism [PE], limb artery thrombosis, thrombotic stroke, myocardial infarction, adrenal hemorrhagic necrosis [indicating adrenal vein thrombosis]); (3) skin lesions at heparin injection sites[18]; or (4) acute systemic (anaphylactoid) reactions (*eg*, fever/chills, tachycardia, hypertension, dyspnea, cardiopulmonary arrest) that occur after IV heparin bolus administration.[7] Diagnostic specificity can be further increased by use of a sensitive washed platelet activation assay; a positive platelet activation assay is much more specific for clinical HIT than a positive platelet factor 4 (PF4)-dependent immunoassay.[19–23] With such a clinicopathologic viewpoint, clinicians can diagnose clinical HIT even when the patient's platelet count does not fall by as much as 30% (*eg*, a patient with heparin-induced necrotizing skin lesions and adrenal necrosis associated with formation of platelet-activating anti-PF4/heparin antibodies[18]).[21,24] Indeed, in about 25% of HIT patients, a thrombotic event during heparin treatment *precedes* the subsequent HIT-associated platelet count fall.[1,16]

The neoepitopes recognized by HIT antibodies are located on PF4, and are formed when PF4 binds to heparin.[25–27] HIT antibodies activate platelets intravascularly, causing release of platelet microparticles and increased thrombin generation. However, only a subset of anti-PF4/heparin antibodies activate platelets,[19,20,28] which explains the greater diagnostic specificity of certain platelet activation assays (*eg*, platelet serotonin release assay [SRA], heparin-induced platelet activation (HIPA) assay] for HIT compared with the PF4-dependent EIA.[19,20,23,29] There is a correlation between the degree of reactivity in the EIA, expressed in optical density (OD) units, and the presence of platelet-activating anti-PF4/heparin antibodies. Thus, the greater the magnitude of a positive EIA test result, the greater the likelihood that the patient has HIT, given a certain pretest probability. However, a very strong EIA test result does not necessarily mean that platelet-activating IgG antibodies are present; conversely, only about 5 to 10% of sera showing reactivity 0.4 to 1.0 OD U in an EIA nonetheless contain strong platelet-activating antibodies.[29]

This chapter is organized into sections on the recognition, treatment, and prevention of HIT. The scope of our recommendations include platelet count monitoring for HIT as well as management of HIT, both in patients detected by thrombocytopenia alone ("isolated HIT") and in 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 be detected only by platelet count monitoring. Furthermore, even in patients with thrombosis complicating HIT, the availability of serial platelet counts often provides the key information to prompt consideration of the diagnosis of HIT. 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 occurs most commonly in certain patient populations, such as postoperative patients who receive standard, unfractionated heparin (UFH) for ≥ 1 week (for review, see Lee and Warkentin[6]). One definition classifies an adverse reaction as "common" if its incidence is $> 1\%$.[30] In other clinical settings, the estimated risk of HIT can be described as "uncommon" (0.1 to 1%) or "rare" ($< 0.1\%$).[30] As described later, there is evidence that initial isolated HIT has a substantial risk of evolving to 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 addition, HIT can lead to life- and limb-threatening complications, a risk that could increase with delay in diagnosis or increase in heparin dose (to treat unrecognized HIT-associated thrombosis), or through use of warfarin. These considerations suggest that routine platelet count monitoring for HIT is appropriate in at least some clinical situations, and that the greater the risk of HIT, the stronger the rationale for regular monitoring.

Another consideration that supports a role for platelet count monitoring is that HIT antibody seroconversion and resulting "typical-onset" HIT usually

Table 1—*Question Definition and Study Eligibility Criteria (Section: Introduction)*

Section	Inclusion Criteria				Exclusion Criteria
	Population	Intervention(s) or Exposure	Outcome	Methodology	
1.1	Hospitalized medical, surgical, or obstetric patients	UFH or LMWH for 5–20 d vs no anticoagulation	HIT (platelet count decrease > 30%) and/or new thrombosis/skin lesions (secondary to platelet-activating anti-PF4/heparin antibodies); anti-PF4/heparin antibody formation (platelet activation assays and/or PF4/polyanion EIA)	Metaanalyses, RCTs, cohort studies	< 25 patients
1.2	Cardiac surgery patients undergoing on-pump and off-pump surgery	No anticoagulation vs anticoagulation (UFH, LMWH, fondaparinux) after surgery	HIT; HIT-associated VTE; HIT antibody formation	Metaanalyses; RCTs; cohort studies	< 50 patients
2.1	HIT patients (with or without thrombosis)	Non-heparin anticoagulation (lepirudin, argatroban, bivalirudin, danaparoid, or fondaparinux)	New thrombosis; mortality; limb amputation; composite of above; drug anaphylaxis	RCTs; cohort studies	< 25 patients (no exclusions for reports on drug-associated anaphylaxis)
2.2	HIT patients (with or without thrombosis)	VKAs (coumarins)	VKA therapy-associated thrombosis, including venous limb gangrene, skin necrosis	Cohort studies	Patients without HIT antibodies
2.3	HIT patients (with or without thrombosis)	LMWH	Thrombosis; platelet count recovery	Cohort studies	< 25 patients
2.4	HIT patients (with or without thrombosis)	Platelet transfusions vs no platelet transfusions	New thrombosis	Cohort studies and case series	< 5 patients
3.1	Patients with previous HIT undergoing cardiac surgery	Repeat heparin exposure	Recurrence of HIT; repeat formation of HIT antibodies	Prospective cohort studies; retrospective cohort studies	< 5 patients
3.2	Patients with acute or subacute HIT undergoing cardiac surgery	Anticoagulant approaches during cardiac surgery: lepirudin, argatroban, danaparoid, bivalirudin, UFH plus epoprostenol, UFH plus tirofiban	Procedural success (as defined by study authors)	Prospective cohort studies; retrospective cohort studies	< 5 patients
3.3	Patients with previous or acute HIT undergoing PCI	Non-heparin anticoagulation	Procedural success (as defined by study authors)	Prospective cohort studies; retrospective cohort studies	< 5 patients
3.4	Patients with acute HIT undergoing hemodialysis	Non-heparin anticoagulation	Procedural success (as defined by study authors)	Retrospective cohort studies	< 5 patients
4.1	Hospitalized medical, surgical, or obstetric patients; cardiac surgery patients	Comparison of UFH and LMWH/fondaparinux	Frequency of HIT (using explicit criteria); frequency of HIT antibody formation	Metaanalyses; RCTs; nonrandomized controlled studies; retrospective cohort studies	< 100 patients

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), when the first day of the immunizing heparin exposure is considered to be "day 0."[1,2,6,7,31,32] (Day 4 can be included within the period of platelet count monitoring for HIT because it can provide a com-

parative preimmunization reference point.) 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, and especially the last 30 days).[31,32]

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]),[19,20,33–41] the type of heparin-exposed patient population (postsurgery > medical > pregnancy),[19,20,41–46] duration of heparin exposure,[7] and patient sex (female > male).[41] Thus, whether to perform platelet count monitoring, and the intensity of such monitoring, depends on these considerations, particularly heparin and patient type and the duration of heparin use. 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. Furthermore, the rationale for platelet count monitoring is stronger when monitoring is relatively easy (*ie*, in a hospital inpatient), and weaker when monitoring is more difficult (*ie*, out-patient settings. Table 2 summarizes the various risk factors for HIT, and classifies risk into three different groups: high (> 1.0%), intermediate (0.1 to 1.0%), and low (< 0.1%).[1,2,4,6,15,17,19,20,34–71]

A potential downside of platelet count monitoring is that patients with a decrease in platelet counts for reasons other than HIT may be wrongly suspected of having this diagnosis. As the alternative nonheparin anticoagulants have a relatively high risk of bleeding, there is the potential for treatment-related adverse events as a consequence of platelet count monitoring.

Underlying Values and Preferences: The following recommendations regarding monitoring of platelet count share the same underlying values and preferences, as follows. The recommendations place a high value on the possible benefits of early diagnosis and consequent early treatment of HIT to prevent sequelae and a lower value on the burden and cost of monitoring platelet counts, including the consequences of further investigation and management of the high proportion of patients with a significant fall in platelet count who do not have HIT and the risks associated with unnecessary withdrawal of heparin and unnecessary use of alternative agents with a higher bleeding risk.

Recommendation

1.1. For patients receiving heparin in whom the clinician considers the risk of HIT to be > 1.0%, we recommend platelet count monitoring over no platelet count monitoring (Grade 1C)**. For patients receiving heparin who have an estimated risk of HIT of 0.1 to 1.0%, we suggest platelet count monitoring over no platelet count monitoring** (Grade 2C)**.**

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.[31,32] 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.[31,32] 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. 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 recommend obtaining a baseline platelet count and then a repeat platelet count within 24 h of starting heparin over not obtaining a repeat platelet count (Grade 1C)**.**

1.1.2 Anaphylactoid Reactions After IV UFH Bolus

Rarely, patients develop acute inflammatory (*eg*, fever, chills) or cardiorespiratory (*eg*, hypertension, tachycardia, dyspnea, chest pain, cardiorespiratory arrest) symptoms and signs within 30 min following an IV heparin bolus.[7,47] Also termed *acute systemic reactions*, these can also mimic acute PE (*pseudopulmonary embolism*[48]) and strongly suggest acute *in vivo* platelet activation secondary to HIT. This presentation mandates a prompt platelet count measurement, as an abrupt platelet count fall in this clinical context supports the diagnosis of HIT. The platelet count drop is frequently transient,[2] and thus a delay in determining the platelet count, especially if heparin is stopped, may result in a missed diagnosis.

Recommendation

1.1.2. For patients in whom acute inflammatory, cardiorespiratory, neurologic, or other unusual symptoms and signs develop within 30 min following an IV UFH bolus, we recommend

Table 2—*Risk Factors for HIT: Implications for Platelet Count Monitoring (Section: 1.1)

Risk Factors	Relative Importance of Risk Factor		
	Major (OR > 5)	Moderate (OR 3–5)	Minor (OR 1–3)
Heparin duration > 4 d†	Yes		
Recent heparin (past 100 d)‡	Yes		
UFH > LMWH§	Yes		
Postsurgery > medical > obstetric		Yes	
Dose of heparin			
Immunizing: prophylaxis > therapeutic‖		Yes	
Manifesting: therapeutic > prophylaxis > "flushes"¶		Yes	
Gender: female > male			Yes
Examples of patient groups with risk estimated to be > 1%			
Postoperative patients receiving prophylactic-dose UFH > 4 d			
Postoperative patients receiving therapeutic-dose UFH > 4 d#			
Examples of patient groups with risk estimated to be 0.1–1%			
Medical/obstetric patients receiving prophylactic or therapeutic-dose UFH > 4 d			
Postsurgery patients receiving LMWH > 4 d			
Postsurgery patients receiving UFH "flushes" > 4 d			
Medical/obstetric patients receiving LMWH after first receiving UFH			
Examples of patients groups with risk estimated to be < 0.1%			
Medical/obstetric patients receiving LMWH > 4 d**			
Medical/obstetric patients receiving only heparin flushes			
Any patient receiving UFH or LMWH < 4 d			

*Based upon assessment of the published literature.[1,2,4,6,15,17,19,20,34–71]

†Risk declines after 14 days (in the absence of intervening surgery).

‡Risk of rapid-onset HIT if heparin is restarted in a patient exposed within the past 100 days (and especially the last 30 days).

§Difference in risk between UFH and LMWH best established in postsurgery patients and in females.

‖Theoretically, stoichiometric concentrations of PF4/UFH and PF4/LMWH are most likely to be achieved at prophylactic doses.

¶Among patients who have HIT antibodies, higher doses of heparin usually result in greater platelet count falls.

#Best established in post-cardiac surgery patients.

**One study[38] suggested that the frequency of HIT in medical patients receiving LMWH could be between 0.1–1%, but this study is a statistical outlier and its conclusions remain to be confirmed.[39,41]

performing an immediate platelet count measurement, and comparing this value to recent prior platelet counts, over not performing a platelet count (Grade 1C)**.**

1.1.3 Platelet Count Monitoring in Patients Receiving Therapeutic-Dose UFH

For patients receiving porcine UFH in therapeutic doses, by either the IV or subcutaneous (SC) route, for the treatment of venous or arterial thrombosis, the risk of HIT has been estimated to be at most about 1%,[6] based on a review of studies of the frequency of HIT in patients receiving porcine UFH for venous thromboembolism.[4,36,49–62] However, the two most recent studies[4,36] identified only 1 patient with HIT among 594 treated with therapeutic-dose UFH, suggesting that the frequency among this patient population is likely < 1%.

Recommendation

1.1.3. For patients who are receiving therapeutic-dose UFH, we suggest platelet count monitoring at least every 2 or 3 days from day 4 to day 14 (or until heparin is stopped, whichever occurs first) over less frequent platelet count monitoring (Grade 2C)**.**

1.1.4 Platelet Count Monitoring in Postoperative Patients Receiving UFH Antithrombotic Prophylaxis (Highest Risk Group for HIT)

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,[15,17,19,20,33,63–67] and, likely, other postsurgery patient populations.

Recommendation

1.1.4. For patients who are receiving postoperative antithrombotic prophylaxis with UFH, *ie*, the patient population at highest risk for HIT (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) over less frequent platelet count monitoring (Grade 2C)**.**

While we gave a strong recommendation overall in favor of performing platelet count monitoring when the risk of HIT was judged to be ≥ 1% (see Recommendation 1.1), our recommendation for the specific intensity of platelet count monitoring in this and other patient populations (see also Recommendations 1.1.3 and 1.1.5) 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 2 to 3 days from the postoperative peak to a ≥ 50% platelet count decline).[1,2,7]**

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 "uncommon" (*ie*, 0.1 to 1%). These include medical (including patients with acute coronary syndrome) or obstetrical patients receiving prophylactic-dose UFH[4,6,46,60–62,68–70]; postoperative patients receiving LMWH[1,2,6,17,19,20,63,66]; postoperative/critical care patients receiving UFH flushes[6,71]; and, theoretically, medical patients receiving LMWH after having received one or more preceding doses of UFH. In some settings (*eg*, patients receiving outpatient LMWH), it may be impractical to obtain platelet counts. Thus, less frequent (or no) 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 signs or symptoms of venous thromboembolism (the most common complication of HIT) occur or painful skin lesions develop at the heparin injection sites (see also Recommendation 1.1.8).

Recommendation

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/obstetrical patients receiving LMWH after first receiving UFH (estimated HIT risk, 0.1 to 1%), we suggest platelet count monitoring at least every 2 or 3 days from day 4 to day 14 (or until heparin is stopped, whichever occurs first), when practical, over less frequent platelet count monitoring (Grade 2C)**.**

1.1.6 Platelet Count Monitoring When HIT is Rare (< 0.1%): UFH and LMWH

In medical and obstetrical patients receiving LMWH, the risk of HIT appears to be rare (< 0.1%).[36,37,39,42–45] For example, only one possible case[43] of HIT was observed among 1,167 pregnancies treated with LMWH in three studies[42–44]; a more recent review[45] of LMWH use during 2,777 pregnancies identified no cases of HIT. Although fewer data exist with respect to medical patients receiving LMWH or UFH as flushes (*eg*, oncology patients with indwelling catheters),[72,73] the experience of the authors is that HIT is rare in this setting. However, one prospective, multicenter study[38] of LMWH administered to medical patients reported the frequency of HIT to be 0.8%. Limitations of this study suggest, however, that it provides an overestimate of HIT incidence: (1) not all patients underwent testing with the more specific platelet activation assays, and (2) some of the clinical features (*eg*, early onset of thrombocytopenia) were not characteristic of this adverse drug reaction. Furthermore, the data represent a statistical outlier compared with other studies,[39,41] and in our view further studies are required before recommending that platelet count monitoring be performed routinely in medical patients receiving LMWH.

Recommendation

1.1.6. For medical/obstetrical patients who are receiving only 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 Platelet Count Monitoring When HIT is Rare (< 0.1%): Fondaparinux

Fondaparinux is an indirect (antithrombin-mediated) inhibitor of factor Xa modeled after the pentasaccharide region of heparin. A syndrome resembling immune HIT was not reported in any of the regulatory trials for this anticoagulant in various clinical settings (*eg*, orthopedic surgery,[74] treatment of venous thromboembolism[75,76]). However, anti-PF4/heparin antibodies—some with platelet-activating properties—have been observed to occur in association with fondaparinux thromboprophylaxis in a frequency similar to that seen with the LMWH enoxaparin.[77,78]

Unlike the situation with UFH or enoxaparin, these antibodies—as well as antibodies obtained from patients with typical HIT—do not bind well to PF4 *in vitro* in the presence of fondaparinux, even though they recognize well the epitopes on PF4 in the presence of UFH or LMWH.[77–81] Further, several dozen patients with putative HIT have been reported to have shown platelet count recovery during administration of fondaparinux.[82–84] It therefore seems that the risk of inducing a syndrome resembling immune HIT is negligible. To our knowledge, only one possible case of HIT that occurred in association with postoperative fondaparinux thromboprophylaxis has been reported after 4 years in the marketplace.[85] In our view, this negligible frequency of immune thrombocytopenia indicates that routine platelet count monitoring for HIT should not be performed.

Recommendation

1.1.7. For patients who are receiving fondaparinux thromboprophylaxis or treatment, we recommend that clinicians do not use routine platelet count monitoring (Grade 1C)**.**

1.1.8 Management of Patients in Whom Platelet Counts Are Not Monitored

Clinicians should consider informing patients receiving UFH or LMWH about the potential for the adverse effect of HIT. For patients not under close platelet count monitoring, clinicians should describe the most common resulting signs and symptoms, *ie*, new thrombosis and painful skin lesions at the heparin injection sites. Outpatients should be advised to seek medical advice immediately if these events occur. This will increase awareness of HIT in both the patient and the treating physician.

Recommendation

1.1.8. In outpatients who will receive heparin prophylaxis or treatment, informed consent should include HIT and its typical sequelae (new thrombosis, skin lesions) and the patient should be advised to seek medical advice if these events occur (Grade 2C)**.**

1.1.9 Screening for Subclinical HIT Antibody Seroconversion

Prospective studies of HIT and HIT antibody formation[1,2,6,19,20,34–36,67,86] indicate that HIT occurs in a minority of patients who form anti-PF4/heparin antibodies. The serologic profile in about 99% of patients with clinical HIT is positive testing in both of two sensitive and complementary assays: (1) platelet activation (or "functional") assay using washed platelets (*eg*, ^{14}C-SRA, HIPA test), or (2) PF4-dependent EIA.[19,20,87] However, even though both assays are sensitive in detecting HIT antibodies, neither is completely specific for the HIT syndrome (although the functional assays are far more specific than the EIA).[13] Consequently, serology is more effective in ruling out a possible diagnosis of HIT than in confirming the diagnosis, *ie*, the negative tests have a very low likelihood ratio, but positive tests only a moderately high likelihood ratio. 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) was associated with a high likelihood ratio for HIT in patients after orthopedic surgery (approximately 100), whereas a weak positive test result (*eg*, 0.40–1.00 absorbance units in one study using an in-house PF4-dependent EIA that detected IgG class antibodies) was associated with a relatively low risk for HIT.[19,21,29] For patients after cardiac surgery, the corresponding risks for HIT for "strong" and "weak" serologic results are likely to be lower.[21,29] The risk of HIT is even lower when using commercial EIAs that detect antibodies of all three Ig classes. The diagnostic interpretation of these laboratory tests must be made in the context of the clinical estimation of the pretest probability of HIT.[13,21,88]

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 develop antibodies without a significant platelet count decline.[1,2] In our view, it is not useful to perform anti-PF4/heparin antibody testing in the absence of clinical indication of HIT, by either an unexpected fall in the platelet count or an unexpected clinical event. Thus, routine platelet count monitoring, rather than routine anti-PF4/heparin antibody studies, is most useful (and most practical) to identify patients who are at risk for developing thrombosis because of immunization triggered by heparin therapy.

In addition, there is no evidence that routine testing for anti-PF4/heparin antibodies prior to cardiac or vascular surgery—in the absence of thrombocytopenia or thrombosis or other clinical evidence of HIT—leads to identification of clinically significant antibodies or improves patient outcomes. In our view, such routine testing is much more likely to identify subclinical antibodies that do not pose in-

creased risk for perioperative complications attributable to the intraoperative or postoperative use of heparin.

Recommendation

1.1.9. In patients who receive heparin, or in whom heparin treatment is planned (*eg*, for cardiac or vascular surgery), we recommend against routine HIT antibody testing in the absence of thrombocytopenia, thrombosis, heparin-induced skin lesions, or other signs pointing to a potential diagnosis of HIT (Grade 1C)**.**

1.1.10 When Should HIT Be Suspected?

Retrospective and prospective studies suggest that > 90% of patients with clinical HIT have a platelet count fall that is > 50% during their heparin treatment.[2,12] In patients with HIT who have lesser degrees of platelet count decline, almost all are identified because of thrombotic complications or other sequelae, such as heparin-induced skin lesions or anaphylactoid reactions following IV bolus UFH.[21] 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 (*eg*, perioperative hemodilution, sepsis/multiorgan system dysfunction, cancer-associated coagulopathy, glycoprotein IIb/IIIa antagonist administration, clearance of previously transfused platelets).[21,89] PE poses a special problem: Whereas HIT is strongly associated with PE (OR, ~ 40),[7] PE itself can be associated with prominent thrombocytopenia (with associated consumptive coagulopathy) even in the absence of HIT antibodies,[89,90] thus emphasizing the important diagnostic role of laboratory testing for HIT antibodies.

Clinicians should consider a diagnosis of HIT 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 0), or when thrombosis or other sequelae of HIT occur in patients treated (or recently treated) with heparin.[21] 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.[21] The strong association between HIT and thrombosis indicates that clinicians should suspect HIT and draw a platelet count (and compare the result with previous values) in a patient who develops symptomatic venous or arterial thrombosis while receiving heparin prophylaxis or treatment, or within several days after heparin prophylaxis or treatment. A recent study[16] found that in approximately one quarter of patients recognized with HIT, HIT-associated thrombosis *preceded* the development of thrombocytopenia by 1 day or a few days. In such cases, administration of higher doses of heparin to treat the thrombosis can "unmask" HIT.[91]

About two thirds of HIT patients evince typical-onset HIT, *ie*, the platelet count begins to fall 5 to 10 days after starting heparin,[31,32] although thrombocytopenic levels (*eg*, > 50% fall or to < 150×10^9/L) are usually not reached until a few days later (about 7 to 14 days after beginning heparin). In about 25 to 30% of patients, the platelet count falls abruptly on beginning a course of heparin.[31] Such rapid-onset HIT occurs in patients who recently (within the previous 100 days) have been exposed to heparin,[31,32] and represents abrupt onset of platelet activation in a patient who has residual circulating HIT antibodies related to the recent prior heparin exposure.

In about 3 to 5% of patients with HIT, the onset of thrombocytopenia begins several days after heparin has been stopped (delayed-onset HIT).[92–98] This last syndrome is consistent with a transient autoimmune nature of HIT, as these patients have PF4/heparin-reactive antibodies that can activate platelets even in the absence of heparin.[92,99] Sometimes even relatively minor exposures to heparin (≤ 5,000 U), particularly when given in a perioperative or inflammatory setting, have resulted in this syndrome. In December 2006, the US Food and Drug Administration (FDA) notified health-care professionals of revisions to the WARNINGS section of the prescribing information for heparin to inform clinicians of the possibility of delayed onset of HIT.

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.[2] 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).[1,2] 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.[1,2,7] 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.[4] On occasion, the platelet count declines by < 50% even though the clinical and serologic findings otherwise strongly suggest HIT-associated thrombosis.[12,18]

Although there are fewer data on an appropriate definition of HIT applicable to medical patients,[4] it appears that a proportional (> 50%) fall in platelet count beginning between days 5 and 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 150×10^9/L, is used to define thrombocytopenia, especially as transient thrombocytosis does not often occur in medical patients.

We are making a strong recommendation regarding the approach to defining thrombocytopenia in HIT because there is good evidence that a proportional fall in platelet count of ≥ 50% is superior to an absolute threshold of 150×10^9/L for the detection of HIT, at least in postoperative patients (improved sensitivity for HIT without loss of diagnostic specificity).[2,7] However, no single definition of thrombocytopenia is appropriate in all clinical situations.

Recommendation

1.1.10. For patients who are receiving heparin or have received heparin within the previous 2 weeks, we recommend investigating for a diagnosis of HIT if the platelet count falls by ≥ 50%, and/or a thrombotic event occurs, between days 5 and 14 (inclusive) following initiation of heparin, even if the patient is no longer receiving heparin therapy when thrombosis or thrombocytopenia has occurred (Grade 1C)**.**

1.2 Special Situation: Anticoagulant Prophylaxis and Platelet Count Monitoring After Cardiac Surgery

The risk of symptomatic venous thrombosis is relatively low in postcardiac surgery patients, even when no antithrombotic prophylaxis is given (although subclinical DVT can be detected in 20% of patients).[100] Many cardiac surgery centers give antithrombotic prophylaxis with UFH (in North America more than in Europe) or LMWH (Europe more than North America). Even if anticoagulant prophylaxis is not routinely given, individual patients who have undergone cardiac surgery may receive anticoagulants because of a prosthetic mechanical valve or unexpected complications such as prolonged postoperative atrial fibrillation, thrombotic stroke, or prolonged immobilization.

The risk of anti-PF4/heparin antibody formation is especially high in this population of cardiac surgery patients, ranging from 35 to 65% by days 7 to 10, even when postoperative anticoagulant prophylaxis with heparin is not given[17,19,65–67,101] or if "off-pump" surgery is performed.[35] More importantly, the absolute risk of clinical HIT in such patients who receive UFH following surgery ranges from 1 to 3%.[6,17,65–67,102,103] 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.[7,16]

An ongoing nonrandomized comparison[17,66] between UFH and LMWH antithrombotic prophylaxis after cardiac surgery found a substantially lower frequency of HIT with LMWH use than with UFH use (11/437, or 2.5%, vs 8/1,874, or 0.4%; $p < 0.0001$). However, there were differences in the patient populations that led to one or the other drug being selected for use. Thus, whether LMWH reduces the risk of HIT in this patient population—though likely—remains unproven. Further, HIT antibodies resulting from UFH therapy frequently cross-react with LMWH, and because patients receiving LMWH after cardiac surgery 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. However, because (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, it is difficult to provide any firm recommendations.

Given the known high risk of HIT in this patient population, we believe that monitoring for HIT is especially important if surgeons prescribe postoperative UFH or LMWH.[102] A practical problem in monitoring for HIT after cardiac 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 after surgery. However, HIT is rare in the first 4 days after cardiac surgery, even in patients who have received heparin during the preoperative 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 identify 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 thrombocytotic levels following perioperative hemodilution. Accordingly, in patients who have undergone cardiac surgery, clinicians should consider a fall in the platelet count ≥ 50% that occurs between postoperative days 5 and 14 (inclusive) to represent potential HIT and should prompt laboratory investigations for HIT antibodies (day of cardiac surgery = day 0).[2,17,102,104]

Recommendation

1.2. For postoperative cardiac surgery patients, we recommend investigating for HIT antibodies if the platelet count falls by ≥ 50%, and/or a thrombotic event occurs, between postoperative days 5 and 14 (inclusive; day of cardiac surgery = day 0) [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[105]) and thus can be considered an acquired, hypercoagulability syndrome.[13] 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.[31] 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.

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 (DIC) 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 VKAs (see Section 2.2).[106–115] Finally, recognition of the role for *in vivo* thrombin generation in HIT provides a rationale for current therapies that emphasize reduction of thrombin generation,[11,105] either via direct inhibition of thrombin (*eg*, argatroban, lepirudin, bivalirudin) or by inhibiting factor Xa indirectly (*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, about 50 to 60 $\times 10^9$/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.[1,2,9,16] 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 about 5%.[12] These event-rates resemble those in other clinical situations in which antithrombotic management is generally considered mandatory (*eg*, after hip fracture).

Treatment Recommendations Depend on the Likelihood of HIT: Unlike other conditions (*eg*, 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. Furthermore, only about 30 to 60% of the patients with anti-PF4/polyanion antibodies by EIA also have detectable heparin-dependent platelet-activating antibodies (using a sensitive platelet activation assay); this suggests that a false diagnosis of HIT is possible in about one third to two thirds of patients who are antibody positive by EIA.[23,29,116,117] 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 on clinical grounds (pending laboratory confirmation), or has already been confirmed by (usually) strong positive test results for HIT antibodies in the appropriate clinical context of intermediate or high pretest probability.

In clinical settings in which HIT is considered unlikely, it may be appropriate to continue heparin or (in settings of antithrombotic prophylaxis) to give usual prophylactic doses of an alternative anticoagulant, *eg*, prophylactic-dose danaparoid (750 U bid or tid SC),[117–119] prophylactic-dose fondaparinux (2.5 mg od SC),[74] or prophylactic-dose recombinant hirudin (15 mg bid SC).[120] We suggest to continue heparin in patients with a low likelihood of HIT requiring therapeutic-dose anticoagulation because

the risk of bleeding complications is high when alternative anticoagulants are used in therapeutic doses (as the risk of major bleeding is probably higher than the risk of HIT-associated thrombosis). In contrast, the risk of major bleeding is low when an alternative anticoagulant is given in prophylactic doses. It might therefore be safer to switch to an alternative agent instead of maintaining heparin in this situation.

Scoring systems to help physicians estimate the pretest probability of HIT have been developed.[12,21,24] Prospective and retrospective evaluations of one scoring system, the "4 T's," indicates that low scores have very low likelihood ratios and thus make HIT very unlikely, whereas a high score confers moderate to high risk of HIT.[24,104,121]

2.1 Nonheparin Anticoagulants for Treating HIT (With or Without Thrombosis)

Table 3 lists five agents that clinicians can consider for treatment or prevention of HIT-associated thrombosis, and presents pharmacokinetic information, including site of organ clearance.[84,122–126] Of these, only three (argatroban, lepirudin, bivalirudin) are approved for treatment of HIT in the United States (although bivalirudin is approved only for patients with HIT, or at risk of HIT, undergoing PCI).[122–124] A fourth agent, danaparoid, is currently approved for thrombosis prophylaxis but neither approved for HIT nor currently available in the United States. Danaparoid is, however, approved (for HIT and/or non-HIT indications) and available for treatment and prevention of HIT-associated thrombosis in Canada, Europe, Australia, New Zealand, Japan, and Korea.[125]

A fifth agent, fondaparinux,[84,126] is a pentasaccharide that inactivates factor Xa in an antithrombin-dependent manner. As described above, it does not "cross-react" *in vitro* with HIT antibodies (*ie*, it does not react with PF4 in such a way as to cause sites for HIT antibody binding).[77,79–81] Therefore, theoretically it could be effective for treatment of HIT, although its reported use in this indication to date is limited to case reports and small case series, often without convincing serologic support for the diagnosis of HIT.[82–84] Furthermore, there is uncertainty whether the usual prophylactic or therapeutic doses of fondaparinux would be effective in a patient with severe HIT-associated hypercoagulability.[85,105] As both prophylactic- and therapeutic-dose protocols and approvals exist for fondaparinux in various non-HIT settings, fondaparinux (like danaparoid) may be appropriate in those patients encountered in clinical practice in whom the patient is judged to be at relatively low risk of having HIT, but in whom ongoing use of UFH or LMWH is not desired.

The evidence for the efficacy of nonheparin anticoagulants for HIT is not based on large randomized controlled trials (RCTs), due to the infrequent occurrence of serologically confirmed HIT and the clinical heterogeneity of affected patients. Indeed, only one RCT has evaluated HIT treatment: this open-label study compared danaparoid (plus warfarin) with dextran-70 (plus warfarin).[127] In addition, several retrospective cohort studies and case series have assessed danaparoid therapy.[128–136] In contrast, prospective cohort studies (with historical controls) have been performed for the two direct thrombin inhibitors (DTIs), lepirudin[137–142] and argatroban[143,144] (with several subsequent subanalyses also reported for argatroban[145–158]). Among these prospective cohort studies, the primary efficacy endpoint was a composite end point consisting of new thrombosis, limb amputation, and all-cause mortality. This end point may overestimate the occurrence of new apparent thrombosis or thrombosis growth, as deaths and limb amputations could be related to clinical factors already established when an alternative anticoagulant therapy is begun.[5] Indeed, more favorable hazard ratios for outcomes of argatroban treatment of HIT were reported when a "thrombotic end point" that emphasized new thrombotic events and their sequelae was evaluated in a recent argatroban substudy.[153] In addition, retrospective postmarketing studies of DTI therapy for HIT have been reported, both for lepirudin and for argatroban (discussed subsequently; see Sections *Lepirudin Dose and Monitoring Recommendations Deviating From the Package Insert Recommendations*, and *Argatroban Dose Recommendations*).

Antihirudin antibodies are commonly generated during treatment with lepirudin;[159–161] reports of anaphylaxis[162–165] in patients reexposed to lepirudin (as high as 1 in 625 in patients re-exposed to lepirudin)[160] led the European Agency for the Evaluation of Medicinal Products (EMEA) to recommend that nonhirudin anticoagulants be considered in patients who have previously been exposed to lepirudin (Public Statement of EMEA, October 2002).

Considerations in Choice and Dosing of Alternative Anticoagulation for HIT: The following factors should be taken into consideration when selecting the appropriate anticoagulant among the five main options (lepirudin, argatroban, bivalirudin, danaparoid, fondaparinux).

- Most experience with HIT treatment is with danaparoid (outside the United States), argatroban,

Table 3—*Non-Heparin Anticoagulants for Use in HIT (Section: 2.1)

Anticoagulant	Therapeutic Dosing	Elimination (t½)	Comments
DTIs			
Lepirudin (Refludan; Bayer HealthCare; West Haven, CT)[122]	± Bolus 0.2–0.4 mg/kg IV; maximum initial infusion rate, 0.10 mg/kg/h IV (target, 1.5–2.0 × patient's baseline or mean of laboratory normal range)*	Renal (80 min)	Approved and available in the United States, Canada, Europe, and Australia for treatment of thrombosis complicating HIT; t½ rises greatly in renal failure; lower target APTT range (1.5–2.0× baseline) has similar efficacy and less bleeding risk; high rate of anti-hirudin 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
Argatroban (Novastan in some jurisdictions; GlaxoSmithKline; Research Triangle Park, NC)[123]	Initial infusion rate, 2 μg/kg/min IV (no initial bolus); a reduced initial infusion rate (0.5–1.2 μg/kg/min) is appropriate in certain patient populations†	Hepatobiliary (40–50 min)	Approved in the United States, Canada, and several countries in Europe for both prevention and treatment of HIT-associated thrombosis; identical therapeutic-dose regimens are used for both indications; argatroban increases the INR, and thus a higher INR therapeutic range may be required during overlapping argatroban/warfarin therapy; also, argatroban is approved in the United States for anticoagulation for patients with or at risk of HIT undergoing PCI
Bivalirudin (Angiomax, The Medicines Company; Parsippany, NJ)[124]	Initial infusion rate, 0.15–0.20 mg/kg/h IV (target, 1.5–2.5 × patient's baseline or mean of laboratory normal range (no initial bolus)	Both enzymic (80%) and renal (20%) metabolism (25 min)	Approved in the United States, Canada, Europe, Australia, New Zealand, Israel, Argentina, Chile, Peru, and Venezuela for anticoagulation during percutaneous transluminal coronary angioplasty; also, in the United States, for PCI with provisional use of glycoprotein IIb/IIIa antagonist therapy, and for patients with, or at risk of HIT (or HIT with thrombosis syndrome) undergoing PCI; also approved in Canada for patients with, or at risk of HIT (or HIT with thrombosis syndrome) undergoing cardiac surgery; shorter t½ and minor renal excretion (20% component) suggests theoretical advantages over lepirudin, particularly for cardiac surgery
Factor Xa inhibitors			
Danaparoid (Orgaran; Organon USA, Schering-Plough Corporation; Roseland, NJ)[125]	Bolus: 2,250 U‡ IV; infusion, 400 U/h × 4 h, then 300 U/h × 4 h, then 200 U/h IV, subsequently adjusted by anti-Xa levels (target, 0.5–0.8 anti-Xa U/mL)	Renal (24 h, anti-Xa activity)	Withdrawn from US market in April 2002, but remains approved and/or available for treatment and/or prevention of HIT-thrombosis in several other jurisdictions, *eg*, Canada, Europe, Israel, Japan, Australia, and New Zealand; potential *in vivo* cross-reactivity (rare) is not predictable by *in vitro* testing; thus cross-reactivity testing not recommended prior to use
Fondaparinux (Arixtra; GlaxoSmithKline)[84,126]	Not established for HIT	Renal (17–20 h)	Approved in the United States, Canada, Europe, and Australia for DVT prophylaxis after orthopedic surgery, and after abdominal surgery, and for DVT/PE treatment; also approved in Japan for VTE prophylaxis after orthopedic surgery, and in Canada and Europe for treatment of acute coronary syndrome; theoretically, lack of *in vitro* cross-reactivity with HIT antibodies suggests it may be useful in HIT (minimal data)

*The initial IV bolus should be given only in case of life- or limb-threatening thrombosis; note that the recommended dosing differs from that of the package insert (note also that the target therapeutic APTT range per the package insert [1.5–2.5 times baseline] differs from the recommended target range [1.5–2.0 times baseline]); also, the dosing is even lower than that indicated for patients with serum creatinine > 90 μmol/L.
†Patients with heart failure, multiple organ system failure, severe anasarca, and during the early post-cardiac surgery period.
‡Adjust IV danaparoid bolus for body weight: < 60 kg, 1,500 U; 60–75 kg, 2,250 U; 75–90 kg, 3,000 U; > 90 kg, 3,750 U.

and hirudin (lepirudin); for these three drugs, American College of Chest Physicians dosing recommendations for management of HIT (Table 3) differ somewhat from manufacturer recommendations, with generally higher dosing recommended for danaparoid and lower dosing recommended for hirudin and argatroban. For bivalirudin (outside the setting of PCI) and fondaparinux, dosing, efficacy, and safety for the management of HIT are not established.

- For non-HIT situations, most experience is with fondaparinux (VTE prevention/treatment; acute coronary syndrome treatment) and bivalirudin (PCI).

- Due to the severe hypercoagulability of HIT, low-dose (prophylactic) regimens effective in non-HIT situations, such as DVT prophylaxis with danaparoid or fondaparinux, may not be similarly effective in acute HIT.
- In the absence of renal or hepatic dysfunction, the relative elimination half-lives are: bivalirudin < argatroban < lepirudin ≪ fondaparinux < danaparoid. However, the advantages of a short half-life (*eg*, in a patient with bleeding or who requires an invasive procedure) must be balanced against the greater risk of rebound hypercoagulability and thrombosis in acute HIT.
- In non-HIT patients, lepirudin increases risk of bleeding over heparin when used in therapeutic doses, whereas danaparoid, fondaparinux, and bivalirudin do not increase risk of bleeding compared with heparin (argatroban has undergone minimal evaluation in non-HIT settings).
- In renal failure, argatroban is safer than hirudin; danaparoid and bivalirudin can be used with moderate dose reductions and increased anticoagulant monitoring; fondaparinux is not recommended in this situation.
- In hepatic insufficiency/failure, the half-life of argatroban is prolonged; although the half-lives of hirudin, danaparoid, fondaparinux, and bivalirudin are not significantly prolonged in these patients, they too may need dose reduction and increased anticoagulant monitoring.
- Factors increasing the activated partial thromboplastin time (APTT)—*eg*, decompensated DIC, hepatic dysfunction, antiphospholipid syndrome, VKA therapy—can lead to underdosing or inappropriate discontinuation of APTT-monitored therapy (*eg*, DTIs); in contrast, danaparoid and fondaparinux dosing is not influenced by the APTT.
- The DTIs raise the INR (and can interfere with other functional clotting assays) as follows: argatroban > bivalirudin > hirudin, whereas danaparoid and fondaparinux have no effect; accordingly, overlapping VKA therapy is safest with danaparoid and fondaparinux. Especially with argatroban, VKA therapy should be postponed pending substantial resolution of thrombocytopenia.
- In thrombocytopenic patients judged to be at low risk of HIT, and in whom no definite indication for therapeutic-dose anticoagulation exists, the safest approach likely is low-dose danaparoid or fondaparinux (pending results of HIT antibody testing).

Treatment of HIT-Associated Thrombosis

DTIs in HIT With Thrombosis: Lepirudin, Argatroban, Bivalirudin: Table 4a summarizes the results of the efficacy and major bleeding endpoints for the lepirudin[137–141] and argatroban[143,144] prospective cohort studies of patients with HIT complicated by thrombosis, including their respective historical control data (in addition, Table 4b summarizes the results for lepirudin and argatroban for treatment of "isolated HIT," which are discussed in a later section). For both agents, pooled data from their respective prospective cohort studies (lepirudin: HAT-1, -2, and -3 trials; argatroban: Arg-911 and -915/915X trials) are also shown, including the efficacy results (composite end point [new thrombosis, limb amputation, all-cause mortality; maximum, one event per patient], and the individual end points of new thrombosis and limb amputation), taken from start of treatment to day 35 (lepirudin) or day 37 (argatroban). Major bleeding rates for both agents are also shown.

Risk ratios (pooled data compared with historical controls) for the composite end point were 0.48 (lepirudin) and 0.75 (argatroban), and for new thrombosis the RRs were 0.28 (lepirudin) and 0.45 (argatroban). The corresponding absolute event rates (categorical analysis) were 19.2% (lepirudin) and 42.3% (argatroban) for the composite end point, and 7.0% (lepirudin) and 15.5% (argatroban) for new thrombosis. A large (n = 496) postmarketing study of lepirudin showed an even lower absolute frequency 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 (by HIPA test), 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-915/915X studies are not reported). Moreover, patients received lepirudin for a mean of 15.8 days, but argatroban only for 6.6 days. 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 in the studies were relatively long (35 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 (12/214 [5.6%] vs 51/373 [13.7%]; p = 0.0022 by Fisher exact test, two-tailed). Further, the RR values for limb amputation were 0.70 for lepirudin (compared with historical controls), but were 1.26 for argatroban, *ie*, the limb amputation

Table 4a—*Section 1: Cohort Studies of Argatroban and Lepirudin for the Treatment of Thrombosis Complicating HIT: Clinical Description and Results (Section: 2.1)

Author/yr	Intervention/Dosing (Mean DTI Duration)	Patients Analyzed, No./Total	Duration of Follow-up, d	New Thrombosis, No./Total (95% CI)	Limb Amputation, No./Total (95% CI)	Composite End Point†, No./Total (95% CI)	Major Bleeds, No./Total (95% CI)	Percentage of Major Bleeds/Treatments per d	Comment
Lepirudin									
Cohort studies with historic controls									
Lubenow et al[140]/2005	Lep: bolus 0.4 mg/kg; 0.15 mg/kg‡ (16.4 d) Con: varied (see below)	Lep: 98/98; Con: 75/75	35	Lep: 5/98 (5.1%) Con: 19/75 (25.3%) RR: 0.20 (0.08, 0.51)	Lep: 6/98 (6.1%) Con: 6/75 (8.0%) RR: 0.77 (0.26, 2.28)	Lep: 18/98 (18.4%) Con: 30/75 (40.0%) RR: 0.46 (0.28, 0.76)	Lep: 20/98 (20.4%) Con: 5/75 (6.7%) RR: 3.06 (1.20, 7.78)	Lep: 1.24%	HAT-3 study results; all patients tested positive for HIT antibodies; analysis from start of treatment
	Lep: bolus 0.4 mg/kg; 0.15 mg/kg‡ (16.7 d) Con: varied (see below)	Lep: 65/65; Con: 75/75	35	Lep: 7/65 (10.8%) Con: 19/75 (25.3%) RR: 0.43 (0.19, 0.95)	Lep: 4/65 (6.2%) Con: 6/75 (8.0%) RR: 0.77 (0.23, 2.61)	Lep: 16/65 (24.6%) Con: 30/75 (40.0%) RR: 0.62 (0.37, 1.02)	Lep: 6/65 (9.2%) Con: 5/75 (6.7%) RR: 1.38 (0.44, 4.33)	Lep: 0.55%	HAT-2 study results; all patients tested positive for HIT antibodies; analysis from start of treatment
	Lep: bolus 0.4 mg/kg; 0.15 mg/kg‡ (13.6 d) Con: varied (danaparoid, n = 24; phenprocoumon, n = 21; other, n = 30)	Lep: 51/51; Con: 75/75	35	Lep: 3/51 (5.9%) Con: 19/75 (25.3%) RR: 0.23 (0.07, 0.74)	Lep: 2/51 (3.9%) Con: 6/75 (8.0%) RR: 0.49 (0.10, 2.33)	Lep: 7/51 (13.7%) Con: 30/75 (40.0%) RR: 0.34 (0.16, 0.72)	Lep: 7/51 (13.7%) Con: 5/75 (6.7%) RR: 2.06 (0.69, 6.13)	Lep: 1.01%	HAT-1 study results; all patients tested positive for HIT antibodies; analysis from start of treatment
	Pooled data: above three studies (15.8 d)	Lep: 214/214; Con: 75/75	35	Lep: 15/214 (7.0%) Con: 19/75 (25.3%) $p < 0.001$ RR: 0.28 (0.15, 0.52)	Lep: 12/214 (5.6%) Con: 6/75 (8.0%) $p = 0.58$ RR: 0.70 (0.27, 1.80)	Lep: 41/214 (19.2%) Con: 30/75 (40.0%) $p < 0.001$ RR: 0.48 (0.32, 0.71)	Lep: 33/214 (15.4%) Con: 5/75 (6.7%) $p = 0.072$ RR: 2.31 (0.94, 5.71)	Lep: 0.97%	Pooled analysis of HAT-1, -2, and -3 studies; all patients tested positive for HIT antibodies; analysis from start of treatment
Case series									
Lubenow et al[141]/2002	Lep: bolus 0.4 mg/kg; 0.15 mg/kg‡ (12.1 d); mean infusion rate = 0.12 mg/kg/h (no bolus, n = 141)	Lep: 496	To end of treatment (mean, 12.1 days)	Lep: 26/496 (5.2%)	Lep: 29/496 (5.8%)	Not reported	Lep: 27/496 (5.4%)	Lep: 0.45%	77% of patients tested positive for HIT antibodies; thrombotic death rate = 1.8%; postmarketing study (lepirudin dose reductions began to be applied)

Table 4a—*Continued*

Author/yr	Intervention/Dosing (Mean DTI Duration)	Patients Analyzed, No./Total	Duration of Follow-up, d	New Thrombosis, No./Total (95% CI)	Limb Amputation, No./Total (95% CI)	Composite End Point†, No./Total (95% CI)	Major Bleeds, No./Total (95% CI)	Percentage of Major Bleeds/Treatments per d	Comment
Argatroban									
Cohort studies with historic controls									
Lewis et al[144]/ 2003	Arg: 2 μg/kg/min§ (no bolus) [7.1 d] Con: varied (typically heparin discontinuation and oral anticoagulation)	Arg: 229/229; Con: 46/46	37	Arg: 30/229 (13.1%) Con: 16/46 (34.8%) RR: 0.38 (0.22, 0.63)	Arg: 34/229 (14.8%) Con: 5/46 (10.9%) RR: 1.37 (0.56, 3.31)	Arg: 95/229 (41.5%) Con: 26/46 (56.5%) RR: 0.73 (0.55, 0.99)	Arg: 14/229 (6.1%) Con: 1/46 (2.2%) RR: 2.81 (0.38, 20.86)	Arg: 0.85%	Argatroban-915 study; positive testing for HIT antibodies not required (No. testing positive not reported)
Lewis et al[143]/ 2001	Arg: 2 μg/kg/min§ (no bolus) [5.9 d] Con: various (typically heparin discontinuation and oral anticoagulation)	Arg: 144/144; Con: 46/46	37	Arg: 28/144 (19.4%) Con: 16/46 (34.8%) RR: 0.56 (0.33, 0.94)	Arg‖: 17/144 (11.8%) Con‖: 5/46 (10.9%) RR: 1.09 (0.42, 2.78)	Arg: 63/144 (43.8%) Con: 26/46 (56.5%) RR: 0.77 (0.57, 1.06)	Arg: 16/144 (11.1%) Con: 1/46 (2.2%) RR: 5.11 (0.7, 37.50)	Arg: 1.88%	Argatroban-911 study; positive testing for HIT antibodies not required (65% of patients shown to have HIT antibodies (remainder negative or not tested)
	Pooled studies (6.6 d)	Arg: 373/373; Con: 46/46	37	Arg: 58/373 (15.5%) Con: 16/46 (34.8%) p = 0.0032 RR: 0.45 (0.28, 0.71)	Arg: 51/373 (13.7%) Con: 5/46 (10.9%) p = 0.81 RR: 1.26 (0.53, 2.99)	Arg: 158/373 (42.3%) Con: 26/46 (56.5%) p = 0.083 RR: 0.75 (0.57, 0.99)	Arg: 30/373 (8.0%) Con: 1/46 (2.2%) p = 0.23 RR: 3.70 (0.52, 26.50)	Arg: 1.25%	

*Lep = lepirudin; Con = control; Arg = argatroban; HAT = heparin-associated thrombocytopenia; end points shown represent categorical analyses; p values indicate Fisher exact test (two-tailed). The methodologic quality description portion of this table can be found in the online version of this article as a data supplement.
†Composite end point: all-cause mortality, all-cause limb amputation, and/or new thrombosis (each patient counted only once).
‡APTT adjusted to 1.5–2.5 times baseline APTT (or the mean laboratory normal range if the baseline APTT is unavailable).
§APTT adjusted to 1.5–3.0 times baseline APTT.
‖Data reported differ from primary publication (here, ranking by severity of specific end point is not used).

Table 4b—*Section 1: Cohort Studies of Lepirudin and Argatroban for the Treatment of Isolated HIT; Clinical Description and Results (Section: 2.1)

Author/yr	Intervention /Dosing (Mean DTI Duration)	Patients Analyzed, No./Total	Duration of Follow-up, d	New Thrombosis, No./ Total (95% CI)	Limb Amputation, No./ Total (95% CI)	Composite End Point§ No./Total (95% CI)	Major Bleeds, No./ Total (95% CI)	Percentage of Major Bleeds/Treatment per d	Comment
Lepirudin									
Lubenow et al[142]/ 2004	Lep: 0.10 mg/kg† [no bolus] (13.9 d) Con: varied [nil, n = 31; phenprocoumon, n = 11; aspirin, n = 5]	Lep: 91/91 Con: 47/47	Lep: 24 (median) Con: 15 (median)	Lep: 4/91 (4.4%) Con: 7/47 (14.9%) p = 0.045 RR: 0.30 (0.09, 0.96)	Lep: 3/91 (3.3%) Con: 0/47 (0%) p = 0.55 RR: 3.65 (0.19, 69.27)	Lep: 18/91(19.8%) Con: 14/47 (29.8%)† p = 0.22 RR: 0.66 (0.36, 1.21)	Lep: 13/91 (14.3%) Con: 4/47 (8.5%) p = 0.42 RR: 1.68 (0.58, 4.86)	Lep: 1.03%	Pooled data from subgroup of patients with isolated HIT from the three HAT studies; all patients tested positive for HIT antibodies
Argatroban									
Arg-915 and -915X studies: Lewis et al[144]/2003	Arg: 2 μg/kg/ min‡ (no bolus) [5.1 d] Con: various (typically heparin discontinuation and oral anticoagulation)	Arg: 189/189 Con: 139/139	37	Arg: 11/189 (5.8%) Con: 32/139 (23.0%) RR: 0.25 (0.13, 0.48)	Arg: 8/189 (4.2%) Con: 4/139 (2.9%) RR: 1.47 (0.45, 4.79)	Arg: 53/189 (28.0%) Con: 54/139 (38.8%) RR: 0.72 (0.53, 0.98)	Arg: 10/189 (5.3%) Con: 12/139 (8.6%) RR: 0.61 (0.27, 1.38)	Arg: 1.04%	Arg-915 and -915X studies; positive testing for HIT antibodies not required (number testing positive not reported)
Arg-911 study: Lewis et al[143]/ 2001	Arg: 2 μg/kg/ min‡ (no bolus) [5.3 d] Con: various (typically heparin discontinuation and oral anticoagulation)	Arg: 160/160 Con: 147/147	37	Arg: 13/160 (8.1%) Con: 33/147 (22.4%) RR: 0.36 (0.2, 0.66)	Arg: 3/160 (1.9%) Con: 4/147 (2.7%)‖ RR: 0.69 (0.16, 3.03)	Arg: 41/160 (25.6%) Con: 57/147 (38.8%) RR: 0.66 (0.47, 0.92)	Arg: 5/160 (3.1%) Con: 12/147 (8.2%) RR: 0.38 (0.14, 1.06)	Arg: 0.59%	Arg-911 study (31/160 [19.4%] of argatroban patients had a history of HIT rather than acute HIT); positive testing for HIT antibodies not required (81% of controls but only 50% of cases shown to have HIT antibodies [remainder negative or not tested])
	Pooled studies	Arg: 349/349 Con: 147/147	37	Arg: 24/349 (6.9%) Con: 33/147 (22.4%) p < 0.001 RR: 0.31 (0.19, 0.50)	Arg: 11/349 (3.2%)‡ Con: 4/147 (2.7%) p = 1.00 RR: 1.16 (0.37, 3.58)	Arg: 94/349 (26.9%) Con: 57/147 (38.8%) p = 0.010 RR: 0.69 (0.53, 0.91)	Arg: 15/349 (4.3%) Con: 12/147 (8.2%) p = 0.088 RR: 0.53 (0.25, 1.10)	Arg: 0.84%	8.9% of cases and 5.4% of controls were treated for history of HIT, rather than for acute HIT

*See Table 4a for expansion of abbreviations. End-points shown represent categorical analyses; p values indicate Fisher exact test (two-tailed). The methodologic quality description portion of this table can be found in the online version of this article as a data supplement.

†APTT adjusted to 1.5–2.5 times baseline APTT (or the mean laboratory normal range if the baseline APTT is unavailable).

‡APTT adjusted to 1.5–3.0 times baseline APTT.

§Composite end point: all-cause mortality, all-cause limb amputation, and/or new thrombosis (each patient counted only once).

‖Data reported differ from primary publication (here, ranking by severity of specific end point is not used).

rates tended to be greater than the corresponding historical controls for the latter agent.

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, combined with the greater potential of argatroban and VKA to prolong the 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. Indeed, a *post hoc* analysis in the prospective argatroban treatment studies showed that thrombotic events and/or limb amputation exceeded bleeding complications (10 events vs 1 event) among the 111 patients whose INR exceeded 4.0 during overlapping argatroban/warfarin therapy.[148] Our recommendations for managing DTI-VKA overlap are discussed later in section 2.2.

Trends to greater bleeding among patients receiving lepirudin or argatroban (compared with historical controls) were observed. The apparent higher absolute rate of bleeding with lepirudin (15.4%) compared with argatroban (8.0%) should be considered in the context of greater duration of lepirudin therapy: when the respective major bleeding rates are expressed on a per treatment day basis, the major bleeding rates for both DTIs are similar (lepirudin, 0.97%; argatroban, 1.25%).

Although bivalirudin appears to be promising as a treatment for HIT-associated thrombosis, based on case series,[166–169] 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, lead to weaker evidence in support of its use. Compared with lepirudin and argatroban, however, bivalirudin offers some significant pharmacologic advantages (short half-life, enzymic metabolism, low immunogenicity, minimal effect on INR prolongation). However, as discussed later in this chapter, bivalirudin has an important role for the management of PCI or in cardiac surgery in patients in whom heparin is contraindicated because of acute HIT. Further, its use during acute HIT in patients with acute coronary syndrome may be preferred by cardiologists who have experience with the use of this particular DTI in the cardiology patient population.

Lepirudin Dose and Monitoring Recommendations Deviating From the Package Insert Recommendations: Further analyses of prospective and retrospective studies with lepirudin, and increasing clinical experience, provide evidence that the lepirudin dosages used in the approval studies were too high. We therefore recommend not using the dosages provided by the manufacturer.

Fatal bleeding occurred in 5 of 403 (1.2%) patients in the prospective lepirudin studies (HAT-1, 2, 3),[140] and 7 of 181 (3.9%) patients in a retrospective observational study performed in France.[170] In the HAT-1, 2, 3 studies, among patients with thrombosis complicating HIT (with protocolized initial infusion rates starting at 0.15 mg/kg/h in patients with serum creatinine < 140 μmol/L), the mean lepirudin infusion rate actually given was only 0.11 mg/kg/h. Among the patients without thrombosis, in whom the protocol initial infusion rate was 0.10 mg/kg/h, the steady-state infusion rate actually given was 0.06 mg/kg/h. In the French observational study (with about half the patients having thrombosis at study entry), the mean infusion rate employed was also 0.06 mg/kg/h, with a progressive reduction in mean dose (from 0.09 to 0.06 to 0.04 mg/kg/h) observed during three successive years examined (1997, 2001, 2004, respectively). Thus, actual dosing administered is at least one-third to two-thirds lower than that recommended for initial dosing. A median infusion rate of 0.04 mg/kg/h was found in another small study[171] of nine patients treated with the recommended lepirudin dosing, in which overdosing developed in eight of nine patients, as shown by supratherapeutic APTT levels and measurement of drug levels using the ecarin clotting time.

Furthermore, analyses within each study provided evidence for greater bleeding effects without superior efficacy among patients with higher dosing or drug accumulation.[139,140,170] A serum creatinine > 90 μmol/L (about 1.0 mg/dL) was associated with greater risk of bleeding in one study.[140] Further, Tardy et al[170] observed significantly higher bleeding rates among patients treated with higher doses (> 0.07 mg/kg/h) of lepirudin, without any reduction in frequency of thrombotic outcomes.

For these reasons, we recommend that in most situations, the highest starting lepirudin infusion rate should be 0.10 mg/kg/h (patients with creatinine < 90 μmol/L), with lower infusion rates for patients with higher serum creatinine levels (creatinine, 90 to 140 μmol/L, starting infusion rate = 0.05 mg/kg/h; creatinine, 140 to 400 μmol/L, starting infusion rate, 0.01 mg/kg/h; creatinine > 400 μmol/L, 0.005 mg/kg/h). Furthermore, we recommend that the initial iv bolus be either omitted, or in case of perceived life- or limb-threatening thrombosis, be given at a reduced dose (0.2 mg/kg). Further, we recommend that APTT monitoring be performed at 4-h intervals until it is apparent that steady state within the normal range (1.5 to 2.0-times patient baseline [or mean laboratory] APTT) is achieved.

Argatroban Dose Recommendations: For prophylaxis or treatment of thrombosis in HIT, the initial dose of argatroban (as recommended by the manufacturer) is 2 μg/kg/min, except for patients with at least moderate hepatic impairment (*eg*, defined as a Child-Pugh score > 6, or more commonly as a total serum bilirubin > 1.5 mg/dL), where the initial dose is reduced to 0.5 μg/kg/min.[123,152] However, there is evidence that a reduced initial dose may also be prudent for patients with heart failure, multiple organ system failure, severe anasarca, or after cardiac surgery, *ie*, conditions associated with hepatic congestion/dysfunction, and thus potentially associated with decreased argatroban clearance.[152,172–177] Indeed, in recent reports of argatroban-treated patients (used in a variety of indications and clinical settings) in single centers,[169,178–181] or in a multicenter registry,[182,183] mean (or median) doses of 0.5–1.2 μg/kg/min achieved target APTTs. However, these studies did not assess argatroban drug levels, and so there is some uncertainty as to how often these lower doses—but therapeutic APTT levels—indicate appropriate drug levels. No initial dosage adjustment is required in patients with renal impairment, however, in the absence of the conditions listed above.

Danaparoid: Tables 5a and 5b (each presented in two sections) show studies that have evaluated danaparoid as treatment of HIT complicated by thrombosis.[127,128,130] Danaparoid was studied in a randomized open-label study which compared danaparoid (plus warfarin) against dextran-70 (plus warfarin).[127] Patients received danaparoid without prior testing for *in vitro* cross-reactivity against HIT antibodies. This study, despite its small size (41 patients), showed a lower composite end point among danaparoid vs dextran-treated controls (25.0% vs 58.8%; p = 0.050), and a trend to reduced new thrombosis (12.5% vs 41.2%; p = 0.063). No patient developed major bleeding.

Additional corroborating evidence for danaparoid's efficacy 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 diagnosed as having HIT in the same laboratory during the identical time period.[128] Thus, unlike the prospective cohort studies of lepirudin and argatroban that utilized historical controls, this evaluation included contemporaneous controls. The study suggested that danaparoid (when given in *therapeutic* doses) and lepirudin have similar efficacy for treatment of HIT-associated thrombosis (9.4% new thrombosis rate with danaparoid, 7.9% new thrombosis rate with lepirudin), with similar risks of major bleeding (3.8% vs 6.1%; p = 0.72). However, when

Table 5a—*Section 1: Randomized Trials of Danaparoid for the Treatment of Thrombosis Complicating HIT; Clinical Outcomes and Results (Section: 2.1)**

Study/yr	Intervention/ Dosing	Patients Analyzed, No./Total	Duration of Follow-up, d	New Thrombosis, No./Total (95% CI)	Limb Amputation, No./ Total (95% CI)	Composite End Point, No./Total (95% CI)	Major Bleeds No./Total (95% CI)	Comments
Chong et al[127]/2001	Dan: danaparoid bolus 2,400 U, then 200 U/h for 5 d (mean, 6.4 d given)† Dex: dextran 70 1,000 mL infusion day 1, then 500 mL for 4 d (mean, 4.8 d given)	Dan: 24/25 (96%)‡ Dex: 17/17 (100%)	Until hospital discharge or death (median 14)	Dan: 3/24 (12.5%) Dex: 7/17 (41.2%), p = 0.063 RR: 0.30 (0.09, 1.01)	Dan: 1/24 (4.2%) Dex: 3/17 (17.6%) p = 0.29 RR: 0.24 (0.03, 2.08)	Dan: 6/24 (25.0%) Dex: 10/17 (58.8%) p = 0.050 RR: 0.43 (0.19, 0.94)	Dan: 0/24 Dex: 0/17 p = N/A	Open-label trial (stratified for thrombosis severity); all patients received warfarin (10 mg on days 1 and 2, 5 mg on d 3; then as per INR); 34/37 (91.9%) patients tested positive for HIT-antibodies (4 patients untested); patients entered without prior in vitro cross-reactivity testing; fatal thrombosis (Dan, 1/24 [4.2%] vs Dex 4/17 [23.5%]; RR = 0.177 [0.02, 1.45]; p = 0.14)

*Dan = danaparoid; Dex = dextran. The methodologic quality description portion of this table can be found in the online version of this article as a data supplement.
†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 days.
‡One patient with a negative test for HIT antibodies was later considered not to have had HIT, and is not included in the analysis shown here.

Table 5b—*Section 1: Cohort Studies of Danaparoid for the Treatment of Thrombosis Complicating HIT; Clinical Outcomes and Results (Section 2.1)

Study/yr	Intervention/Dosing (Mean Duration)	Patients Analyzed, No./Total	Duration of Follow-up, d	New Thrombosis, No./Total (95% CI)	Limb Amputation, No./Total (95% CI)	Composite End Point, No./Total (95% CI)	Major Bleeds, No./Total (95% CI)	Percentage of Major Bleeds/Treatment per d	Comment
Cohort studies with historic controls									
Lubenow et al[130]/2006	Dan: Varied (inclusion criterion, minimum, 3,000 anti-factor Xa U danaparoid given in first 24 h)† (mean duration of danaparoid treatment, 12.74 d‡) Con: varied§	Dan: 62/62 Con: 56/56	35	Dan: 11/62 (17.7%) Con: 24/56 (42.9%) p = 0.0044 RR: 0.41 (0.22, 0.77)	Dan: 3/62 (4.8%) Con: 4/56 (7.1%) p = 0.71 RR: 0.68 (0.16, 2.90)	Dan: 15/62 (24.2%) Con: 28/56 (50.0%) p = 0.0043 RR: 0.48 (0.29, 0.81)	Dan: 8/62 (12.9%) Con: 19/56 (33.9%) p = 0.0084 RR: 0.38 (0.18, 0.80)	Dan: 1.01%	All patients tested positive for HIT antibodies; analysis from start of treatment; significantly more (ancrod-treated) controls than danaparoid-treated patients received coumarin while their platelet counts were still $< 100 \times 10^9$/L (25/31 [80.7%] vs 11/53 [20.8%]; $p < 0.001$)
Cohort studies with contemporaneous controls									
Farner et al[128]/2001	Dan (prophylactic-dose): 750 U bid or tid SC Con: prophylactic-dose lepirudin (patients entered into prospective cohort studies): 0.10 mg/kg/h (aPTT-adjusted)	Dan: 43/43 Con: 58/58	Discharge or day 42, whichever came first (Dan, mean = 29.2; Lep, mean = 27.6)	Dan: 8/43 (18.6%) Con: 5/58 (8.6%) p = 0.22 RR: 2.16 (0.76, 6.14)	Dan: 1/43 (2.3%) Con: 4/58 (6.9%) p = 0.39 RR: 0.34 (0.04, 2.91)	Dan: 13/43 (30.2%) Con: 12/58 (20.7%) p = 0.35 RR: 1.46 (0.74, 2.88)	Dan: 0/43 (0.0%) Con: 10/58 (17.2%) p = 0.0045 RR: 0.06 (0.0, 1.06)	Not reported	18/43 (41.9%) of Dan and 19/58 (32.8%) of Lep-treated patients had thrombosis at study entry; frequency of new thrombosis was similar whether danaparoid-treated patients had thrombosis at study entry or not (4/18 = 22.2% and 4/25 = 16.0%, respectively; p = 0.70)
Farner et al[128]/2001	Dan (therapeutic-dose): 2,500 U bolus, then 400 U/h for 4 h, then 300 U/h for 4 h, then 200 U/h Con: therapeutic-dose lepirudin (patients entered into prospective cohort studies): 0.4 mg/kg IV bolus, then 0.15 mg/kg/h (aPTT-adjusted)	Dan: 53/53 Con: 114/114	Discharge or day 42, whichever came first (Dan, mean = 30.0; Lep, mean 26.6)	Dan: 5/53 (9.4%) Con: 9/114 (7.9%) p = 0.77 RR: 1.20 (0.42, 3.39)	Dan: 4/53 (7.5%) Con: 7/114 (6.1%) p = 0.74 RR: 1.23 (0.38, 4.02)	Dan: 10/53 (18.9%) Con: 21/114 (18.4%) p = 1.00 RR: 1.02 (0.52, 2.02)	Dan: 2/53 (3.8%) Con: 7/114 (6.1%) p = 0.72 RR: 0.62 (0.13, 2.86)	Not reported	47/53 (88.7%) of Dan and 105/114 (92.1%) of Lep-treated patients had thrombosis at study entry; frequency of new thrombosis was low whether danaparoid-treated patients had thrombosis at study entry or not (5/47 = 10.6% and 0/6 = 0%, respectively; p = 1.00).

*See Tables 4a and 4b for expansion of abbreviations; all p values shown are Fisher exact test (two-tailed). The methodologic quality description portion of this table can be found in the online version of this article as a data supplement.

†Twenty-eight of 62 patients (45.2%) received "standard" danaparoid dosing (initial weight-adjusted IV bolus; then 400 U/h for 4 h, 300 U/h for 4 h, then 150–200 U/h IV with rate adjustments guided by anti-factor Xa levels); 13/62 patients (21.0%) received initial danaparoid bolus followed by maintenance IV infusion; 10/62 patients (16.1%) received standard IV danaparoid dosing with no initial bolus; 5/62 patients (8.1%) received IV maintenance infusion only; 5/62 patients (8.1%) received SC only; and 1/62 patients (1.6%) received other dosing.

‡Data obtained from investigators.

§Thirty-eight of 56 patients (67.9%) received ancrod (31 also received warfarin); 18/56 patients (32.1%) were treated by coumarin alone (warfarin, n = 11; phenprocoumon, n = 7).

given in prophylactic doses, the efficacy of danaparoid appeared somewhat less than that of lepirudin (18.6% vs 8.6%; p = 0.22), although significantly less major bleeding was observed with danaparoid (0% vs 17.2%; p = 0.0045). A retrospective comparison of therapeutic-dose danaparoid compared with ancrod and/or coumarin (warfarin, phenprocoumon) found significantly greater efficacy with danaparoid (composite end point; new thrombosis end point) together with a significantly lower risk of major bleeding with danaparoid.[130]

Certain of the pharmacokinetic features of danaparoid, such as its long half-life, lack of effect on the INR, and 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,[125] and has been used in at least 59 pregnant patients,[136] and is the anticoagulant of choice for managing a pregnant patient with HIT.

Danaparoid Dose Recommendations: Retrospective reports[128,133,184,185] indicate that when using danaparoid for the treatment of acute HIT (with or without thrombosis), low doses (*eg*, 750 U bid or tid, or 1,250 U bid SC) are often associated with new or recurrent thrombosis. Two other retrospective reports[186,187] did not observe increased rates of thrombosis with low-dose danaparoid was used; however, one of these studies involved ICUs (ICU) patients (in whom non-HIT disorders could have explained the thrombocytopenia) and in the other study the majority of patients did not have serologic findings consistent with the diagnosis of HIT. Since studies that have shown superior (vs dextran-70[127] or ancrod[130]) or similar (vs lepirudin[128]) outcomes with danaparoid therapy utilized therapeutic-dose regimens, we recommend therapeutic-dose administration of danaparoid administered (at least initially) by the IV route in most situations when HIT is strongly suspected or confirmed. Therapeutic dosing for danaparoid is described in Table 3.

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 absent/weak (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 od 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 give 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 uncertainty regarding appropriate dosing, precludes us from making any recommendations. The occurrence of several thrombotic events in a patient who developed HIT while already receiving prophylactic-dose fondaparinux suggests that therapeutic-dose fondaparinux is likely to be required to inhibit severe HIT-associated hypercoagulability.[85]

A potential strategy involving fondaparinux could be useful for avoiding problems during the "transition" from DTI to warfarin therapy in patients with HIT-associated thrombosis, using the following two-step approach. First, once the platelet count has recovered during initial DTI therapy, the DTI can be replaced by fondaparinux in therapeutic doses. Second, VKA therapy (*eg*, warfarin) is then begun during this phase of fondaparinux (rather than DTI) therapy, with the fondaparinux being stopped when the INR is in the therapeutic range, and after a minimum 5-day fondaparinux-VKA overlap period. This approach avoids using fondaparinux during the acute phase of HIT (in which its efficacy and safety are not currently established), and avoids DTI-warfarin overlap (with its potential for warfarin-associated thrombotic complications—see Section 2.2.1, Management of DTI-VKA Overlap). However, there are no systematic studies using this approach. Danaparoid can also be used in place of fondaparinux to avoid DTI-VKA overlap.

Treatment of Isolated HIT

Definition and Natural History: 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."[6] Previously, it was believed that simple discontinuation of heparin might avoid subsequent thrombosis in these patients. However, several observational studies suggest that there is a substantial risk for symptomatic thrombosis among patients with isolated HIT.[1,9,10,128,139,143,144,188–190] (Table 6). The three largest retrospective studies[9,10,143] 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%. In a large prospective cohort (n = 113),[139] 10.4% developed 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.[189]

A large retrospective study by Wallis et al[10] 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%; $p = 0.24$).[10] 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 developed 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%); $p = 0.12$.

Anticoagulation in Isolated HIT: The optimal management strategy for isolated HIT remains uncertain. A retrospective study[128] found that low-dose (prophylactic-dose) danaparoid was associated with a high failure rate when given for isolated HIT (composite end point, 53% at 42-day follow-up 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[189] is uncertain. Second, the recommended lepirudin regimen in these patients was associated with low risk of new thrombosis (4.4% and 2.1%, respectively) in two large studies (meta-analysis of 3 prospective studies of 91 patients [Tables 5a, 5b] and a postmarketing observational study of 612 patients[141]), with the composite end point being observed in 18 of 91 (19.8%) patients in the prospective studies.[142] Although this lepirudin dosing regimen omits the initial lepirudin bolus, and begins with a 33% lower initial infusion rate compared with the therapeutic regimen (0.10 instead of 0.15 mg/kg/h), it includes dose adjustments according to the APTT and thus effectively achieves "therapeutic" dosing within 24 h. Third, the two 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 endpoint 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%; $p = 0.04$).[143,144] Major bleeding in these studies of DTIs for isolated HIT ranged from 5.9–14.4%[141,142] to 3.1–5.3%[143,144] of patients receiving lepirudin and argatroban, respectively. Expressed on a per treatment day basis, the major bleeding rate was 1.03% for lepirudin and 0.84% for argatroban. 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),[107] 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) and evidence of impaired hemostasis on physical examination. In patients with strongly suspected isolated HIT, or when the diagnosis is supported by serological 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[189] suggests that routine ultrasonography is appropriate in these patients, since if silent venous thrombosis is identified, it could influence the duration of anticoagulant therapy and need for overlapping VKA therapy.

The study by Farner et al[128] 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 receiving 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 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 confi-

dence 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.

Vena caval filters are sometimes used to manage patients judged to be at high risk for life-threatening PE. However, their use can be complicated by massive vena cava thrombosis, including the renal veins, and severe venous limb ischemia (including progression to venous limb gangrene), especially if pharmacological anticoagulation is not given.[191,192] In our opinion, these devices are risky in the setting of acute HIT, and we do not recommend their use.

Recommendation

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 (danaparoid [Grade 1B]**, lepirudin** [Grade 1C]**, argatroban** [Grade 1C]**, fondaparinux** [Grade 2C]**, bivalirudin** [Grade 2C]**) over the further use of UFH or LMWH therapy or initiation/continuation of a VKA** (Grade 1B)**.**

Dose and Administration

2.1.2. For patients receiving lepirudin, the initial lepirudin infusion rate should be no higher than 0.10 mg/kg/h (patients with creatinine < 90 μmol/L), with lower infusion rates for patients with higher serum creatinine levels (creatinine, 90 to 140 μmol/L: starting infusion rate, 0.05 mg/kg/h; creatinine, 140 to 400 μmol/L: starting infusion rate, 0.01 mg/kg/h; creatinine > 400 μmol/L: starting infusion rate, 0.005 mg/kg/h) [Grade 1C]**. Furthermore, we recommend that the initial IV bolus either be omitted or, in case of perceived life- or limb-threatening thrombosis, be given at a reduced dose (0.2 mg/kg)** [Grade 1C]**. Further, we recommend that APTT monitoring be performed at 4-h intervals until it is apparent that steady state within the therapeutic range (1.5 to 2.0-times patient baseline [or mean laboratory] APTT) is achieved** (Grade 1C)**.**

This dosage regimen—in contrast to the regimen in the lepirudin package insert—is designed to reduce the risk of major bleeding at the possible cost of more slowly achieving a therapeutic level of lepirudin. The greatly reduced dosing in patients with a creatinine > 140 μmol/L takes into consideration that in patients with HIT who have already compromised renal function, additional complications besides HIT often result in further impairment of renal function.

Recommendations

2.1.3. When argatroban is used to treat patients who have heart failure, multiple organ system failure, or severe anasarca or who are postcardiac surgery, we suggest beginning the initial infusion at a rate between 0.5 and 1.2 μg/kg/min, with subsequent adjustments using the APTT, over the usual recommended starting dose of 2.0 μg/kg/min (Grade 2C)**.**

2.1.4. When danaparoid is used to treat patients with strongly suspected (or confirmed) HIT, we recommend a therapeutic-dose regimen (see text) administered (at least initially) by the IV route over prophylactic-dose regimens or initial SC administration (Grade 1B)**.**

To establish rapid therapeutic-dose anticoagulation with danaparoid for acute HIT, this agent should be given by initial IV bolus administration (2,250 U for patient weighing 60–75 kg [1,500 U for patient weighing < 60 kg; 3,000 U for patient weighing 75–90 kg; 3,750 U for patient weighing > 90 kg]) followed by accelerated IV infusion (400 U/h for 4 h, then 300 U/h for 4 h); followed by an initial maintenance IV infusion rate of 200 U/h (150 U/h in the case of moderate or severe renal failure). Ideally, anti-factor Xa levels (danaparoid standard curve) should be measured (if available) soon after the completion of the accelerated infusion protocol (target range, 0.5–0.8 anti-Xa U/mL), and additional bolus(es) of 750 to 1,500 U administered, and/or increase in the infusion rate, if the level is subtherapeutic. Monitoring of anti-factor Xa levels is suggested during maintenance therapy, every 24 h. It should be noted that danaparoid was more effective than controls in an RCT,[127] despite anti-factor Xa levels not being performed, and so lack of availability of anti-factor Xa monitoring is not a contraindication to use of danaparoid.

Once stable anticoagulation with danaparoid within the therapeutic range has been achieved, subsequent dosing can be given by SC injection, if desired. As danaparoid bioavailability is high, 2,250 U bid SC is approximately equal to 188 U/h by IV infusion, and 1,500 U bid SC is approximately equal to 125 U/h by IV infusion.

Recommendation

2.1.5. 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.[107–115] 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.[107,193] 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 controls.[107] 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 develop venous limb gangrene in the absence of VKA therapy, but this occurs only rarely.[7,107]

Venous limb gangrene occurred in 8 of 66 patients (12.1%; 95% CI, 5.4–22.5%) 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 over 15 years in one medical community.[107] Venous limb gangrene also occurred in 1 of 21 patients (4.8%; 95% CI, 0.12–23.8%) treated with phenprocoumon (patients identified from the historical control group for the lepirudin treatment trial).[139] In contrast, a large retrospective cohort study[194] 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 0/16 = 20.6%). These three studies[107,139,194] have overlapping CIs that indicate the actual risk of warfarin-induced venous limb gangrene could be between 5% and 20%. Since ancrod (defibrinogenating snake venom) increases thrombin generation in HIT,[195] 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.[196–198]

2.2.1 Management of DTI/Danaparoid-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 early. Indeed, there are reported cases of venous gangrene in patients with HIT[110,112,115] 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[199–202] also makes the conversion to warfarin anticoagulation more complex. Whereas lepirudin[139,201,202] and bivalirudin[167,201,202] 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[200]). These clinical observations and theoretical considerations lead to our strong 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 and at a stable plateau.

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 (*ie*, usually to at least 150 × 10^9/L) over starting VKA therapy at a lower platelet count (Grade 1B)**; that VKA therapy be started only with low, maintenance doses (maximum, 5 mg of warfarin or 6 mg of phenprocoumon) rather than with higher initial doses** (Grade 1B)**; and that the nonheparin anticoagulant (*eg*, lepirudin, argatroban, danaparoid) be continued until the platelet count has reached a stable plateau, the INR has reached the intended target, and after a minimum overlap of at least 5 days between nonheparin anticoagulation and VKA therapy rather than a shorter overlap** (Grade 1B)**.**

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 giving vitamin K, either by oral or IV route (5–10 mg), with repeat dosing if the INR remains prolonged. There are three reasons for this recommendation. First, coumarin does not inhibit any activated clotting factor, and thus does not inhibit thrombin generation

Table 6—*Natural History of Isolated HIT: Composite End Point = All-Cause Mortality, Limb Amputation, New Thrombosis (Section: 2.1)*

Study Design (Follow-up)	No.	Frequency of Thrombosis, %*	Comment	References
Prospective (to hospital discharge)	4	75.0	Nine patients identified with HIT (platelet count $< 150 \times 10^9$/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 (75%) after stopping heparin	Warkentin et al[1]/1995
Retrospective (30-day)	62	51.6†	Patients‡ 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: post-trauma/orthopedic/general surgery (40%), post-cardiac surgery (8%), medical (45%), other (7%)	Warkentin and Kelton[9]/1996, Warkentin[188]/2002
Retrospective (not stated)	16	50.0	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 8/16 (50.0%)	Tardy et al[189]/1999
Retrospective (to hospital discharge)	113	38.1 (23.1§)	Patients tested positive for HIT antibodies (platelet aggregation test); all-cause mortality, 27.4%; patients: post-trauma/orthopedic/general surgery (21%), post-cardiac surgery (59%), medical patients (12%), other (8%)	Wallis et al[10]/1999
Prospective (1.7 d [mean])	113	10.4 (first 1.7 d)	Patient cohort awaiting entry into prospective lepirudin trials (positive washed platelet activation assay): 6.1% per day composite end point event-rate = 10.4% event rate over 1.7 (mean) d	Greinacher et al[139]/2000
Retrospective (42 d)	35	20.0	Patients tested positive for HIT antibodies (washed platelet activation assay); 83% of patients received low-dose danaparoid; composite end point = 31.4% (categorical analysis) and 53% (time-to-event analysis)	Farner et al[128]/2001
Retrospective cohort (37 d)	139	23.0	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%	Lewis et al[143]/2001, Lewis et al[144]/2003
Retrospective cohort (30 d)	14	35.7	Fourteen-patient cohort with isolated HIT and having a positive EIA > 1.0 optical density units; among patients with positive EIA but OD 0.4 – 1.0, only 3 of 34 (9%) had thrombosis	Zwicker et al[190]/2004

*Denominator shown as "No." in the second column.

†Thrombosis developed in 32 of 62 patients; by time-to-event analysis, the risk of thrombosis was 52.8%.

‡Definition of "isolated HIT" did not exclude patients with thrombosis prior to onset of HIT: 19 of 62 (30.6%) patients had thrombosis pre-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 (11/19 vs 21/43; p = 0.70).

§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, 21/91 (23.1%): of these patients, early heparin cessation was associated with a trend to higher thrombosis rate than late heparin cessation (11/33 [33.3%] vs 10/58 [17.2%]; p = 0.12 by two-sided Fisher exact test).

in HIT.[107] Second, in HIT, coumarin-induced microvascular thrombosis (resulting from protein C depletion) can begin abruptly, and evolve quickly to coumarin necrosis (venous limb gangrene or skin necrosis syndromes). And third, prolongation of the APTT by VKA therapy can lead to *underdosing* of DTI therapy used to manage the HIT.[115] The combination of coumarin-induced protein C depletion and associated subtherapeutic dosing of DTI therapy can produce the circumstances that favor progression to microvascular thrombosis.

Recommendation

2.2.2. For patients receiving a VKA at the time of diagnosis of HIT, we recommend use of vitamin K (10 mg po or 5 to 10 mg IV) [Grade 1C]**.**

2.3 LMWH for HIT

Although LMWH is less likely to cause HIT antibody formation,[1,2,6,36] and less likely to cause HIT in patients who have formed HIT antibodies,[1,2,6] compared with UFH, LMWH is equally reactive as UFH in activation assays of HIT sera using washed platelets.[1,203] Further, there is a substantial risk for persisting/recurrent thrombocytopenia and/or new thrombosis during treatment of HIT with LMWH.[204] 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 (13/36 = 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 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 1B)**.**

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.[105,205,206] This is because petechiae and other mucocutaneous bleeding typical of thrombocytopenia are not clinical features of HIT, despite even severe thrombocytopenia,[7] and platelet transfusions have been linked with thrombotic events, albeit only in anecdotal reports.[207,208] A recent preliminary report[209] that described a retrospective study of patients with EIA-positive HIT identified a greater risk of thrombosis among patients with EIA-positive HIT who had received platelet transfusions (however, the confounding role of severity of thrombocytopenia—itself a risk factor for thrombosis in HIT[16]—cannot completely be excluded). 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 should not be given (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 trend to earlier onset of HIT in those patients with a history of previous heparin exposure.[31] Second, among patients with rapid-onset HIT preexisting HIT antibodies can be detected in patient blood obtained immediately before the repeat heparin exposure that caused the rapid-onset HIT. Moreover, in rapid-onset HIT, there is a strong association with recent (< 100 days), rather than remote (> 100 days) prior heparin exposure.[31,32] Third, HIT antibodies are transient, with the median time to antibody disappearance of 50 to 80 days, depending upon the assay performed.[31] Fourth, 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.[31] 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.[31] All these observations argue strongly against the presence of typical immune anamnesis in HIT.

Three reports include five or more patients who have undergone heparin rechallenge in the setting of previous HIT[31,210,211] (although seropositivity was not established for all patients for the suspected previous episode of HIT in one study[211]). Other studies describe single-case anecdotes in similar circumstances.[212–215] In most instances, the heparin rechallenge was performed

to permit cardiac or vascular surgery. None of the patients developed rapid-onset HIT or rapid regeneration of HIT antibodies. Two patients formed anti-PF4/heparin antibodies that were weaker, and occurred later, than those they had developed during their prior episode of HIT, although such development of antibodies did not present a clinical problem as heparin was not used in the postoperative period. Since there is limited information regarding 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.

Despite the absence of large prospective studies of deliberate heparin reexposure, the strong scientific rationale (especially the inability to reprise an HIT immune response before day 5), the limited experience with alternative anticoagulants for cardiac surgery, and the inability to readily reverse their anticoagulant effects following surgery, are other important considerations that makes this a strong recommendation. On balance, we consider the risk resulting from a potential (and only theoretical) boostering of HIT antibodies (especially occurring well into the postoperative period) to be much lower than the risk of (peri)operative complications, especially major bleeding (and, potentially, catastrophic intraoperative cardiopulmonary bypass [CPB] thrombosis[216]), associated with the nonheparin anticoagulants.

In general, detectability of HIT antibodies disappears first using the platelet activation assay, followed later by the PF4-dependent EIA. In addition, considerable evidence exists indicating that nonplatelet-activating antibodies (*ie*, EIA-positive but washed platelet activation assay-negative sera) are not associated with risk for clinical HIT; accordingly, when a washed platelet functional assay performed by an experienced laboratory gives a negative test result, it is likely that intraoperative UFH exposure is safe. The familiarity with UFH use and reversal of UFH anticoagulation with protamine are important reasons why this option is preferred, unless a particular center has relevant (and favorable) experience with the other main options (*eg*, bivalirudin; UFH plus epoprostenol).

Recommendations

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 1B)**.**

3.1.2. For patients with a history of HIT who are antibody positive by PF4-dependent EIA but antibody negative by washed platelet activation assay, we recommend the use of UFH over a nonheparin anticoagulant (Grade 2C)**.**

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

3.2 Patients With Acute or Subacute HIT Undergoing Cardiac Surgery

Table 7[31,102,210–247] 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.[31,102,210–215] This is because HIT antibodies are generally undetectable (or weak) by this time, and are usually not regenerated during the brief heparin re-exposure required to permit cardiac surgery. Ideally, clinicians should ascertain that HIT antibodies are no longer detectable serologically before planning heparin reexposure. Although the risk of regenerating pathogenic antibodies and developing HIT again appears to be low, it is prudent to restrict heparin use to the period of 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"), are at risk of developing rapid-onset HIT on heparin reexposure, unless a washed platelet activation assay (*eg*, SRA, HIPA test) is negative and the antigen assay is only weakly positive or strongly positive because of nonplatelet-activating (IgM, IgA) antibodies (discussed subsequently).

In patients with acute or subacute HIT who require cardiac surgery, there are several anecdotal reports describing various strategies. However, one strategy, intraoperative anticoagulation with bivalirudin, has undergone systematic investigations for use during cardiac surgery (both on-pump and off-pump), in both HIT and non-HIT settings (Table 7). No studies have compared these various strategies, and so the actual treatment selected should be based on both patient- and 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. However, we give preference for two strategies that likely have the greatest risk-benefit tradeoffs: UFH anticoagulation (after disappearance of HIT antibodies), and bivalirudin anticoagulation.

The use of bivalirudin for intraoperative anticoagulation during cardiac surgery has been systematically investigated.[220–227] These studies included early investigations of hemostatic markers of coagulation system activation with intraoperative anticoagulation with bivalirudin during CPB,[220] including one study that compared activation markers with and without use of

Table 7—*Anticoagulant Protocols Used for Cardiac Surgery (Section 3.2)*

Anticoagulant Approaches	Protocol	Comments
Preferred (level 1) options (when warranted based on patient- and center-specific considerations)		
Give heparin when HIT antibodies no longer detectable[31,102,210–215]	Standard UFH dosing for CPB; avoid UFH before and after cardiac surgery	Demonstrate absence of HIT antibodies before surgery, if possible; 0/15 patients regenerated HIT antibodies in one study;[210] even if antibodies are regenerated, this is unlikely to occur before day 5[31]
Bivalirudin[102,217–231]	Off-pump: bolus, 0.75 mg/kg, then 1.75 mg/kg/h infusion to maintain ACT > 300 s; CPB: 1 mg/kg bolus, 50 mg bolus added to priming solution of CPB, 2.5 mg/kg/h infusion, additional 0.1–0.5 mg boluses to maintain ACT > 2.5-fold baseline ACT	Shorter t½ (25 min) and minor renal excretion (20%) are advantageous for cardiac surgery; special considerations are required due to elimination of bivalirudin by proteolytic cleavage by thrombin within the blood itself: 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 stasis and consequent clotting of CPB circuit during or after surgery[218,219]
Heparin plus prostacyclin analogue (epoprostenol[236,237] or iloprost[238])	Standard UFH dosing for CPB; epoprostenol: step-wise increments of 5 ng/kg/min, beginning at 5 ng/kg/min, until target rate of 30 ng/kg/min reached	Epoprostenol: t½ = 3–6 min; can cause severe hypotension (managed with norepinephrine); successful outcomes reported in two studies (9 patients) and one study of 22 patients using iloprost; epoprostenol (but not iloprost) is available in the United States (approval: primary pulmonary hypertension)
Nonpreferred (level 2) options		
Lepirudin[102,217,218,232–235]	Detailed protocol published elsewhere[102,217]	ECT monitoring recommended; however, commercial ECT currently not available; risk for drug accumulation if postoperative renal failure occurs; no antidote; relatively long half-life of 60–80 min
Heparin plus tirofiban[239–241]	Standard UFH dosing for CPB; tirofiban: 10 μg/kg bolus, then 0.15 μg/kg/min until 1 h before anticipated conclusion of CPB	47 patients reported: 44/47 patients discharged on schedule from hospital (2 deaths, 1 prolonged ICU stay); HIT-antibodies detectable in 35/47 patients (remaining patients had HIT diagnosed previously); however, manufacturer of tirofiban does not recommend this approach, as fatal bleeds have been reported
Danaparoid[125,217,243–245]	Detailed protocols for CPB are published elsewhere[125,217,243]	High bleeding risk (no antidote and long t½); anti-Xa monitoring recommended; severe bleeding is frequent; lower doses of single bolus danaparoid (40 anti-Xa U/kg) may be appropriate for off-pump cardiac surgery
Argatroban[246]	Off-pump experience reported	Minimal experience

cardiotomy suction.[221] Bivalirudin concentrations appropriate for successful anticoagulation (10–15 μg/mL) have been established.[102] Subsequently, three RCTs have compared bivalirudin against UFH (with protamine reversal) in non-HIT patients, two performed "off-pump"[222] (including the EVOLUTION-OFF study[223,224]) and the other performed during on-pump surgery (EVOLUTION-ON study[225]). Two further prospective cohort studies have utilized bivalirudin for on- and off-pump anticoagulation for patients with (sub)acute or previous HIT (CHOOSE-ON and CHOOSE-OFF studies, respectively[226,227]).

The following conclusions and observations can be drawn from these studies of bivalirudin anticoagulation during cardiac surgery. First, the use of fixed-dose bivalirudin protocols, utilizing routine intraoperative coagulation studies (*eg*, activated clotting time [ACT]) to ensure a minimal threshold level of anticoagulation, is feasible (cf. lepirudin). Second, careful attention to special intraoperative surgical, anesthesiology, and perfusion techniques are required due to the unique pharmacology of bivalirudin, in particular its progressive, nonenzymic degradation in area of stagnant blood flow. For example, use of cardiotomy suction is not recommended, as this increases coagulation system activation.[221] Information for the cardiac surgeon/anesthesiologist/ perfusionist is available describing the important technical considerations relevant for safe management of bivalirudin anticoagulation during cardiac surgery.[218,219] Third, compared with UFH/protamine, bivalirudin gives comparable efficacy and safety results, particularly with regard to bleeding data and transfusion requirements, both in off- and on-pump settings.

Case series using lepirudin for intraoperative management of CPB anticoagulation in patients with (sub)acute or previous HIT have helped establish[211,232–234] target drug levels appropriate for CPB (lepirudin, 3.5 to 4 μg/mL[102,234]). However, there are key factors limiting the safe use of lepirudin in cardiac surgery: (1) the need for monitoring drug levels with the ecarin clotting time (ECT), a coagulation assay that is not commercially available as a point-of-care test in the operating room; (2) the lack of an antidote; and (3) a relatively long plasma half-life of 60 to 80 min, which (due to its exclusive renal excretion) is greatly increased in the setting of renal impairment, thus leading to persistence of high lepirudin levels and consequent bleeding complications. The largest study of lepirudin for CPB in patients with acute or previous HIT reported survival without thrombosis in 54 of 57 patients (95%).

Coadministration of UFH with either a prostacyclin analog (epoprostenol or iloprost) or tirofiban (platelet glycoprotein IIb/IIIa antagonist) so as to attenuate the HIT antibody-induced platelet activation response has been used with success for CPB surgery in patients with acute or previous HIT. Two reports[236,237] described epoprostenol use in nine patients and observed successful outcomes in all. One study[238] reported successful use of iloprost in 22 patients after having established in individual patients the necessary concentrations of iloprost to inhibit HIT antibody-induced platelet activation. 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. However, the manufacturer discourages use of tirofiban for cardiac surgery because fatal bleeding outcomes have occurred in two patients with anuria (they did not undergo hemofiltration, which can be used for extracorporeal elimination of tirofiban[242]).

Despite its long half-life and the unavailability of a point-of-care monitoring assay, reports of danaparoid use for heart surgery include a series of 53 patients undergoing CPB, most of whom received a fixed-dose regimen without laboratory monitoring.[243] Severe postoperative bleeding (> 20 U of blood product required) occurred in 21% of patients, and clots in the operative field and/or CPB circuit were observed in 34% of patients. Subsequently, some investigators have advocated use of intraoperative monitoring, but it remains uncertain whether this reduces bleeding.[125,217] Off-pump cardiac surgery requires significantly lower doses of danaparoid (about one half to one third), and this option may be appropriate, as one study reported successful use of a danaparoid bolus of 40 anti-Xa U/kg in non-HIT patients undergoing off-pump coronary artery bypass surgery.[245]

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 has resolved and antibodies are negative (then see recommendation 3.1.1.) or weakly positive (then see recommendation 3.1.2.) [Grade 1B]**; using bivalirudin for intraoperative anticoagulation during cardiopulmonary bypass (if techniques of cardiac surgery and anesthesiology have been adapted to the unique features of bivalirudin pharmacology)** [Grade 1B] **or during off-pump cardiac surgery** [Grade 1B]**; using lepirudin for intraoperative anticoagulation (if ECT is available and patient has normal renal function and is judged to be at low risk for postcardiac surgery renal dysfunction)** [Grade 2C]**; using UFH plus the antiplatelet agent epoprostenol (if ECT monitoring is 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 for off-pump coronary artery bypass surgery** (Grade 2C) **over performing the surgery with UFH when platelet-activating anti-PF4/heparin antibodies are known to be present in a patient with acute or recent HIT.**

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 (washed platelet activation assay) are negative, then using heparin (see Recommendation 3.1.1.) over using a nonheparin anticoagulant (Grade 1C)**. If surgery cannot be delayed, we suggest the use of a nonheparin anticoagulant (see Recommendation 3.2.1.) over the use of UFH** (Grade 2C)**.**

3.3 PCIs

Invasive cardiologic procedures such as angioplasty and stent placement are generally performed with anticoagulation by UFH, LMWH, or bivalirudin. For patients with acute or recent HIT, alternative agents include argatroban (FDA approved for PCI when heparin is contraindicated),[123,248] bivalirudin (FDA- and EMEA-approved anticoagulant for PCI in non-HIT situations[249,250] and in HIT pa-

tients[251,252]), and lepirudin or desirudin (studies in HIT[253–255] and non-HIT[256,257] patients undergoing PCI). Argatroban anticoagulation has been studied for PCI in patients with acute or previous HIT receiving standard dosing (bolus, 350 μg/kg followed by infusion at 25 μg/kg/min, with adjustments to achieve and maintain ACTs of 300–450 s).[248] A total of 112 PCIs were performed on 91 patients (14 with platelet counts $< 100 \times 10^9$/L during their first PCI). The primary outcome was a satisfactory PCI (subjective assessment of the investigator), which occurred in 86 of 91 patients (94.5%) 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 one patient in the first group.

Investigations of bivalirudin for use during PCI in patients with acute or previous HIT[252] have specified a primary endpoint of major bleeding within 48 h after completion of the bivalirudin infusion (or by discharge, if that occurred sooner). Investigators defined clinical success 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 > 300 s). Later in the study, based on the results of clinical studies with bivalirudin during coronary intervention in patients without HIT,[250] the dose was reduced to 0.75 mg/kg bolus, followed by a 1.75 mg/kg/h infusion given for the duration of the procedure (the current FDA-approved dose). Among the 52 patients studied, procedural success (TIMI 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. Further, in non-HIT patients, there is extensive experience of bivalirudin for PCI (> 20,000 patients treated in FDA approval studies). We therefore gave bivalirudin the highest grade of recommendation for use during PCI in patients with acute or previous HIT.

For lepirudin, the lack of FDA approval (cf. argatroban and bivalirudin) and concerns regarding bleeding in HIT and non-HIT populations, as well as its potential for inducing acute anaphylaxis/anaphylactoid reactions following IV bolus administration in sensitized patients[162–165] raise concerns about its use during PCI. Similarly, although anecdotal reports support the use of danaparoid during cardiac catheterization,[125,258,259] it is not approved in any jurisdiction for this indication, and has a far greater half-life than the other agents.

Although UFH could be used safely in a patient with remote previous HIT (in whom HIT antibodies are no longer detectable), the theoretical potential for recurrent immunization several days later, and the possibility that UFH might be required for subsequent cardiac surgery, as well as the favorable experience with alternative nonheparin anticoagulants such as bivalirudin and argatroban, lead us to avoid recommending use of UFH for this situation. However, UFH would be an appropriate choice for PCI in a patient with previous HIT in health care settings in which alternative, nonheparin anticoagulants are not available. Recommendations regarding use of alternative anticoagulants in PCI also are given in the chapter "The Primary and Secondary Prevention of Coronary Artery Disease" by Becker et al in this supplement.

Recommendations

3.3.1. For patients with strongly suspected (or confirmed) acute HIT who require cardiac catheterization or PCI, we recommend a nonheparin anticoagulant (bivalirudin [Grade 1B]**, argatroban** [Grade 1C]**, lepirudin** [Grade 1C]**, or danaparoid** [Grade 1C]**) over UFH or LMWH** (Grade 1B)**.**

3.3.2. For patients with previous HIT (who are antibody negative) who require cardiac catheterization or PCI, we suggest use of a nonheparin anticoagulant (see Recommendation 3.3.1.) over UFH or LMWH (Grade 2C)**.**

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, argatroban, and long-term VKA use.[260–263] We have not made any specific recommendations for anticoagulation of this patient population.

3.5 Pregnancy

Although there are case reports of HIT complicating use of UFH during pregnancy[264–266] or the postpartum period,[267] HIT seems to be rare during pregnancy,[45] especially with LMWH.[42–45,268] The alternative nonheparin anticoagulant with the most data for use during pregnancy is danaparoid,[134–136,269,270] including also for use in prophylactic doses during pregnancy in patients with a previous history of HIT.[271] Danaparoid does not appear to cross the placenta.[125,133,268] Fondaparinux is another therapeutic option,[272,273] although one study found that about 10% of the maternal blood concentration of fondaparinux could be measured in the cord blood of a newborn.[274] Secretion of either anticoagu-

lant into the breast milk is not a contraindication for breast feeding as GI absorption of danaparoid and fondaparinux is negligible.

A few reports describe use of lepirudin during pregnancy,[275–278] but this agent can cross the placenta[279] and has caused embryopathy in rabbits given high doses of hirudin.[280] Further, a zebrafish model reveals that thrombin plays a role in early embryogenesis.[281]

In general, for all of the major nonheparin anticoagulants (lepirudin, bivalirudin, argatroban, danaparoid, fondaparinux), only limited human data exist describing use during pregnancy. Thus, for a pregnant patient with a history of HIT who requires anticoagulation during pregnancy, use of LMWH should also be considered, given its successful use during pregnancy, the overall negligible risk of inducing HIT with LMWH during pregnancy, and the apparent lack of immune memory in HIT. If this option is taken, it would be prudent to measure platelet counts between days 5 and 14 after start of LMWH, as in theory this should be the time period during which HIT (though unlikely) would be expected to manifest.

4.0 Prevention of HIT

4.1 Reducing the Risk of Clinical HIT

4.1.1 UFH vs LMWH

A metaanalysis[40] of five studies (two RCTs) of postoperative thromboprophylaxis (post-orthopedic, n = 4; post-cardiac, n = 1) that examined the frequency of serologically confirmed HIT found a marked reduction in the risk of HIT with LMWH compared with UFH (common OR = 0.10 [95% CI, 0.03–0.33]; $p < 0.001$). A more recent metaanalysis[41] confirmed the lower risk of HIT with LMWH in postsurgical thromboprophylaxis (OR = 0.072 [95% CI, 0.02–0.23]; $p < 0.0001$). Further evidence supporting a lower risk of HIT with LMWH in the postoperative or trauma setting includes studies showing a lower frequency of anti-PF4/heparin antibody formation (both platelet-activating and nonplatelet-activating) with LMWH compared with UFH.[1,15,20,282]

One metaanalysis[41] also identified female gender (common OR = 2.37 [95% CI, 1.37–4.09]; $p = 0.0015$) and postoperative (vs medical) thromboprophylaxis (common OR = 3.25 [95% CI, 1.98–5.35]; $p < 0.0001$) as additional risk factors for HIT. Among females undergoing surgical thromboprophylaxis, the reduction in risk of HIT with LMWH compared with UFH was considerable: common OR = 0.057 (95% CI, 0.013–0.24); $p < 0.0001$. (Although males undergoing surgical thromboprophylaxis also developed fewer cases of HIT, the smaller numbers precluded a firm conclusion.) Given that the highest risk of HIT occurs in females receiving postoperative thromboprophylaxis, the greatest *absolute* benefit in using LMWH as a HIT prevention strategy is in females undergoing postsurgical thromboprophylaxis.[41]

In contrast to postsurgical patients, the relative effect of LMWH compared with UFH on risk of HIT among medical patients is less certain. The overall low numbers of HIT in studies of medical patients currently do not allow for any definite conclusions. One metaanalysis[41] of medical patients found no significant increase in risk of HIT with UFH compared with LMWH (common OR = 1.75 [95% CI, 0.73–4.22]; $p = 0.23$). A recent metaanalysis of 13 RCTs comparing UFH vs LMWH for treatment of DVT and PE found no evidence to indicate a reduced risk of HIT with LMWH.[283] However, a recent large retrospective single-institution study of medical patients found significantly less HIT with LMWH compared with UFH: 1/1,189 (0.084%) vs 43/8,420 (0.51%); $p = 0.037$).[284] Other data supporting the concept that HIT is less likely to occur in medical patients receiving LMWH, compared with UFH, are two studies indicating significantly lower frequencies of antibody formation among medical patients receiving LMWH.[36,37]

The antithrombin-binding pentasaccharide anticoagulant, fondaparinux, was compared with the LMWH, enoxaparin, with respect to HIT and anti-PF4/heparin antibody formation in two large postorthopedic surgery thromboprophylaxis RCTs.[77] No patients developed clinical HIT in either study. However, although the frequency of anti-PF4/heparin antibody generation was similar in the patient groups receiving fondaparinux or enoxaparin, the antibodies generated against PF4/polysaccharide differed greatly: whereas the antibodies reacted *in vitro* against both PF4/UFH and PF4/LMWH complexes, they did not react against PF4/fondaparinux (even when serum was used from patients who had formed antibodies while receiving fondaparinux). This absence of *in vitro* cross-reactivity of anti-PF4/heparin antibodies against PF4/fondaparinux, together with the paucity of reports to date implicating fondaparinux as a cause of HIT (cf. LMWH), and considering the favorable (though small) experience using fondaparinux to treat patients with HIT, indicate that the risk of HIT with fondaparinux will not be greater than that of LMWH, and may well be much lower (perhaps negligible).[77]

This chapter does not make any overall recommendations in favor of one particular type of heparin preparation over another with respect to the risk of HIT. This is because the decision to use one type of anticoagulant (heparin or otherwise) over another involves many considerations (*eg*, efficacy, safety, cost) in addition to the potential for inducing HIT

(or other adverse effects). However, the risk of HIT is a factor worth considering when making anticoagulant treatment decisions.

Conflict of Interest Disclosures

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Professor Koster discloses that he has received consultant fees from The Medicines Company, and that he is on the speakers bureaus for the Medicines Company and Mitsubishi Pharma Europe. Professor Koster also has received fees from The Medicines Company.

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