CHEST Supplement

ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

Treatment and Prevention of Heparin-Induced Thrombocytopenia

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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Background: **Heparin-induced thrombocytopenia (HIT) is an antibody-mediated adverse drug reaction that can lead to devastating thromboembolic complications, including pulmonary embolism, ischemic limb necrosis necessitating limb amputation, acute myocardial infarction, and stroke.**
Methods: **The methods of this guideline follow the Methodology for the Development of Antithrombotic Therapy and Prevention of Thrombosis Guidelines: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines in this supplement.**
Results: **Among the key recommendations for this article are the following: For patients receiving heparin in whom clinicians consider the risk of HIT to be > 1%, we suggest that platelet count monitoring be performed every 2 or 3 days from day 4 to day 14 (or until heparin is stopped, whichever occurs first) (Grade 2C). For patients receiving heparin in whom clinicians consider the risk of HIT to be < 1%, we suggest that platelet counts not be monitored (Grade 2C). In patients with HIT with thrombosis (HITT) or isolated HIT who have normal renal function, we suggest the use of argatroban or lepirudin or danaparoid over other nonheparin anticoagulants (Grade 2C). In patients with HITT and renal insufficiency, we suggest the use of argatroban over other nonheparin anticoagulants (Grade 2C). In patients with acute HIT or subacute HIT who require urgent cardiac surgery, we suggest the use of bivalirudin over other nonheparin anticoagulants or heparin plus antiplatelet agents (Grade 2C).**
Conclusions: **Further studies evaluating the role of fondaparinux and the new oral anticoagulants in the treatment of HIT are needed.** ***CHEST 2012; 141(2)(Suppl):e495S–e530S***

Abbreviations: ACT = activated clotting time; aPTT = activated partial thromboplastin time; CPB = cardiopulmonary bypass; CVA = cerebrovascular accident; DTI = direct thrombin inhibitor; ECT = ecarin clotting time; ELISA = enzyme-linked immunosorbent assay; FDA = US Food and Drug Administration; GP = glycoprotein; GTI = Genetics Testing Institute; HIPA = heparin-induced platelet activation; HIT = heparin-induced thrombocytopenia; HITT = heparin-induced thrombocytopenia with thrombosis; INR = international normalization ratio; LMWH = low-molecular-weight heparin; OD = optical density; 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

Note on Shaded Text: Throughout this guideline, shading is used within the summary of recommendations sections to indicate recommendations that are newly added or have been changed since the publication of Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Recommendations that remain unchanged are not shaded.

2.1.1. For patients receiving heparin in whom clinicians consider the risk of HIT to be > 1%, we suggest that platelet count monitoring be performed every 2 or 3 days from day 4 to day 14

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(or until heparin is stopped, whichever occurs first) (Grade 2C).

2.1.2. For patients receiving heparin in whom clinicians consider the risk of HIT to be < 1%, we suggest that platelet counts not be monitored (Grade 2C).

3.1. In patients with HITT, we recommend the use of nonheparin anticoagulants, in particular lepirudin, argatroban, and danaparoid, over the further use of heparin or LMWH or initiation/continuation of a vitamin K antagonist (VKA) (Grade 1C).

3.2.1. In patients with HITT who have normal renal function, we suggest the use of argatroban or lepirudin or danaparoid over other nonheparin anticoagulants (Grade 2C).

Remarks: Other factors not covered by our analysis, such as drug availability, cost, and ability to monitor the anticoagulant effect, may influence the choice of agent.

3.2.2. In patients with HITT and renal insufficiency, we suggest the use of argatroban over other nonheparin anticoagulants (Grade 2C).

3.3. In patients with HIT and severe thrombocytopenia, we suggest giving platelet transfusions only if bleeding or during the performance of an invasive procedure with a high risk of bleeding (Grade 2C).

3.4.1. In patients with strongly suspected or confirmed HIT, we recommend against starting VKA until platelets have substantially recovered (ie, usually to at least 150×10^9/L) over starting VKA at a lower platelet count and that the VKA be initially given in low doses (maximum, 5 mg of warfarin or 6 mg phenprocoumon) over using higher doses (Grade 1C).

3.4.2. We further suggest that if a VKA has already been started when a patient is diagnosed with HIT, vitamin K should be administered (Grade 2C).

Remarks: We place a high value on the prevention of venous limb gangrene and a low value on the cost of the additional days of the parental nonheparin anticoagulant.

3.5. In patients with confirmed HIT, we recommend that that the VKA be overlapped with a nonheparin anticoagulant for a minimum of 5 days and until the INR is within the target range over shorter periods of overlap and that the INR be rechecked after the anticoagulant effect of the nonheparin anticoagulant has resolved (Grade 1C).

4.1. In patients with isolated HIT (HIT without thrombosis), we recommend the use of lepirudin or argatroban or danaparoid over the further use of heparin or LMWH or initiation/continuation of a VKA (Grade 1C).

4.2. In patients with isolated HIT (HIT without thrombosis) who have normal renal function, we suggest the use of argatroban or lepirudin or danaparoid over other nonheparin anticoagulants (Grade 2C).

Remarks: Other factors such as drug availability, cost, and ability to monitor the anticoagulant effect may influence the choice of agent. The dosing considerations are the same as for patients with HITT (see section 3.2). For a recommendation on choice of nonheparin anticoagulants in the setting of renal insufficiency, see Recommendation 3.2.2.

5.1.1. In patients with acute HIT (thrombocytopenic, HIT antibody positive) or subacute HIT (platelets recovered, but still HIT antibody positive) who require urgent cardiac surgery, we suggest the use of bivalirudin over other nonheparin anticoagulants and over heparin plus antiplatelet agents (Grade 2C).

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5.1.2. In patients with acute HIT who require nonurgent cardiac surgery, we recommend delaying the surgery (if possible) until HIT has resolved and HIT antibodies are negative (see section 6.1) (Grade 2C)**.**

Remarks: Other factors not covered by our analysis, such as drug availability, cost, and ability to monitor the anticoagulant effect may influence the choice of agent. For recommendations for patients with a past history of HIT (>3 months previous) who require cardiac surgery, see section 6.1.

5.2. In patients with acute HIT or subacute HIT who require percutaneous coronary interventions, we suggest the use of bivalirudin (Grade 2B) **or argatroban** (Grade 2C) **over other nonheparin anticoagulants.**

Remarks: Other factors, such as drug availability, cost, and ability to monitor the anticoagulant effect, may influence the choice of agent.

5.3.1. In patients with acute or subacute HIT who require renal replacement therapy, we suggest the use of argatroban or danaparoid over other nonheparin anticoagulants (Grade 2C)**.**

Remarks: We acknowledge that the cost of argatroban may be prohibitive at some clinical centers. We further suggest that if the prothrombotic state of HIT appears to have resolved (as seen by normalization of the platelet count), saline flushes during dialysis would be a reasonable option. This suggestion is based on the presumed pathogenesis of thrombosis in this condition and not on the results of clinical trials.

5.3.2. In patients with a past history of HIT who require ongoing renal replacement therapy or catheter locking, we suggest the use of regional citrate over the use of heparin or LMWH (Grade 2C)**.**

5.4. In pregnant patients with acute or subacute HIT, we suggest danaparoid over other nonheparin anticoagulants (Grade 2C)**. We suggest the use of lepirudin or fondaparinux only if danaparoid is not available** (Grade 2C)**.**

Remarks: Other factors, such as drug availability, cost, and ability to monitor the anticoagulant effect, may influence the choice of agent.

6.1.1. In patients with a history of HIT in whom heparin antibodies have been shown to be absent who require cardiac surgery, we suggest the use of heparin (short-term use only) over nonheparin anticoagulants (Grade 2C)**.**

6.1.2. In patients with a history of HIT in whom heparin antibodies are still present who require cardiac surgery, we suggest the use of nonheparin anticoagulants (see Recommendation 5.1.1) over heparin or LMWH (Grade 2C)**.**

6.2. In patients with a history of HIT in whom heparin antibodies have been shown to be absent who require cardiac catheterization or percutaneous coronary interventions, the recommended treatment is the same as in Recommendation 5.2.

6.3. In patients with a past history of HIT who have acute thrombosis (not related to HIT) and normal renal function, we suggest the use of fondaparinux at full therapeutic doses until transition to a VKA can be achieved (Grade 2C)**.**

This article offers recommendations on diagnosis and management of heparin-induced thrombocytopenia (HIT). Table 1 describes the question definition (ie, population, intervention, comparator, and outcome) addressed by the recommendations.

1.0 Methods and Overview of HIT

We adhered to the general approach to developing recommendations described in the methodology article of these guidelines.[1] We searched the PubMed English language literature from January 1976 to June 2010 using the following search terms: "heparin-induced thrombocytopenia," "clinical trial," "cohort," "randomized clinical trial," "argatroban," "lepirudin," "hirudin," "bivalirudin," "fondaparinux", "diagnosis," "laboratory assay," "clinical prediction rule," "platelet count monitoring," "coronary artery bypass," "cardiac surgery," "cardiopulmonary bypass" (CPB), "angioplasty," "transluminal percutaneous coronary," "treatment," "venous limb gangrene," "platelet transfusion," "renal replacement therapy," "hemodialysis," "hemofiltration," "pregnancy," "re-exposure," and "recurrence."

The primary efficacy outcome measures of interest were new thrombosis, limb amputation, major bleeding, and death (due to thrombosis or bleeding). In the cohort studies with historical controls, outcome events were counted if they occurred after treatment with the nonheparin anticoagulant was initiated, and from the date heparin was discontinued in the control group.

1.1 Value and Preferences

Based on the relevant literature and the value and preference rating exercise conducted by the Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines panel,[2] we infer that from the patient's perspective, a venous thromboembolic event (eg, pulmonary embolism [PE], proximal DVT) carries similar weight as a major bleeding event (eg, gastrointestinal bleeding event), and that a stroke carries 2.5 times the weight of a major bleeding event.

1.2 Overview of HIT

1.2.1 Pathogenesis of HIT: HIT is an adverse immune-mediated drug reaction that is associated with a high risk of venous

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Table 1—*[Introduction] Treatment and Prevention of HIT: Question Definitions*

Section	PICO Question				
	Population	Intervention(s)	Comparator	Outcome(s)	Methodology
2.0 Screening for HIT					
2.1	Patients receiving heparin or LMWH for ≥ 5 d	Platelet count monitoring combined with the 4Ts Score	No platelet count monitoring	False negatives (increased risk of thrombosis if not treated with nonheparin anticoagulants) False positives (increased risk of bleeding if treated with nonheparin anticoagulants) True negatives (do not have HIT) True positives (do have HIT)	Decision analysis
3.0 Management of HITT (HIT with thrombosis)					
3.1	Patients with strongly suspected or confirmed HIT with thrombosis	Discontinue heparin with or without starting a VKA	Treatment with nonheparin anticoagulants	Death (thrombosis, bleeding) Limb amputation	Cohort studies with historical controls
3.2		Treatment with nonheparin anticoagulants	Treatment with other nonheparin anticoagulants	New thrombosis (arterial, venous) Major bleeding	RCT, cohort studies
3.3		Platelet transfusions	No platelet transfusions		Case series
3.4		Starting VKA before platelet recovery	No VKA until after platelet recovery	Venous limb gangrene Limb amputation New thrombosis (arterial, venous)	Case series
3.5		Discontinuing thrombin inhibitor after minimum of 5 d of overlap with a VKA	Discontinuing thrombin inhibitor after < 5 d of overlap with a VKA		Secondary analysis of cohort studies
4.0 Management of isolated HIT (HIT without thrombosis)					
4.1	Patients with strongly suspected or confirmed HIT without thrombosis	Discontinue heparin with or without starting a VKA	Treatment with nonheparin anticoagulants	Death (thrombosis, bleeding) Limb amputation	Cohort studies with historical controls
4.2		Treatment with nonheparin anticoagulants	Treatment with other nonheparin anticoagulants	New thrombosis (arterial, venous) Major bleeding	Cohort studies
5.0 Management of patients with acute or subacute HIT in special situations					
5.1	Patients who require urgent cardiac surgery	Treatment with nonheparin anticoagulants	Treatment with other nonheparin anticoagulants	Death (thrombosis, bleeding) Limb amputation New thrombosis (arterial, venous)	Cohort studies
5.2	Patients who require urgent PCI				Cohort studies
5.3	Patients who require renal replacement therapy			Major bleeding Procedural success	Case series
5.4	Pregnant patients				Case series

(Continued)

Table 1—*Continued*

Section	PICO Question				Methodology
	Population	Intervention(s)	Comparator	Outcome(s)	
	6.0 Management of patients with a past history of HIT				
6.1	Patients who require cardiac surgery	Heparin or LMWH	Nonheparin anticoagulants	Recurrence of HIT Reemergence of HIT antibodies	Case series
6.2	Patients who require PCI				Cohort studies
6.3	Patients who require VTE prophylaxis or treatment				Case reports

HIT = heparin-induced thrombocytopenia; HITT = heparin-induced thrombocytopenia with thrombosis; LMWH = low-molecular-weight heparin; PCI = percutaneous coronary intervention; PICO = population, intervention, comparator, and outcome; VKA = vitamin K antagonist.

and arterial thrombosis.[3-6] Heparin exposure leads to the formation of IgG antibodies that recognize multimolecular complexes of platelet factor 4 (PF4) and heparin that form on the surface of platelets.[7,8] These complexes bind to the FcγIIa (IgG) receptors of platelets,[9,10] resulting in platelet activation and release of procoagulant, platelet-derived microparticles.[11,12] The end result is marked generation of thrombin and the formation of venous and arterial thromboses that are the clinical hallmark of HIT.

Risk factors for HIT include duration and type of heparin exposure,[13] patient population,[14-16] severity of trauma,[17] and gender.[18] Differences in the stoichiometry of heparin/PF4 complexes are believed to explain the 10-fold higher likelihood of HIT in patients who receive unfractionated heparin (UFH) compared with patients who receive low-molecular weight heparin (LMWH) or fondaparinux.[19,20] Patients who undergo cardiac or orthopedic surgery and receive UFH have a higher risk of HIT (1%-5%) than medical or obstetric patients (0.1%-1%).[13,14,21-24] Women have approximately twice the risk of developing HIT as men.[18] Table 2[25-35] presents the incidence of HIT in various patient populations.

1.2.2 Clinical Features: Thrombocytopenia (defined as a platelet count $< 150 \times 10^9$/L) is the most common clinical manifestation of HIT and occurs in 85% to 90% of patients.[4] If this definition is broadened to include a proportional fall in the platelet count (eg, 30%-50% fall even if the nadir remains $> 150 \times 10^9$/L), this increases to 90% to 95% of HIT cases.[4,5,27] The characteristic onset of the platelet count fall in HIT is 5 to 10 days after initiation of heparin (first day of heparin = day 0), particularly when heparin is administered perioperatively (typical-onset HIT).[36] "Rapid-onset HIT" refers to an abrupt platelet count fall (within 24 h) that occurs in patients who already have circulating HIT antibodies because of recent exposure to heparin (usually within the past month, occasionally as long as 100 days earlier).[36,37] Occasionally, thrombocytopenia can occur as long as 3 weeks after cessation of heparin (delayed-onset HIT).[38] Although thrombocytopenia is the most common presenting feature of HIT, in up to 25% of patients with HIT the development of thrombosis precedes the development of thrombocytopenia.[3,5]

The pattern of thrombocytopenia following cardiac surgery using heparin is worthy of special mention. Although approximately 50% of patients who undergo cardiac surgery will develop HIT antibodies, only 1% to 2% will develop clinical HIT (thrombocytopenia with or without thrombosis).[14] In general, the platelet count falls by approximately 38% immediately after CPB (and continues to decline for the first 1-2 postoperative days before rising in a continuous fashion to a level above the preoperative

Table 2—*[Overview of HIT] Incidence of HIT According to Patient Population and Type of Heparin Exposure*

Patient Population (Minimum of 4-d Exposure)	Incidence of HIT, %
Postoperative patients	
Heparin, prophylactic dose[3,4,14,25]	1-5
Heparin, therapeutic dose[26]	1-5
Heparin, flushes[a]	0.1-1
LMWH, prophylactic or therapeutic dose[14,25]	0.1-1
Cardiac surgery patients[14,27,28,29]	1-3
Medical	
Patients with cancer[24,30,31]	1
Heparin, prophylactic or therapeutic dose[24]	0.1-1
LMWH, prophylactic or therapeutic dose[26,30]	0.6
Intensive care patients[32]	0.4
Heparin, flushes[33]	< 0.1
Obstetrics patients[21,22,34,35]	< 0.1

See Table 1 legend for expansion of abbreviations.
[a]Case reports only.

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count).[39,40] The following two patterns of thrombocytopenia should alert clinicians to the possibility of HIT following cardiac surgery: a fall in platelet count that begins > 4 days postoperatively (day of surgery = day 0), and thrombocytopenia that persists for > 4 days after surgery.[41]

The most common complication of HIT is venous thrombosis; 17% to 55% of untreated patients who present with thrombocytopenia develop DVT and/or PE.[6,14,42] Arterial thrombotic events, including limb artery thrombosis, thrombotic stroke, and myocardial infarction (MI), also occur, but less often (from 3%-10%).[6,43] After cardiac surgery, the majority of HIT-related thrombotic events are arterial.[44,45] Approximately 5% to 10% of patients with HIT die, usually as a result of thrombotic complications.[6,42]

Less common manifestations of HIT include venous limb gangrene (5%-10% of patients with HIT with DVT treated acutely with a vitamin K antagonist [VKA] [eg, warfarin]),[46] necrotizing skin lesions at heparin injection sites,[47,48] adrenal hemorrhagic necrosis (due to adrenal vein thrombosis), and acute systemic reactions within 30 min of an IV heparin bolus injection (eg, fever/chills, tachycardia, hypertension, dyspnea, cardiopulmonary arrest).[48] HIT can be complicated by disseminated intravascular coagulation severe enough to deplete fibrinogen.[38,49] Despite severe thrombocytopenia (but with a nadir rarely $< 20 \times 10^9$/L), petechiae or other signs of bleeding are rarely seen.[3]

HIT is recognized as a clinicopathologic syndrome because diagnosis is based on the combination of a compatible clinical picture and the presence of platelet-activating anti-PF4 antibodies.[50] Clinical prediction rules to assist physicians with determining the probability that a patient has HIT have been developed,[51-55] the best studied of which is the 4Ts score (Fig 1).[56-59] Evidence is emerging that patients with a low 4Ts score have a very low probability of HIT (0%-3%).[51,56] However, many patients (24%-61%) with a high 4Ts score prove not to have HIT.[51,56] Clinical assessment plays an essential role in the diagnosis of HIT for two reasons: (1) there is commonly a delay before the results of laboratory testing for HIT are available, and management decisions must be made immediately (the rate of thrombosis prior to treatment is approximately 5% per day)[60]; and (2) isolated HIT antibodies are both frequent and not diagnostic of HIT.

1.2.3 Laboratory Diagnosis of HIT: A large number of laboratory assays are currently used to diagnose HIT. A recent survey of specialized coagulation laboratories in North America identified eight different assays and wide discrepancies in practice between centers using the same assay.[61] The assays can be divided into

	Score = 2	Score = 1	Score = 0
Thrombocytopenia Compare the highest platelet count within the sequence of declining platelet counts with the lowest count to determine the % of platelet fall. **(Select only 1 option)**	○ > 50% platelet fall AND nadir of ≥ 20 AND no surgery within preceding 3 days	○ > 50% platelet fall BUT surgery within preceding 3 days OR ○ any combination of platelet fall and nadir that does not fit criteria for Score 2 or Score 0 (eg, 30-50% platelet fall or nadir 10-19)	○ < 30% platelet fall ○ any platelet fall with nadir < 10
Timing (of platelet count fall or thrombosis*) Day 0 = first day of most recent heparin exposure **(Select only 1 option)**	○ platelet fall day 5-10 after start of heparin ○ platelet fall within 1 day of start of heparin AND exposure to heparin within past 5-30 days	○ consistent with platelet fall days 5-10 but not clear (eg, missing counts) ○ platelet fall within 1 day of start of heparin AND exposure to heparin in past 31-100 days ○ platelet fall after day 10	○ platelet fall ≤ day 4 without exposure to heparin in past 100 days
Thrombosis (or other clinical sequelae) **(Select only 1 option)**	○ confirmed new thrombosis (venous or arterial) ○ skin necrosis at injection site ○ anaphylactoid reaction to IV heparin bolus ○ adrenal hemorrhage	○ recurrent venous thrombosis in a patient receiving therapeutic anticoagulants ○ suspected thrombosis (awaiting confirmation with imaging) ○ erythematous skin lesions at heparin injection sites	○ thrombosis not suspected
oTher cause for Thrombocytopenia** **(Select only 1 option)**	○ no alternative explanation for platelet fall is evident	**Possible other cause is evident:** ○ sepsis without proven microbial source ○ thrombocytopenia associated with initiation of ventilator ○ other	**Probable other cause present:** ○ within 72 h of surgery ○ confirmed bacteremia/ fungemia ○ chemotherapy or radiation within past 20 days ○ DIC due to non-HIT cause ○ posttransfusion purpura (PTP) ○ platelet count < 20 AND given a drug implicated in causing D-ITP (see list) ○ non-necrotizing skin lesions at LMWH injection site (presumes DTH) ○ other

Drugs implicated in drug-induced immune thrombocytopenia (D-ITP)

Relatively Common: glycoprotein IIb/IIIa antagonists (abciximab, eptifibatide, tirofiban); quinine, quinidine, sulfa antibiotics, carbamazepine, vancomycin
Less Common: actinomycin, amitriptyline, amoxicillin/piperacillin/nafcillin, cephalosporins (cefazolin, ceftazidime, ceftriaxone), celecoxib, ciprofloxacin, esomeprazole, fexofenadine, fentanyl, fucidic acid, furosemide, gold salts, levofloxacin, metronidazole, naproxen, oxaliplatin, phenytoin, propranolol, propoxyphene, ranitidine, rifampin, suramin, trimethoprim. Note: This is a partial list.

FIGURE 1. 4Ts score. *Timing of clinical sequelae, such as thrombocytopenia, thrombosis, or skin lesions. **Two points if necrotizing heparin-induced skin lesions even if thrombocytopenia not present. (Modified with permission from Warkentin and Linkins.[59])

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two major categories according to the end point they measure: (1) antigen assays that detect the presence of HIT antibodies, and (2) functional assays that detect evidence of platelet activation (by HIT antibodies) in the presence of heparin.[62] Only a small proportion of patients who form HIT antibodies (seroconversion) will develop thrombocytopenia, and a smaller proportion will develop HIT-associated thrombosis. Antigen assays, the most commonly used being enzyme-linked immunosorbent assays (ELISA) that test for antibodies that are reactive against PF4/heparin or PF4/polyvinyl sulfonate, are very sensitive for HIT because they detect seroconversion.[15,63] However, not all of the antibodies these assays detect are capable of causing clinical HIT; hence, the specificity of these assays is only moderate. In contrast, functional assays, such as the serotonin release assay (SRA) and heparin-induced platelet activation (HIPA), are sensitive and specific for HIT because they only detect antibodies that are capable of activating platelets.[15]

The washed platelet SRA and HIPA are generally accepted as the reference standard assays for HIT. However, they are only available at a few centers because they are technically difficult, require human platelets from known reactive donors, and, in the case of the SRA, require working with radiation.[64,65] Most clinical centers use commercially available ELISAs because they do not have these limitations. The primary drawback of the ELISAs is their potential to overdiagnose HIT by detecting antibodies that are not pathogenic. ELISAs that only detect IgG antibodies appear to have better specificity for HIT (IgM and IgA antibodies are unlikely to cause HIT).[15,66]

In patients recovering from HIT, there can be a lag time of several weeks between full platelet recovery and disappearance of the HIT antibodies (subacute HIT), particularly when using the ELISA for serologic testing. These patients are still at risk for developing rapid-onset HIT on heparin re-exposure (unless the washed platelet SRA or HIPA is negative and the ELISA is only weakly positive or strongly positive because of non-platelet-activating IgM or IgA antibodies).

A class of commercial antigen assays that are designed to have a faster turnaround time than the ELISA (approximately 15 min vs 3.5 h [or days, if batched]) have entered the market. One of these assays, the ID-PaGIA Heparin/PF4 antibody test (DiaMed), is a gel centrifugation assay that uses the binding of antibodies to antigen-coated (PF4/heparin) high-density, red polystyrene beads.[67] This method can be performed in any blood bank that utilizes a gel centrifugation system for red cell antibody screening. The operating characteristics for this assay are reviewed in section 1.2.4.

1.2.4 Commercial Antigen Assays Compared With Reference Standard Assays for Diagnosis of HIT: To determine the accuracy of the commercially available antigen assays for HIT, we searched the literature for studies that: (1) compared the operating characteristics of these assays with at least one of the reference standard assays (ie, SRA or HIPA), and (2) used blood samples collected prospectively from consecutive patients with suspected HIT. The three studies that met our criteria evaluated two antigen assays: GTI-PF4 (Genetics Testing Institute [GTI]) and ID-PaGIA Heparin/PF4 antibody test (DiaMed AG)[56,68,69] (Table 3). Both of these assays detect all classes of immunoglobulin. The sensitivity of the GTI-PF4 assay was 100% (if negative, HIT ruled out), whereas the specificity (82%-85%) was lower. Thus, many patients with positive tests, particularly those with moderate or low pretest

Table 3—*[Overview of HIT] Comparison of Commercial Antigen Assays With Reference Standard Assays*

Study/Year	Population	Intervention	Comparator	Outcomes	Comments, %
Bakchoul et al[68]/2009	500 consecutive surgical and medical patients with suspected HIT	GTI-PF4 polyanion ELISA (OD > 0.4 units) PaGIA (DiaMed) (positive/negative)	HIPA Clinical assessment: 4Ts score (Greifswald modification) HIT positive = HIPA positive and high or intermediate 4Ts score	GTI-PF4 ELISA TP 35 of 35 TN 376 of 465 FP 89 of 124 FN 0 of 376 PaGIA TP 33 of 35 TN 408 of 465 FP 57 of 90 FN 2 of 410	GTI-PF4 ELISA PPV = 28 NPV = 100 Sens = 100 Spec = 81 PaGIA PPV = 37 NPV = 99 Sens = 94 Spec = 88
Warkentin et al[69]/2008	417 consecutive patients with suspected HIT (excludes 18 patients with indeterminate SRA or insufficient sample for ELISA testing)	GTI-PF4 polyanion ELISA (OD > 0.4 units)	SRA (positive > 50% release) HIT positive = SRA pos	GTI-PF4 ELISA TP 41 of 41 TN 309 of 364 FP 55 of 96 FN 0 of 309	GTI-PF4 ELISA PPV = 43 NPV = 100 Sens = 100 Spec = 85
Pouplard et al[56]/2007	213 consecutive patients with suspected HIT	GTI-PF4 polyanion ELISA (OD > 0.4 units) PaGIA (DiaMed) (positive/negative) Clinical assessment: 4Ts score	SRA (positive > 20% release) HIT positive = SRA pos	GTI-PF4 ELISA TP 22 of 22 TN 156 of 191 FP 35 of 57 FN 0 of 156 PaGIA TP 21 of 22 TN 175 of 191 FP 16 of 37 FN 1 of 176	GTI-PF4 ELISA PPV = 39 NPV = 100 Sens = 100 Spec = 82 PaGIA PPV = 57 NPV = 99 Sens = 95 Spec = 92

ELISA = enzyme-linked immunosorbent assay; FN = false negative; FP = false positive; GTI = Genetics Testing Institute; HIPA = heparin-induced platelet activation; NPV = negative predictive value; PF4 = platelet factor 4; PPV = positive predictive value; Sens = sensitivity; Spec = specificity; SRA = serotonin release assay; TN = true negative; TP = true positive. See Table 1 legend for expansion of other abbreviation.

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probability, will not have HIT. The sensitivity of the PaGIA is lower than the GTI-PF4 (94%-95%), and the specificity is higher (88%-92%) than the GTI-PF4.

In summary, both of these antigen assays can exclude a diagnosis of HIT, but neither assay is ideal as a stand-alone test to confirm the diagnosis of HIT. A negative ELISA or PaGIA in a patient with a low pretest probability of HIT excludes the diagnosis of HIT. A positive ELISA or PaGIA in a patient with a low pretest probability of HIT should not be interpreted as diagnostic for HIT and requires confirmation with a functional assay.

1.2.5 Commercially Available ELISA Using Manufacturer's Optical Density Threshold Compared With an Elevated Optical Density Threshold: There is a correlation between the strength of the reaction with an ELISA (measured using optical density units [OD]) and the likelihood of clinical HIT.[70,71] Three studies have addressed the question (retrospectively) of whether raising the OD threshold that is used to define a positive result with an ELISA would improve the specificity of the assay.[69,70,72] All three used the GTI-PF4 assay, which detects all classes of immunoglobulin (positive threshold set at 0.40 OD) (Table 4). Two of the studies showed that raising the OD threshold to 1.0 increased the likelihood of a positive SRA result (specificity increased from 85% to 95%)[69] and increased the likelihood of new thromboembolic events (24% of patients at a threshold of 0.40 OD had a new thrombotic event compared with 59% at a threshold of 1.0 OD).[70] The third study showed that increasing the threshold of the GTI-PF4 to 1.20 OD and combining it with an intermediate or high 4Ts score identified all of the same HIT-positive patients as the SRA alone.[72]

In summary, it appears that the combination of a threshold > 1.0 OD with a high clinical suspicion for HIT (eg, intermediate or high 4Ts score) may have a similar accuracy for diagnosing HIT as the reference standard assay (SRA). However, this strategy requires validation in prospective studies.

For laboratories using the GTI-PF4 ELISA, we suggest reporting the quantitative value of the test result, together with the threshold used to define a positive result, over reporting the result only as positive or negative. For clinicians ordering the GTI-PF4 ELISA to determine whether a patient has HIT, we suggest taking into consideration both the pretest probability of HIT and the quantitative level of the GTI-PF4 ELISA result. A GTI-ELISA result between 0.40 and 1.0 OD in a patient with a low or moderate pretest probability for HIT should, if possible, be confirmed with a functional assay.

2.0 Screening for HIT

2.1 Platelet Count Monitoring Combined With the 4Ts Score for Patients Receiving Heparin/LMWH

Platelet count monitoring is warranted when the benefits of early diagnosis and treatment of HIT exceed the potential harms of frequent platelet count monitoring, including cost, unnecessary anxiety and additional testing, unnecessary withdrawal of heparin, and the use of nonheparin anticoagulants with a higher bleeding risk. No studies have directly addressed the issue of whether advantages of platelet monitoring outweigh the disadvantages in patients receiving UFH/LMWH. Three retrospective studies showed a low rate of compliance with platelet count monitoring recommendations (4%-42%), a low rate of testing

Table 4—*[Overview of HIT] Studies Comparing Different OD Threshold Levels for Commercial ELISAs*

Study/Year	Study Samples	Participants	Outcome	ELISA OD
Warkentin et al[69]/2008	41 patients identified as HIT positive by SRA	HITT (n = 19) HIT (n = 22)	Frequency SRA positive ≥ 50% release (95% CI)	PF4/hep polyanion ELISA (GTI)
			0% (0-1.2)	OD < 0.4
			3% (0.1-14.2)	OD 0.4-1.0
			18% (2.3-51.8)	OD 1.0-1.4
			50% (18.7-81.3)	OD 1.4-2.0
			89% (74.6-97)	OD > 2.0
Lo et al[72]/2007	16 patients identified as HIT positive according to different definitions (of laboratory and clinical criteria)	Classic HIT: SRA > 50% +, GTI-PF4 ELISA > 0.40 +, IgG ELISA > 0.45 +, 4Ts high or intermediate	Clinical Events 11 of 16 (69%) TECs (2 TEC postdiagnosis)	PF4/hep polyanion ELISA (GTI) Median, 2.39 (IQR, 2.09-2.70)
		Liberal HIT: (GTI-PF4 ELISA > 0.40)	12 of 32[a] (37%) TECs (2 TEC postdiagnosis)	Median, 0.89 (IQR, 0.54-1.13)
		Modified conservative: GTI-PF4 ELISA > 1.20 + 4Ts high or intermediate	Identified same 16 patients as classic HIT definition	Median, 2.39 (IQR, 2.09-2.70)
Zwicker et al[70]/2004	63 patients identified as HIT positive by PF4/hep polyanion ELISA (OD > 0.40) with clinical criteria determined by laboratory[b]	Within 30 d[c]	Clinical events	PF4/hep polyanion ELISA (GTI)
		Thrombosis (n = 23)	OD > 1: 59% TECs OD < 1: 24% TECs (P = .01)	Mean, 1.41; SD, 0.87
		No thrombosis (n = 40)	OD > 1: 36% TECs OD < 1: 9% TECs (P = .07); OR, 5.7; 95% CI, 1.7-19.1	Mean, 0.80; SD, 0.46

IQR = interquartile range; OD = optical density; TEC = thromboembolic complication.

[a]Includes 16 patients identified by the classic HIT definition and an additional 16 patients (one of the additional patients had a TEC).

[b]Recent platelet count < 150×10^9/L, platelet count of ≥ 50% in setting of heparin therapy or a prior history of HIT.

[c]Includes the 15 patients initially diagnosed with HITT and eight patients with HIT who developed thrombosis within 30 d of diagnosis with HIT.

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for HIT antibodies in patients who became thrombocytopenic (5%-19%), and a low rate of initiation of a nonheparin anticoagulant when the suspicion of HIT was high enough to warrant laboratory testing (0%-55%).[73-75]

The findings of the above studies suggest previous recommendations for platelet monitoring have not been widely implemented.[76] Furthermore, when platelet count monitoring is done and platelets drop, heparin is not necessarily stopped nor is a nonheparin anticoagulant started. Possible reasons for these findings include the burden of platelet count monitoring, the limited availability of laboratory assays for serological confirmation of HIT, expense associated with using nonheparin anticoagulants, and a lack of awareness of the guidelines.

We conducted a decision analysis to determine the reduction in HIT-related thrombotic events that could be achieved in an ideal setting if the recommendations for platelet count monitoring, laboratory testing for HIT, and initiation of a direct thrombin inhibitor (DTI) were all followed. To reduce the potential for expensive testing and inappropriate treatment of patients with a low clinical probability of HIT, we assumed that platelet count monitoring would be done as part of a clinical assessment of the patients' probability of HIT using the 4Ts score (see Table 5 for key model assumptions; Table 6 for data sources and model inputs). Table 7 outlines the summary of findings for this decision analysis.

This decision analysis shows that, in an ideal setting, for every 1,000 patients screened with platelet count monitoring and application of the 4Ts Score, the best estimate suggests one episode of thrombosis will be prevented, at the cost of one major bleeding event (although CIs for both thrombosis and bleeding overlap no effect) (Table 7). Both the baseline risk of thrombosis (ie, patient population and type of heparin) (see Table 2) and the availability of the HIT assays influence the benefit-to-risk ratio of platelet count monitoring. Clinical centers that do not have access to the reference standard assays will have a higher number of false-positive results and consequently a higher proportion of major bleeding events (ie, when the ELISA is the only HIT assay available, two episodes of thrombosis are prevented at the cost of 2.6-11.7 major bleeding events for every 1,000 patients screened).

Another factor that influences the feasibility of platelet monitoring with 4Ts screening is the cost. Although individual platelet counts are inexpensive, the cost of the HIT assays and nonheparin anticoagulants can be substantial (eg, in a formal cost-effectiveness analysis the cost of treating one patient with HIT with argatroban for 5 days was estimated at $3,500-$4,500 in the United States 2004 prices).[77] The estimated cost in 2011, for the drug alone, for 5 days is $5,000 US.

The issues with respect to platelet count monitoring outlined above were discussed at the American College of Chest Physicians meeting in February 2011. Criticisms of the decision analysis included the use of bleeding estimates based on doses of argatroban that are no longer used, delay in obtaining prompt results even at centers that have the SRA or HIPA available, and the potential for harm in missing cases of HIT

Table 5—*[Section 2.1.1] Key Model Assumptions for Platelet-Monitoring Decision Analysis*

Platelet count monitoring is intended to identify patients with isolated HIT; therefore, patients who initially present with HIT-related thrombosis were excluded.
Patients with a moderate or high 4Ts score will have heparin discontinued, an ELISA ordered, and argatroban started, whereas patients with a low 4Ts score will be assumed not to have HIT and will continue to receive heparin.
Patients with a positive ELISA will have an SRA performed for confirmation.
Patients with a positive SRA will continue to receive treatment with argatroban, and patients with a negative SRA will resume prophylaxis with heparin (assuming 100% sensitivity and specificity of the SRA for HIT).
The results of the HIT assays are available within 24 h of being ordered.

See Table 1 and 3 legends for expansion of abbreviations.

Table 6—*[Section 2.1.1] Data Sources and Model Inputs for Platelet Monitoring Decision Analysis*

We selected a high-risk setting for HIT for this analysis: postoperative orthopedic surgery patients who are receiving UFH for thromboprophylaxis (incidence of HIT > 1%).[14] The likelihood ratios for low, moderate, and high 4Ts scores were derived from the study by Lo et al.[51] The sensitivity and specificity of the ELISA were assumed to be 100% and 86%, respectively.[15,52]
The assumptions for rates of thrombosis are as follows: (A) Thrombosis rate in patients with HIT who received argatroban = argatroban arm of a pooled analysis of historical controlled studies (0.069).[76] (B) Thrombosis rate in patients with HIT who did not receive argatroban = control group of a pooled analysis of historical controlled studies (0.224).[76] (C) Thrombosis rate in patients without HIT who did not receive argatroban = 1 of 37 of assumption (B) because HIT is reported to increase the risk of thrombosis by 37-fold (0.22/37 = 0.0059).[3] (D) Thrombosis rate in patients without HIT who were treated with argatroban = one-third of Assumption (C) as derived from the hazard ratio in patients treated with argatroban (0.002).[76]
HIT was assumed not to influence the major bleeding rate independently of treatment with nonheparin anticoagulants. Consequently, the major bleeding rate in those treated with argatroban was the same as the major bleeding rate in patients with HITT treated with argatroban in the pooled argatroban studies (0.08), and the major bleeding rate in those who were untreated was the same as the major bleeding rate in the control arm of the pooled argatroban studies (0.022).[76] Sensitivity analyses were performed using different sensitivities and specificities for the ELISA and SRA, and different assay availability (ie, only ELISA available, no HIT assays available).

UFH = unfractionated heparin. See Table 1 and 3 legends for expansion of other abbreviations.

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Table 7—*[Section 2.1.1] Summary of Findings for Platelet Count Monitoring Decision Analysis: Should Platelet Count Monitoring Be Performed in Patients Who Receive Heparin or LMWH for ≥ 5 d?*

Outcomes	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect	Anticipated Absolute Effects, Time Frame for All Outcomes 30 d: Risk Without Monitoring	Anticipated Absolute Effects, Time Frame for All Outcomes 30 d: Risk Difference With Monitoring
New thrombosis	No studies available	Very low due to uncertainty of model assumptions	RR, 0.82-0.84	SRA and ELISA both available	
				8.2 thrombotic events per 1,000	1.3-1.4 fewer thrombotic events per 1,000
			RR, 0.73-0.80	Only ELISA available	
				8.2 thrombotic events per 1,000	1.6-2.2 fewer thrombotic events per 1,000
Major bleeding	No studies available	Very low due to uncertainty of model assumptions	RR, 1.02-1.05	SRA and ELISA both available	
				22 bleeding events per 1,000	0.5-1 more bleeding events per 1,000
			RR, 1.12-1.53	Only ELISA available	
				22 bleeding events per 1,000	2.6-11.7 more bleeds per 1,000

The basis for the risks are provided in Tables 5 and 6. The anticipated absolute effect is expressed as risk difference, and is based on the baseline risk in the comparison group and the relative effect of the intervention. High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. GRADE = Grades of Recommendations, Assessment, Development, and Evaluation; RR = risk ratio.

if platelet count monitoring is not performed. The attendees voted in favor, by a small margin, of providing specific recommendations regarding platelet count monitoring despite the uncertainty of the benefit-to-risk ratio of this practice. It should be noted that for each of the recommendations below, > 20% of the attendees voted in the opposite direction.

Recommendations

2.1.1. For patients receiving heparin in whom clinicians consider the risk of HIT to be > 1% (Table 2), we suggest that platelet count monitoring be performed every 2 or 3 days from day 4 to day 14 (or until heparin is stopped, whichever occurs first) (Grade 2C)**.**

2.1.2. For patients receiving heparin in whom clinicians consider the risk of HIT to be < 1% (Table 2), we suggest that platelet counts not be monitored (Grade 2C)**.**

2.2 Platelet Count Monitoring in Patients Recently Treated With Heparin/LMWH

Platelet count monitoring for HIT in patients who have recently been exposed to heparin or LMWH differs from that described above because the timing of onset of HIT in these patients differs. If a patient still has circulating HIT antibodies from a previous exposure to heparin (typically within the past 30-100 days), re-exposure can lead to a large platelet count fall within 24 h.[36] As with typical-onset HIT, there are no studies evaluating the benefit-to-risk ratio of this approach. Obtaining a baseline platelet count prior to initiating anticoagulant therapy for a patient with VTE is considered standard medical practice; however, obtaining a platelet count 24 h later can be difficult because of the widespread use of outpatient LMWH therapy.

Statement 2.2: For patients exposed to heparin within the past 100 days, we suggest that a baseline platelet count be obtained prior to starting heparin or LMWH therapy, and that a repeat platelet count should be drawn 24 h later, if feasible.

2.3 Platelet Count Monitoring in Patients With Acute Inflammatory Reactions After IV Heparin Bolus

Rarely, a patient who is given an IV heparin bolus will develop an acute inflammatory reaction (eg, fever, chills) and/or cardiorespiratory symptoms (eg, hypertension, tachycardia, dyspnea, chest pain, cardiorespiratory arrest) within 30 min of drug administration. These acute systemic reactions are strongly suggestive of acute HIT.[48]

Statement 2.3: For patients who present with acute systemic reactions within 30 min of an IV heparin bolus, we suggest performing a platelet count.

3.0 Management of HIT Complicated by Thrombosis

3.1 Discontinue Heparin or Initiate VKA vs Treatment With Nonheparin Anticoagulants

The first step in the treatment of HIT complicated by thrombosis (HITT) is discontinuation of all forms of heparin and LMWH (including heparin flushes and heparin-coated catheters). Whether taking this step alone is enough to prevent further thrombotic

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Table 8—*[Section 3.1] Summary of Findings for Argatroban for Treatment of HITT: Should Patients With HITT Receive Argatroban Over Discontinuing Heparin and/or Starting a VKA?*

Outcomes	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects, Time Frame 37 d for All Outcomes	
				Risk With Discontinue Heparin/Start VKA	Risk Difference With Argatroban (95% CI)
Death due to thrombosis[a]	419 (2 cohorts) 37 d[b]	Very low due to risk of bias and imprecision	RR, 0.12 (0.05-0.34)	152 deaths per 1,000	134 fewer deaths per 1,000 (from 100 fewer to 145 fewer)
Limb amputation	419 (2 cohorts) 37 d[b]	Very low due to risk of bias and imprecision	RR, 1.26 (0.53-2.99)	109 amputations per 1,000	28 more amputations per 1,000 (from 51 fewer to 216 more)
New thrombosis	419 (2 cohorts) 37 d[b]	Moderate due to risk of bias, but with large effect	RR, 0.45 (0.28-0.71)	348 thrombotic events per 1,000	191 fewer thrombotic events per 1,000 (from 101 fewer to 250 fewer)
Major bleeding[c]	419 (2 cohorts) 37 d[b]	Very low due to risk of bias and imprecision	RR, 3.70 (0.52-26.5)	22 major bleeding events per 1,000	59 more major bleeding events per 1,000[d] (from 10 fewer to 554 more)

The anticipated absolute effect is expressed as risk difference (and its 95% CI) and is based on the baseline risk in the comparison group and the relative effect of the intervention (and its 95% CI). For evidence profile, see Table S3. High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. PRBC = packed RBCs. See Table 1 and 7 legends for expansion of other abbreviations.

[a]As judged by the investigators

[b]Follow-up was 30 d past cessation of treatment in patients receiving argatroban and 37 d from baseline in control patients.

[c]Defined as a hemoglobin drop of at least 20 g/L or requirement for 2 units of PRBC or an intracranial hemorrhage or a bleed into a joint.

[d]There were three fatal bleeding events in patients who received argatroban (HIT and HITT combined).

complications secondary to HITT has been evaluated in pooled analyses of prospective cohort studies with historical controls.[76,78] DTIs lepirudin and argatroban have each been compared with historical controls who received the best available care at the time.[79-83] (Tables 8, 9). In the majority of cases, best available care consisted of discontinuation of heparin alone or substitution of heparin with a VKA. An overview of the methodology of these studies is available in Table S1 (tables that contain an "S" before the number denote supplementary tables not contained in the body of the article and available instead in an online data

Table 9—*[Section 3.1] Summary of Findings for Lepirudin for Treatment of HITT: Should Patients With HITT Receive Lepirudin Over Discontinuing Heparin and/or Starting a VKA?*

Outcomes	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects, Time Frame 35 d for All Outcomes	
				Risk With Discontinue Heparin/Start VKA	Risk Difference With Lepirudin (95% CI)
Limb amputation	289 (3 cohorts) 35 d	Very low due to risk of bias and imprecision	RR, 0.70 (0.27-1.8)	80 amputations per 1,000	24 fewer amputations per 1,000 (from 58 fewer to 64 more)
New thrombosis	289 (3 cohorts) 35 d	Moderate due to risk of bias, but with large effect	RR, 0.28 (0.15-0.52)	253 thrombotic events per 1,000	182 fewer thrombotic events per 100[a] (from 122 fewer to 215 fewer)
Major bleeding[b]	289 (3 cohorts) 35 d	Very low due to risk of bias and imprecision	RR, 2.31 (0.94-5.71)	67 major bleeding events per 1,000	87 more major bleeding events per 1,000[c] (from 4 fewer to 314 more)

The anticipated absolute effect is expressed as risk difference (and its 95% CI) and is based on the baseline risk in the comparison group and the relative effect of the intervention (and its 95% CI). For evidence profile, see Table S4. High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. See Tables 1, 7, and 8 for expansion of abbreviations.

[a]There were three deaths due to thrombosis in patients who received lepirudin (HITT and HIT combined).

[b]Defined as a fatal bleeding event or an intracranial hemorrhage or a bleeding event that led to permanent disability or requirement for 2 units of PRBC.

[c]There were five fatal bleeding events in patients who received lepirudin (HITT and HIT combined).

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supplement; see the "Acknowledgments" for more information).

From these pooled analyses, we conclude that both agents may be more effective at preventing new thrombosis than discontinuing heparin alone or substituting heparin with a VKA (lepirudin: relative risk [RR], 0.28; argatroban: RR, 0.45). Although the total number of thrombotic events is small, the well-established need for a thrombin inhibitor in patients with acute thrombosis (see Kearon et al[84] in this supplement) and the effectiveness of these agents as anticoagulants in other settings[85-88] was the basis for rating the evidence for this outcome as moderate. Major bleeding may be more likely with lepirudin and argatroban than substituting heparin with a VKA (lepirudin 15.4%, argatroban 8%), and it is unlikely that either agent reduces the risk of limb amputation. Death due to thrombosis (as determined by the investigators) was significantly reduced by argatroban (RR, 0.12), but we are unable to comment on the impact of lepirudin on this outcome because it was not reported separately for patients with HITT (there were a total of three deaths due to thrombosis in the lepirudin trials). Fatal bleeding events were not reported separately for patients with HITT for either nonheparin anticoagulant (five fatal bleeding events out of 403 patients [1.2%] who received lepirudin, and three fatal bleeding events out of 722 patients [0.4%] who received argatroban).

There are no studies comparing danaparoid with discontinuation of heparin alone or substituting heparin with a VKA. However, given the efficacy of danaparoid in treating HITT (reviewed in section 3.2), we have included danaparoid in the recommendation for this section.

Recommendation

3.1. In patients with HITT, we recommend the use of nonheparin anticoagulants, in particular lepirudin, argatroban, and danaparoid, over the further use of heparin or LMWH or initiation/continuation of VKA (Grade 1C)**.**

3.2 Choice of Nonheparin Anticoagulants in Patients With HITT

Inhibition of thrombin generated by HITT can be achieved with DTIs, such as lepirudin (recombinant hirudin), desirudin (recombinant hirudin), argatroban, or bivalirudin, or indirect factor Xa inhibitors, such as danaparoid or fondaparinux. All of these agents have been used to treat patients with HITT, but there are no high-quality prospective head-to-head trials comparing one agent with another. Table 10 presents a comparison of the properties of these five agents.

3.2.1 Normal Renal Function: Argatroban and Lepirudin: The highest level of evidence for argatroban and lepirudin comes from pooled analyses of their respective historical controlled trials as reviewed in section 3.1 (Tables 8, 9). We did not compare the efficacy and safety of argatroban with lepirudin in an evidence profile (using the data from these trials) for the following reasons: (1) because the lepirudin trials required laboratory confirmation of HIT, whereas the argatroban trials did not, results may overestimate the

Table 10—*[Sections 3.2 and 4.2]: Characteristics of Anticoagulants Used to Treat Patients with HIT*

Characteristic	Lepirudin	Argatroban	Danaparoid	Bivalirudin	Fondaparinux
Target	Thrombin	Thrombin	Factor Xa (predominantly)	Thrombin	Factor Xa
Half-life	80 min	40-50 min	24 h	25 min	17-20 h
Elimination	Renal	Hepatobiliary	Renal	Enzymatic (80%) Renal (20%)	Renal
Approved for patients with HIT[a]	Treatment	Treatment/PCI	Treatment	PCI/cardiac surgery	No
Method of administration	IV, SC	IV	IV, SC	IV	SC
Monitoring	aPTT	aPTT	Anti-Xa level	aPTT	Anti-Xa level
	ECT (high doses)	ACT		ACT or ECT (high doses)	
Effect on INR	+	+++	0	++	0
Immunologic features	40%-60% lepirudin Ab[b]	None	5% cross-reactivity with HIT Ab[c]	Potentially cross-reactive with anti-lepirudin Ab	May cause HIT[d]
Antidote available	No	No	No	No	No
Crosses placenta	Unclear[e]	Unclear[e]	No[e]	Unclear[e]	Yes[e]
Dialyzable	High-flux dialyzers	20%	Yes	25%	20%

Ab = antibodies; ACT = activated clotting time; aPTT = activated partial thromboplastin time; ECT = ecarin clotting time; FDA = US Food and Drug Administration; INR = international normalized ratio.

[a]In some countries (check with local health regulatory authorities).

[b]Fatal anaphylaxis has been reported; therefore, patients should only be treated once with this agent.

[c]Clinical significance is uncertain and routine testing for cross-reactivity is not recommended.

[d]Case reports only.

[e]FDA pregnancy category B.

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efficacy of argatroban as patients who do not have HIT are less prone to thrombosis than patients who have HIT; (2) because lepirudin was given for a mean of 15.8 days, whereas argatroban was given for a mean of 6.6 days, results may overestimate the rate of bleeding with lepirudin; and (3) because the proportion of patients who were transitioned to a VKA was lower in the argatroban trials (62%) than in the lepirudin trials (83%), results may overestimate the efficacy of lepirudin because patients who are safely transitioned to VKA are less likely to have thrombotic events.[76,89] An overview of the methodology of these studies is available in the online data supplement (Table S1).

Argatroban and lepirudin have been directly compared in small retrospective cohort studies.[90-92] However, comparison across these studies is problematic because the primary outcome measure differed, and the outcomes we have identified as important were not consistently reported. However, two of these studies contribute to our understanding of the bleeding risk of these two agents. Kiser et al[90] reported that important bleeding occurred in 6% of patients taking argatroban and 5% of patients taking lepirudin, and Smythe et al[91] observed important bleeding in 11.5% of patients taking lepirudin and 10.3% of patients taking argatroban. The doses of argatroban and lepirudin given in these retrospective cohorts were lower than the doses given in the historical controlled trials.

Danaparoid: (Please note: danaparoid was withdrawn from the US market by the manufacturer in 2002; it remains available in other markets.) The highest level of evidence supporting the use of danaparoid for treatment of HITT comes from one randomized controlled trial (RCT),[93] (Table 11, Table S2) and two retrospective cohort studies with historical control subjects.[94,95] In the RCT, danaparoid (plus warfarin) as compared with dextran 70 (plus warfarin) in 42 patients was associated with a trend toward reduced recurrent thrombosis (RR, 0.30; $P = .063$) without increasing the risk of major bleeding.[93] Dextran 70 is a weak antithrombotic agent that has been used for thromboprophylaxis following surgery, and it was the only rapidly acting nonheparin antithrombotic available in Australia at the time of the study. Major limitations of this RCT include a subjective primary efficacy outcome measure and open-label design.

Farner et al[94] reported on 124 patients with HITT enrolled in the first two lepirudin historical controlled trials[79,80] and 91 patients with HITT who received nonprotocolized danaparoid.[94] Comparison of the individual outcomes of interest in patients with HITT in this study is problematic because not all patients with HITT received therapeutic doses of a nonheparin anticoagulant (lepirudin 84.7%, danaparoid 52.8%) and not all outcomes of interest were reported. Rates of recurrent thrombosis were similar (lepirudin 7.9%, danaparoid 9.4%; $P = .74$), and bleeding requiring two or more units of packed RBC occurred more frequently with lepirudin (8.1%) than danaparoid (2.3%); however, lepirudin was more frequently given at a therapeutic dose.

Lubenow et al[95] reported that patients with HIT who received therapeutic doses of danaparoid (with or without a VKA) in comparison with historical controls who received the defibrinogenating snake venom ancrod (with or without VKA) significantly reduced both the risk of new thrombosis (RR, 0.41) and major bleeding (RR, 0.38) (Table 12, Table S1).[96,97]

Desirudin: The highest quality of evidence supporting desirudin for treatment of HITT comes from an open-label randomized trial comparing fixed doses of this agent (30 mg bid) with argatroban.[98] This study was terminated after eight patients were enrolled in each arm due to poor accrual. None of the five patients with laboratory-confirmed HITT (or HIT) in the desirudin arm experienced recurrent VTE or major bleeding.

Bivalirudin: The highest level of direct evidence supporting bivalirudin for treatment of HITT comes from case series (with the largest published only as an abstract).[99-101]

Fondaparinux: The highest quality of evidence supporting fondaparinux for treatment of HITT comes from one small prospective cohort with historical controls[97] and one retrospective cohort with historical controls[96] (Table 12, Recommendation 3.2.1; Table S1, Recommendations 3.1, 3.2.1, 4.1, and 4.2). Lobo et al[97] reported that neither six patients with HITT who were treated with a weight-based dose of fondaparinux nor eight patients treated with DTIs (lepirudin or argatroban) experienced recurrent VTE or major bleeding. Grouzi et al[96] reported that neither 24 patients with HITT who were treated with a weight-based dose of fondaparinux nor a historical control group of 20 patients treated with lepirudin experienced recurrent VTE or major bleeding.

The literature includes three case reports of possible fondaparinux-induced HIT,[102-104] one case in which fondaparinux appeared to exacerbate HIT caused by heparin,[105] and a fifth case in which prophylactic fondaparinux failed to prevent the development of delayed HIT.[106] Although the quality of the evidence for fondaparinux-induced HIT is of low quality and experts dispute its existence, the quality of the evidence in favor of fondaparinux as a treatment of HIT is also very low quality. The use of argatroban, lepirudin, and danaparoid to treat patients with HITT is supported by studies with less risk of bias. There is no published evidence to support the use of novel anticoagulants (such as rivaroxaban or dabigatran) for the treatment of HITT.

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Table 11—*[Section 3.2.1] Description of Randomized Controlled Trials Comparing Nonheparin Anticoagulants for Treatment of HITT*

Study/Year	Type of Study	Participants	Intervention	Outcomes	Follow-up	Results
Chong et al[93]/2001; Warkentin et al[76]/2008	RCT, multicenter, open-label	42 patients with clinical diagnosis of HIT[a] (platelets $\leq 100 \times 10^9$/L and TEC)	Danaparoid 2,400 anti-Xa units IV (bolus) then 400 units/h × 2 h then 300 units/h × 2 h then 200 units/h for 5 d;[b] Warfarin 10 mg daily × 2 then 5 mg (n = 24)[c] OR	Proportion of initial TEC with complete clinical resolution[d]; Number of days for platelet counts to return to normal;	From start of treatment until discharge from hospital or death	Amputation: Danaparoid 1 of 24 (4.2%) Dextran 3 of 17 (17.6%) RR: 0.24 (0.03-2.08); $P = .29$
		Stratified according to mild or severe thrombosis	Dextran 1,000 mL IV on day 1 then 500 mL daily for 4 d; Warfarin 10 mg daily × 2 then 5 mg (n = 17)	Overall clinical response to treatment[d]		New thrombosis: Danaparoid 3 of 24 (12.5%) Dextran 7 of 17 (41.2%) RR: 0.30 (0.09-1.01); $P = .063$
						Major bleeding: none
						Death (all-cause): Danaparoid 3 of 24 (12.5%) Dextran 4 of 17 (23.5%) RR: 0.53 (0.14-2.07); $P = .61$
						Death (thrombosis[d]): Danaparoid 1 of 24 (4.2%) Dextran 3 of 17 (17.6%) RR: 0.24 (0.03-2.08); $P = .37$

See Table 1, 4, and 7 legends for expansion of abbreviations.

[a]HIT confirmed by laboratory testing in 76% of patients given danaparoid and 88% of patients given dextran.

[b]No anticoagulant monitoring was performed.

[c]Excluded one patient in danaparoid group who did not meet inclusion criteria.

[d]Subjective assessment by investigators.

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Table 12—*[Section 3.2.1] Description of Cohort Studies Comparing Nonheparin Anticoagulants for Treatment of HITT*

Study/Year	Type of Study	Participants	Intervention	Outcomes	Follow-up	Results
Grouzi et al[96]/2010	Cohort, historical controls, retrospective	Patients diagnosed with HIT (all confirmed with PF4/H ELISA (Stago) and PaGIA (DiaMed); all had thrombosis)	Fondaparinux 5 mg SC od (< 50 kg), 7.5 mg SC od (50-100 kg), 10 mg SC od (> 100 kg) Lepirudin 0.15 mg/kg/h	Complications: death, limb amputation, new TEC, venous gangrene Major bleeding defined as overt and associated with Hb drop ≥ 2 g/dL, transfusion ≥ 2 units, RPH, ICH, or critical organ or fatal Platelet count recovery Successful bridging to VKA	2 y	Amputations: Fondaparinux 0 of 24[a] Lepirudin 0 of 20 New thrombosis: Fondaparinux 0 of 24 Lepirudin 0 of 20 Major bleeding: Fondaparinux 0 of 24 Lepirudin 0 of 20 Death (all-cause):[b] Fondaparinux 1 of 24 (4.2%) Lepirudin 2 of 20 (10%) Death (thrombosis): Fondaparinux 0 of 24 Lepirudin 0 of 20 All had platelet recovery and successful bridging to VKA
Lubenow et al[95]/2006; Warkentin et al[76]/2008	Cohort, historical controls, multicenter, retrospective	62 patients with HIT[c] and an indication for ongoing therapeutic anticoagulant therapy[d] who received danaparoid with or without a VKA (1993-1999) 56 patients with HIT[c] and an indication for ongoing therapeutic anticoagulant therapy[d] who received ancrod with or without a VKA (1986-1993)	Danaparoid at least 3,000 anti-Xa units IV or SC in first 24 h[e] (53 patients also received VKA) OR Controls Ancrod IV or SC to reduce fibrinogen to < 0.5 g/L or at least 70 units per 24 h (18 received VKA alone and 31 received ancrod + VKA[g])	Composite of new or progressive TEC, and/or amputation, and/or thrombotic death Major bleeding[f]	From start of treatment until day 7 of treatment of primary efficacy and major bleeding Secondary: same outcome measures at day 35	At day 35: Amputation Danaparoid 3 of 62 (4.8%) Controls 4 of 56 (7.1%) RR: 0.68 (0.16-2.90); $P = .71$ New thrombosis Danaparoid 11 of 62 (17.7%) Controls 24 of 56 (42.9%) RR: 0.41 (0.22-0.77); $P = .004$ Major bleeding Danaparoid 8 of 62 (12.9%) Controls 19 of 56 (33.9%) RR: 0.38 (0.18-0.80); $P = .008$ Death (all-cause):[h] Danaparoid 6 of 62 (9.7%) Controls 8 of 56 (14.3%) RR: 0.68 (0.25-1.83); $P = .63$ Death (thrombosis): Danaparoid 2 of 62 (3.2%) Controls 3 of 56 (5.3%) RR: 0.60 (0.10-3.47); $P = .91$

(Continued)

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Table 12—*Continued*

Study/Year	Type of Study	Participants	Intervention	Outcomes	Follow-up	Results
Lobo et al[97]/2008	Cohort, historical controls, prospective	Patients with a diagnosis of HIT (14 had HITT; 3 had HIT) (all had HIT confirmed with heparin PF4 antibody test)	Fondaparinux 5 mg SC od (< 50 kg), 7.5 mg SC od (50-100 kg), 10 mg SC od (> 100 kg) for HITT; 2.5 mg SC od for HIT (n = 1) for at least 7 d or until INR therapeutic for 2 consecutive days[i] Historical controls DTI: lepirudin (n = 6) or argatroban (n = 4) according to FDA-approved monograph	Platelet recovery with definition dependent on presence or absence of thrombocytopenia 1 day prior to treatment Complications: death, limb amputation, new TEC, venous gangrene Major bleeding defined as overt and associated with Hb drop ≥ 2g/dL, transfusion ≥ 2 units, or fatal Successful bridging to VKA: INR 2-3 for two consecutive days while not receiving a DTI	4 wk after discontinuation of fondaparinux	Amputations: Fondaparinux 1 of 7 (14%) DTI 1 of 10 (10%) New thrombosis: Fondaparinux 0 of 7 DTI 0 of 10 Major bleeding: Fondaparinux 0 of 7 DTI 0 of 10 Death (all-cause): Fondaparinux 0 of 7 DTI 2 of 10 (20%) Platelet recovery: Fondaparinux 7 of 7 (100%) DTI 8 of 10 (80%) Successful bridging to VKA: Fondaparinux 2 of 6 (33%) DTI 0 of 10 (0%)

DTI = direct thrombin inhibitor; Hb = hemoglobin; ICH = intracranial hemorrhage; od = once daily; RPH = retroperitoneal hemorrhage. See Table 1, 3, 4, 7, and 10 for expansion of other abbreviations.

[a]One patient in the fondaparinux arm and two patients in the lepirudin arm developed venous gangrene before the study drug was started.

[b]None was classified as secondary to HIT.

[c]HIT confirmed by SRA or heparin-induced platelet activation assay.

[d]HITT at baseline: danaparoid 89% and ancrod 91%.

[e]Dosing of danaparoid varied.

[f]Fatal or life-threatening bleeding or bleeding into a vital organ or that resulted in a hemoglobin fall of > 20 g/L or required 2 or more units of PRBC or bleeding that required an operative intervention.

[g]VKA was started when platelets were < 100×10^9/L in 81% of controls who received ancrod compared with 21% of danaparoid patients, which may have overestimated the efficacy of danaparoid.

[h]Fatal bleeding events: danaparoid 1, controls 2.

[i]Three patients received DTI for < 24 h prior to starting fondaparinux.

Recommendation

3.2.1. In patients with HITT who have normal renal function, we suggest the use of argatroban or lepirudin or danaparoid over other nonheparin anticoagulants (Grade 2C)**.**

Remarks: Other factors not covered by our analysis, such as drug availability, cost, and ability to monitor the anticoagulant effect, may influence the choice of agent.

3.2.2 Renal Insufficiency: Both lepirudin and danaparoid are renally cleared, but argatroban is not. Furthermore, there are retrospective, observational data to suggest that the use of lepirudin in renal failure is associated with an increased risk of major bleeding,[60,107] whereas a secondary analysis of the argatroban historical controlled trials did not show such a relationship.[108]

Recommendation

3.2.2. In patients with HITT and renal insufficiency, we suggest the use of argatroban over other nonheparin anticoagulants (Grade 2C)**.**

Dosing Considerations (modified from Warkentin et al[76]) Lepirudin—We suggest that the initial bolus either be omitted or, in the case of perceived life- or limb-threatening thrombosis, be given at a reduced dose (0.2 mg/kg). The initial infusion rate should be ≤ 0.10 mg/kg/h (in patients with serum creatinine < 90 μmol/L), with lower infusion rates for patients with higher serum creatinine levels (serum creatinine 90-140 μmol/L: starting infusion rate, 0.05 mg/kg/h; 140-400 μmol/L: starting infusion rate, 0.01 mg/kg/h; > 400 μmol/L: starting infusion rate, 0.005 mg/kg/h). Activated partial thromboplastin time (aPTT) monitoring should be performed at 4-h intervals until it is apparent that steady state within the therapeutic range (1.5-2.0 times patient baseline [or mean laboratory] aPTT) is achieved. (These dosing guidelines reflect modifications of the US Food and Drug Administration [FDA] labeling dosing guidelines due to concern about an increased risk of bleeding.[60,107])

Argatroban—We suggest an initial bolus be omitted, and that the initial infusion rate be ≤ 2 μg/kg/min IV. For patients who have heart failure, multiple organ system failure, or severe anasarca, or who are post cardiac surgery, we suggest beginning the initial infusion at a rate between 0.5 and 1.2 μg/kg/min, with subsequent q2h adjustments using the aPTT (target aPTT 1.5-3 times patient baseline). (These dosing guidelines reflect modifications of the FDA labeling dosing guidelines due to concern about an increased risk of bleeding.[109])

Danaparoid—We suggest an initial bolus IV (weight < 60 kg: 1,500 units; 60-75 kg: 2,250 units; 75-90 kg: 3,000 units; > 90 kg: 3,750 units) followed by infusion 400 units/h × 4 h then 300 units/h × 4 h then 200 units/h IV, adjusted subsequently according to anti-Xa levels (target, 0.5-0.8 anti-Xa U/mL).

Bivalirudin—We suggest no initial bolus and a starting infusion rate of 0.15-0.20 mg/kg/h IV (target, 1.5-2.5 times patient's baseline aPTT [or mean of laboratory normal range]).

Fondaparinux—We suggest for patients who weigh < 50 kg: 5.0 mg SC daily; for those who weigh 50-100 kg: 7.5 mg subcutaneously (SC) daily; for those who weigh > 100 kg: 10 mg SC daily.

3.3 Platelet Transfusions

Spontaneous bleeding is uncommon with HIT despite sometimes profound thrombocytopenia. However, patients with HIT may require invasive procedures for which a prophylactic platelet transfusion would normally be given to reduce the risk of bleeding. It has been widely reported that giving a platelet transfusion to a patient with HIT "adds fuel to the fire" and increases the risk of thrombosis.

Two case series reported in the mid to late 1970s suggest that platelet transfusions may exacerbate HIT.[110,111] In the first report, two out of five patients with suspected HIT received a single platelet transfusion, one of whom developed arterial thromboembolism post transfusion (while still receiving heparin).[110] In the second report, one out of 11 patients with suspected HIT received a platelet transfusion and had an inadequate increase in platelet count (but no thrombotic events).[111]

More recently, a case series reported 37 patients with PF4-ELISA-confirmed HIT who received one or more platelet transfusions during a 1-year period at a single center.[112] No thrombotic complications developed in any of the patients following platelet transfusion, and three deaths within a few days of transfusion were deemed unrelated to transfusion. Of the 37 patients, 23 patients had a high 4Ts score, and ELISA results suggesting that at least this many patients actually had HIT. HIT-related thrombosis was documented in eight patients prior to platelet transfusion; six received a platelet transfusion during thrombectomy and none experienced any further thrombotic complications (all six patients received argatroban).

In summary, there is no direct evidence supporting an increased risk of thrombosis in patients with HIT who are given platelet transfusions. However, the evidence is also too limited to support the safety of platelet transfusions.

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Recommendation

3.3. In patients with HIT and severe thrombocytopenia, we suggest giving platelet transfusions only if bleeding or during the performance of an invasive procedure with a high risk of bleeding (Grade 2C)**.**

3.4 Starting a VKA Before Platelet Recovery

Following treatment with a parenteral thrombin or factor Xa inhibitor, transition to a VKA (eg, warfarin) is required for longer-term anticoagulation (HIT-related thrombosis is considered provoked by a transient risk factor and should be treated for a minimum of 3 months; see Kearon et al[84]). The rapid initiation of warfarin in patients with HIT may produce a prothrombotic state because the level of the natural anticoagulant, protein C, falls faster than prothrombin levels. This can lead to serious adverse events, such as warfarin-induced skin necrosis and venous limb gangrene (distal ischemic limb necrosis in the absence of arterial occlusion).

Patients who develop venous limb gangrene typically have the following characteristics: (1) recent discontinuation of a parenteral anticoagulant that was being used to treat a DVT in the affected leg; (2) a supratherapeutic INR (due to a decrease factor VII, which parallels a drop in protein C), and (3) a platelet count $< 150 \times 10^9$/L (reflecting an ongoing prothrombotic state due to HIT).[46] There are no prospective studies comparing the incidence of adverse events, such as venous limb gangrene, when warfarin is started at different platelet thresholds in patients with HIT. The reports that are available suggest the possibility that higher INRs when receiving warfarin are associated with venous limb gangrene,[46,113] although even this finding is not consistent[114] (Table S5).

In summary, there is no direct evidence supporting initiation of VKA at a particular platelet threshold in patients with HIT. However, there is low-quality evidence suggesting a potential for substantial harm if a supratherapeutic INR is reached while a patient with HIT still has a low platelet count and is receiving warfarin without concurrent treatment with a thrombin or factor Xa inhibitor.

Recommendations

3.4.1. In patients with strongly suspected or confirmed HIT, we recommend against starting VKA until platelets have substantially recovered (ie, usually to at least 150×10^9/L) over starting VKA at a lower platelet count and that the VKA be initially given in low doses (maximum, 5 mg of warfarin or 6 mg phenprocoumon) over using higher doses (Grade 1C)**.**

3.4.2. We further suggest that if a VKA has already been started when a patient is diagnosed with HIT, vitamin K should be administered (Grade 2C)**.**

Remarks: We place a high value on the prevention of venous limb gangrene and a low value on the cost of the additional days of the parental nonheparin anticoagulant.

3.5 Discontinuing Thrombin Inhibitor After a Minimum of 5 Days of Overlap With a VKA

There is no direct evidence addressing the optimal duration of treatment with thrombin or factor Xa inhibitors while overlapping with VKAs in patients with HITT. There are, however, data suggesting that premature discontinuation of the thrombin or factor Xa inhibitor may result in an increased risk of recurrent thrombosis. Hursting et al[115] found that seven out of 16 new episodes of thrombosis occurred on the day after argatroban was discontinued in a subgroup of patients who received argatroban and warfarin. Of the patients who had an adverse event during the transition to warfarin, 70% had received < 5 days of treatment with argatroban (5 days is the accepted minimum length of time necessary for warfarin to reduce prothrombin levels to those commonly associated with effective anticoagulation).

The primary reason argatroban was discontinued prematurely was likely misinterpretation of a high INR (secondary to the influence of argatroban) as indicative of therapeutic anticoagulation with warfarin. This is supported by the finding that 21% of patients with an INR > 3.0 while receiving argatroban and warfarin cotherapy had a subtherapeutic INR 4 h after discontinuation of argatroban.[116] The INR should not be interpreted as an indicator of the effect of warfarin alone when administered with argatroban.

Among the advantages of using danaparoid over the DTIs to treat HITT is the lack of influence of this agent on the INR and aPTT. Influence on the INR complicates transition from the DTIs to warfarin, whereas influence on the aPTT complicates drug monitoring, particularly in patients with coagulopathy due to HIT-induced DIC. Fondaparinux shares the same potential advantage, but without the same level of evidence supporting its use as a treatment option for HITT (section 3.2). Some experts have suggested switching from a DTI (eg, argatroban or lepirudin) to fondaparinux once the patient's platelets have recovered ($> 150 \times 10^9$/L) and transition to warfarin is about to begin.[117] Success with this approach has been published in case reports.[118,119]

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Recommendation

3.5. In patients with confirmed HIT, we recommend that that the VKA be overlapped with a nonheparin anticoagulant for a minimum of 5 days and until the INR is within the target range over shorter periods of overlap and that the INR be rechecked after the anticoagulant effect of the nonheparin anticoagulant has resolved (Grade 1C)**.**

3.6 Duration of VKA Therapy in Patients With HITT or HIT

There are no studies evaluating the duration of VKA therapy in patients with HITT or HIT. Given that HIT is generally considered a reversible provoking risk factor for VTE, 3 months of anticoagulant therapy in patients with thrombosis secondary to HIT is consistent with the recommended duration of treatment of VTE in the context of other reversible provoking risk factors (see Kearon et al[84]). HIT investigators have suggested that due to the high risk of thrombosis that extends for 2 to 4 weeks after treatment of HIT is initiated, consideration should be given to continuing anticoagulant therapy with an alternative agent or warfarin for up to 4 weeks in patients with isolated HIT.[120]

Statement 3.6: For patients with HITT, we suggest VKA therapy or an alternative anticoagulant be continued for 3 months. For patients with HIT, we suggest VKA therapy or an alternative anticoagulant be continued for 4 weeks.

4.0 Management of Isolated HIT (HIT Without Thrombosis)

4.1 Discontinue Heparin or Initiate VKA vs Treatment With Nonheparin Anticoagulants

The first step in the treatment of HIT is discontinuation of all forms of heparin and LMWH (including heparin flushes and heparin-coated catheters). Whether taking this step alone is enough to prevent the development of thrombotic complications in patients who have isolated HIT has been evaluated in pooled analyses of prospective cohort studies with historical controls[76,78] and in three retrospective case series.[6,42,70] The prospective studies compared DTIs lepirudin and argatroban with historical controls in whom heparin was discontinued with or without the addition of warfarin[79-83] (Tables 13,14). An overview of the methodology of these studies is available in the online data supplement (Table S1).

From these pooled analyses, we conclude that both agents may be more effective at preventing new thrombosis than discontinuing heparin alone or substituting heparin with a VKA (lepirudin: RR, 0.30; argatroban: RR, 0.29) and may or may not increase

Table 13—*[Section 4.1] Summary of Findings for Argatroban for Treatment of Isolated HIT: Should Patients With Isolated HIT Receive Argatroban Over Discontinuing Heparin and/or Starting a VKA?*

Outcomes	No. of Participants (Studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects, Time Frame 37 d for All Outcomes	
				Risk With Discontinue Heparin/Start VKA	Risk Difference With Argatroban (95% CI)
Death due to thrombosis[a]	488 (2 cohorts) 37 d[b]	Very low due to risk of bias and imprecision	RR, 0.07 (0.01-0.55)	43 deaths per 1,000	40 fewer deaths per 1,000 (from 19 fewer to 43 fewer)
Limb amputation	488 (2 cohorts) 37 d[b]	Very low due to risk of bias and imprecision	RR, 1.10 (0.35-3.38)	29 amputations per 1,000	3 more amputations per 1,000 (from 19 fewer to 68 more)
New thrombosis	488 (2 cohorts) 37 d[b]	Moderate due to risk of bias, but with large effect	RR, 0.29 (0.18-0.47)	237 thrombotic events per 1,000	169 fewer thrombotic events per 1,000 (from 126 fewer to 195 fewer)
Major bleeding[c]	488 (2 cohorts) 37 d[b]	Very low due to risk of bias and imprecision	RR, 0.50 (0.24-1.04)	86 major bleeding events per 1,000	43 fewer major bleeding events per 1,000[d] (from 66 fewer to 3 more)

The anticipated absolute effect is expressed as risk difference (and its 95% CI) and is based on the baseline risk in the comparison group and the relative effect of the intervention (and its 95% CI). For evidence profile see Table S6. High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. See Table 1 and 7 legends for expansion of abbreviations.

[a]As judged by the investigators.

[b]Follow-up was 30 d past cessation of treatment in patients receiving argatroban and 37 d from baseline in control patients.

[c]Defined as a hemoglobin drop of at least 20 g/L or requirement for 2 units of PRBC or an intracranial hemorrhage or bleeding into a joint.

[d]There were three fatal bleeding events in patients who received argatroban (HIT and HITT combined).

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Table 14—*[Section 4.1] Summary of Findings for Lepirudin for Treatment of Isolated HIT: Should Patients With Isolated HIT Receive Lepirudin Over Discontinuing Heparin and/or Starting a VKA?*

Outcomes	No. of Participants (studies) Follow-up	Quality of the Evidence (GRADE)	Relative Effect (95% CI)	Anticipated Absolute Effects, Time Frame 35 d for All Outcomes: Risk With Discontinue Heparin/Start VKA	Anticipated Absolute Effects, Time Frame 35 d for All Outcomes: Risk Difference With Lepirudin (95% CI)
Limb amputation	138 (2 cohorts) 35 d	Very low due to risk of bias and imprecision	RR, 3.65 (0.19-69.27)	0 amputations per 1,000	0 more amputations per 1,000 (from 58 fewer to 64 more)
New thrombosis	138 (2 cohorts) 35 d	Low due to risk of bias	RR, 0.30 (0.09-0.96)	149 thrombotic events per 1,000	104 fewer thrombotic events per 1,000[a] (from 6 fewer to 136 fewer)
Major bleeding[b]	138 (2 cohorts) 35 d	Very low due to risk of bias and imprecision	RR, 1.68 (0.58-4.86)	85 major bleeding events per 1,000	58 more major bleeding events per 1,000[c] (from 36 fewer to 329 more)

The anticipated absolute effect is expressed as risk difference (and its 95% CI) and is based on the baseline risk in the comparison group and the relative effect of the intervention (and its 95% CI). For evidence profile see Table S7. High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. See Table 1, 7, and 8 legends for expansion of abbreviations.

[a]There were three deaths due to thrombosis in patients who received lepirudin (HITT and HIT combined).

[b]Defined as a fatal bleeding event or an intracranial hemorrhage or bleeding that led to permanent disability or requirement for 2 units of PRBC.

[c]There were five fatal bleeding events in patients who received lepirudin (HITT and HIT combined).

the risk of major bleeding (lepirudin 14%, argatroban 4%) and that neither agent is likely to reduce the risk of limb amputation.

The high risk of a thrombotic event in patients with isolated HIT is also supported by data from three retrospective case series (Table 15).[6,42,70] Warkentin et al[6] reported that 55.5% of 62 patients with HIT who just had heparin discontinued, and 47.6% of patients who had heparin substituted by a VKA developed thrombosis. Wallis et al[42] reported new thrombosis in

Table 15—*[Section 4.1] Studies Evaluating Discontinuation of Heparin for Treatment of Isolated HIT*

Study/Year	Type of Study	Participants	Intervention	Outcomes	Follow-up	Results
Warkentin et al[6]/1996	Case series, retrospective, multicenter	62 consecutive patients with SRA-confirmed HIT over 14-y period	Heparin discontinued (n = 36)	New thrombosis	30 d	New thrombosis: Heparin discontinued 20 of 36 (55.5%)
			Warfarin (n = 21)			Warfarin 10 of 21 (47.6%)
			Not specified (n = 5)			Not specified 2 of 5 (40%)
						Death due to thrombosis: 3 of 62[a] (4.8%)
						Death (all-cause): 13 of 62 (21%)
Wallis et al[42]/1999	Case series, retrospective, single center	113 consecutive patients with PAT-confirmed HIT	Heparin discontinued[b]	New thrombosis	Not specified	New thrombosis: 43 of 113 (38%)[c]
				In-hospital death		New thrombosis > 24 h after heparin discontinued:[d] 21 (18.6%)
						Death due to thrombosis: 12 of 113 (10.6%)
						Death (all cause): 31 of 113 (27.4%)
Zwicker et al[70]/2004	Case series, retrospective, single center	48 patients with ELISA-confirmed HIT	Heparin discontinued[e]	New thrombosis	30 d	New thrombosis: 8 of 48 (17%)[f] 2 patients were receiving warfarin

PAT = platelet aggregation test; PE = pulmonary embolism. See Table 1 and 3 legends for expansion of abbreviations.

[a]Two patients had a fatal PE confirmed at post mortem, one was a sudden death with no post mortem.

[b]21 patients received alternate therapy after heparin discontinued (thrombolytics [4], plasmapheresis [3], dextran [17], γ globulin [1], LMWH [1], danaparoid [1], hirudin [1], bivalirudin [1]). Outcomes were not stratified by treatment.

[c]11 patients had more than one thrombotic event.

[d]Thrombotic events within the first 24 h may have been due to the presence of residual heparin.

[e]One patient received a direct thrombin inhibitor; six patients were treated with heparin.

[f]The development of thrombotic complications was correlated with increasing OD of ELISA for HIT antibodies.

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18.6% of 113 consecutive patients with laboratory-confirmed HIT who just had heparin discontinued; 12 of these patients subsequently died. Zwicker et al[70] found that 17% of 48 patients with ELISA-confirmed isolated HIT went on to develop thrombosis. Overall, the risk of thrombosis in patients with isolated HIT who are not treated with a nonheparin anticoagulant is substantial (ranges from 17%-55%).

Based on the data above, the risk of thrombosis in patients with isolated HIT who have heparin discontinued or substituted by a VKA is approximately fivefold higher than patients with isolated HIT who receive lepirudin or argatroban. For this reason, we rated the evidence for this outcome as moderate.

There are no studies comparing danaparoid with discontinuation of heparin alone or substituting heparin with a VKA. However, given the efficacy of danaparoid in treating HIT (reviewed in section 4.2), we have included danaparoid in the recommendation for this section.

Recommendation

4.1. In patients with isolated HIT (HIT without thrombosis), we recommend the use of lepirudin or argatroban or danaparoid over the further use of heparin or LMWH or initiation/continuation of a VKA (Grade 1C)**.**

4.2 Choice of Nonheparin Anticoagulants in Patients With Isolated HIT

Lepirudin, desirudin, argatroban, bivalirudin, danaparoid, and fondaparinux have all been used to treat patients with isolated HIT, but there are no prospective head-to-head trials comparing one agent with another. Table 10 presents a comparison of the properties of these five agents.

Argatroban and Lepirudin: The highest level of evidence for argatroban and lepirudin comes from pooled analyses of their respective historical controlled trials as reviewed in section 3.1 We did not formally compare the efficacy and safety of argatroban with lepirudin in the treatment of isolated HIT in an evidence profile (using the data from their respective historical controlled trials) for the reasons outlined in section 3.2.1. Patients with isolated HIT treated with lepirudin in these trials did not receive an initial bolus, and the infusion rate was 33% lower than in patients with HITT. Dose adjustments following initiation of lepirudin were, however, based on aPTT, and therapeutic levels were therefore generally achieved within 24 h. In the argatroban trials, there was no difference in the dosing regimen used for patients with isolated HIT and patients with HITT.

Danaparoid: (Please note: danaparoid was withdrawn from the US market in 2002 but remains available in other markets.): The highest level of evidence supporting the use of danaparoid for treatment of isolated HIT comes from a small prospective cohort study without internal controls[121] and a small retrospective study with historical controls.[94] Schenk et al[121] reported that none of 24 patients with isolated HIT (15 with laboratory confirmation) who received danaparoid bid (10 International Units/kg) for a mean of 16 days (mean anti-Xa level 0.2 units/mL) developed thrombotic events or major bleeding.

Farner et al[94] reported on 51 patients with isolated HIT enrolled in the first two lepirudin historical controlled trials[79,80] and 35 patients with isolated HIT who received nonprotocolized danaparoid.[94] Rates of recurrent thrombosis were higher for danaparoid compared with lepirudin (20%; 95% CI, 8.4%-36.9% and 6.3%; 95% CI, 1.3%-17.2%, respectively). The investigators attributed this finding to the more frequent use of prophylactic doses of danaparoid in patients with HIT. In contrast, patients with HITT who were treated with danaparoid (and were more likely to have received a therapeutic dose) had a similar risk of new thrombosis compared with patients treated with lepirudin. Other retrospective reports have also suggested that low doses of danaparoid (750 units SC bid or tid, or 1,250 units SC bid) are associated with a higher risk of thrombosis.[122,123]

Desirudin: The highest quality of evidence supporting desirudin for treatment of HIT comes from an open-label randomized trial comparing fixed doses of this agent (15 mg bid) with argatroban.[98] This study was terminated after eight patients were enrolled in each arm due to poor accrual. None of the five patients with laboratory-confirmed HITT (or HIT) in the desirudin arm experienced recurrent VTE or major bleeding.

Bivalirudin: The highest level of evidence supporting bivalirudin for treatment of isolated HIT is limited to case series.

Fondaparinux: The highest level of evidence supporting fondaparinux for treatment of isolated HIT is limited to case series.

Recommendation

4.2. In patients with isolated HIT (HIT without thrombosis) who have normal renal function, we suggest the use of argatroban or lepirudin or danaparoid over other nonheparin anticoagulants (Grade 2C)**.**

Remarks: Other factors such as drug availability, cost, and ability to monitor the anticoagulant effect may

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influence the choice of agent. The dosing considerations are the same as for patients with HITT (see section 3.2). For a recommendation on choice of nonheparin anticoagulants in the setting of renal insufficiency, see Recommendation 3.2.2.

5.0 Management of Patients With Acute HIT or Subacute HIT in Special Situations

5.1 Patients Who Require Urgent Cardiac Surgery

During cardiac surgery, heparin is commonly used to maintain patency in the CPB apparatus and to prevent coagulation in the tissue factor-rich operative field. Heparin is ideally suited for this role because it has a rapid onset of action, has a short half-life, is reversible with protamine sulfate, and has a point-of-care assay (activated clotting time [ACT]). Substituting a nonheparin anticoagulant, such as bivalirudin, lepirudin, or argatroban, for heparin is one strategy that has been used in patients with HIT during cardiac surgery. Another strategy has been combining heparin with a short-acting antiplatelet agent, such as a prostacyclin analog (eg, epoprostenol, iloprost) or a glycoprotein (GP) IIb/IIIa inhibitor (eg, tirofiban) to attenuate platelet activation. There are no prospective head-to-head trials comparing one agent (or strategy) with another in patients with HIT.

Bivalirudin: The highest level of evidence for bivalirudin comes from prospective, cohort studies without internal controls in patients with HIT who underwent cardiac surgery[124,125] and indirectly by small randomized trials in patients without HIT.[126-128] The rate of procedural success (defined as absence of death, Q-wave MI, repeat operation for coronary revascularization, or stroke) was 94% and 92% in patients with HIT who received bivalirudin for either on-pump or off-pump surgery, respectively (Table 16).[129] The incidence of complications, such as MI, cerebrovascular accident (CVA), or major bleeding, were similar to patients without HIT who received either bivalirudin or heparin in the RCTs (Table S8).

Special considerations with respect to intraoperative surgical, anesthesiology, and perfusion techniques are required when bivalirudin is used during cardiac surgery. For example, stasis in the CPB circuit must be minimized to reduce the potential for cleavage of bivalirudin by thrombin in stagnant blood (for a detailed review of dosing and precautions see Warkentin and Greinacher[130]). The ACT has been successfully used to monitor the anticoagulant effect of bivalirudin during cardiac surgery. However, the ecarin clotting time (ECT) is the preferred assay, if available.

Lepirudin: The highest level of evidence for use of lepirudin during cardiac surgery in patients with HIT comes from a retrospective case series (n = 57)[129] (Table 16, Recommendation 5.1.1) and, indirectly, from a small RCT (n = 20) in patients without HIT[131] (Table S8). Although thromboembolic complications were rare, reoperation for bleeding was required in four patients (7%) in the case series, all in patients with postoperative renal insufficiency.[129] An increased risk of bleeding was also noted in another small retrospective case series of patients with HIT who underwent cardiac surgery.[132] The limitations associated with lepirudin during cardiac surgery include difficulty with monitoring (the ACT is not accurate with high doses of lepirudin, and the best alternative, the ECT, is not widely available), long plasma half-life, and the reported increased risk of bleeding, particularly in patients with renal insufficiency. Special considerations with respect to intraoperative surgical, anesthesiologic and perfusion techniques are required when lepirudin is used during cardiac surgery (for a detailed review of dosing and precautions see Warkentin and Greinacher[130]).

Danaparoid: The highest level of data supporting the use of danaparoid in patients with HIT who require urgent cardiac surgery come from a small RCT in patients without HIT.[133] The RCT (n = 71) was terminated early due to concern about higher mediastinal blood loss and transfusion requirements in patients who received danaparoid compared with patients who received heparin (Table S8). The limitations that applied to the use of lepirudin with respect to need for monitoring, long half-life, and increased risk of bleeding in patients with renal failure also apply to danaparoid.

Epoprostenol, Iloprost, and Tirofiban: The data supporting use of these agents are limited to case series in patients with HIT.[134-137]

In summary, there is no direct evidence supporting the use of one alternative nonheparin anticoagulant over another in patients with acute HIT or subacute HIT who undergo cardiac surgery. Of the alternative anticoagulants that have been used for this indication, bivalirudin is the only one that is supported by prospective, multicentre cohort studies (without internal controls) in patients with HIT and indirectly by small randomized heparin-controlled trials in patients without HIT.

Recommendations

5.1.1. In patients with acute HIT (thrombocytopenic, HIT antibody positive) or subacute HIT (platelets recovered, but still HIT antibody positive) who require urgent cardiac surgery, we

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Table 16—*[5.1.1] Studies Evaluating Nonheparin Anticoagulants in Patients With HIT Who Require Urgent Cardiac Surgery*

Study/Year	Type of Study	Participants	Intervention	Outcomes	Follow-up	Results
Koster et al[124]/2007	Cohort without internal controls, prospective, multicenter	49 patients with HIT or suspected HIT undergoing CPB, (42 patients HIT Ab-positive at time of procedure)	Bivalirudin 1 mg/kg bolus then 2.5 mg/kg/h ACT > 2.5-fold increase over baseline	Procedural success[a] Major bleeding[b]	Day 7 or day of discharge, whichever came first for procedural success and major bleeding; procedural success at day 30 and 12 wk	At day 7 Procedural success: 46 of 49 (94%) MI: 0 of 49 CVA: 1 of 49 (2%) Major bleeding: 0 of 49 Death: 1 of 49 (2%)
Dyke et al[125]/2007	Cohort without internal controls, prospective, multicenter	51 patients with HIT or suspected HIT undergoing OPCAB, (35 patients HIT Ab-positive at time of procedure)	Bivalirudin 0.75 mg/kg bolus then 1.75 mg/kg/h ACT > 300 s	Procedural success[a] Major bleeding[b]	Day 7 or day of discharge, whichever came first for procedural success and major bleeding; procedural success at day 30 and 12 wk	At day 7 Procedural success: 47 of 51 (92%) MI: 3 of 51 (6%) CVA: 1 of 51 (2%) Major bleeding: 0 of 51 Death: 0 of 49
Koster et al[129]/2000	Case series, retrospective, single center	57 patients with confirmed HIT undergoing CPB (52 patients HIT Ab-positive at time of procedure)	r-hirudin 0.25 mg/kg bolus then 0.5 mg/min (ECT 350-400 s)	Not prespecified	6 mo	Reoperation for bleeding: 4 of 57 (7%); all 4 had postoperative renal failure Death: 3 of 57 (5%)[c]

CPB = cardiopulmonary bypass; CVA = cerebrovascular accident; MI = myocardial infarction; OPCAB = off-pump coronary artery bypass. See Table 1 and 10 legends for expansion of other abbreviations.

[a]Defined as absence of death, Q-wave MI, repeat operation for coronary revascularization, or stroke.

[b]Defined as intracranial hemorrhage, retroperitoneal or GI bleeding, or persistent postoperative hemorrhage requiring surgical re-exploration.

[c]Deemed unrelated to perioperative anticoagulation by investigators.

suggest the use of bivalirudin over other nonheparin anticoagulants and over heparin plus antiplatelet agents (Grade 2C)**.**

5.1.2. In patients with acute HIT who require nonurgent cardiac surgery, we recommend delaying the surgery (if possible) until HIT has resolved and HIT antibodies are negative (see section 6.1) (Grade 2C)**.**

Remarks: Other factors not covered by our analysis, such as drug availability, cost, and ability to monitor the anticoagulant effect may influence the choice of agent.

For recommendations for patients with a past history of HIT (>3 months previous) who require cardiac surgery, see section 6.1.

5.2 Patients Who Require Urgent Percutaneous Coronary Interventions

Anticoagulants are used to prevent ischemic complications secondary to plaque disruption and endothelial injury during percutaneous coronary interventions (PCI), such as angioplasty and stent placement. Bivalirudin, lepirudin, argatroban, and danaparoid have all been evaluated for use during PCI in patients with acute or subacute HIT. There are no head-to-head trials comparing these anticoagulants in patients with HIT.

Bivalirudin: The highest level of evidence supporting the use of bivalirudin during PCI comes from a pooled analysis of five large RCTs comparing bivalirudin with heparin plus GP IIb/IIIa inhibitors in patients without HIT[138] (Table S9). This analysis of >19,000 patients showed that bivalirudin had a similar risk of ischemic adverse events as the control group (OR, 1.07; 95% CI, 0.96-1.19) but a lower risk of major bleeding (OR, 0.55; 95% CI, 0.44-0.69). Bivalirudin also showed a high procedural success rate (98%) with a low risk of major bleeding (2%) in patients with HIT who underwent PCI in a prospective cohort study of 52 patients[139-141] (Table 17).

Lepirudin (Recombinant Hirudin): In patients without HIT, randomized controlled trials of patients with acute coronary syndromes have shown that hirudin is more effective than heparin at reducing the risk of reinfarction in patients undergoing PCI, but at the cost of an increased risk of major bleeding.[142-144] Experience with patients with HIT is limited to a small prospective cohort study in which 21 patients undergoing PCI (or peripheral vascular interventions) received lepirudin plus a GP IIb/IIIa antagonist[140] (Table 17). Clinical success was achieved in 92% of patients but with an 8% incidence of major bleeding (including one fatal bleeding event).

Argatroban: Data regarding the efficacy and safety of argatroban during PCI in patients with HIT come from a secondary analysis of the argatroban prospective, historical controlled trials.[141] In these trials, 91 patients underwent PCI with a clinical success rate of 98% and an incidence of major bleeding of 1%[141] (Table 17). Laboratory confirmation of HIT was not required for these trials, so the proportion of patients who truly had HIT at the time of the procedure is uncertain. In patients without HIT (n = 152), argatroban alone or in combination with GP IIb/IIIa inhibitors during PCI was evaluated in a prospective cohort study without internal controls.[145] The incidence of the composite efficacy outcome (death, Q-wave MI, and urgent revascularization) and major bleeding was acceptably low in both groups (0%-3%)[145] (Table S9).

Danaparoid and Fondaparinux: The evidence supporting the use of danaparoid is limited to case series in patients with HIT undergoing PCI; fondaparinux has not been evaluated for this indication. The increased rate of catheter-related thrombosis seen in patients who underwent PCI after receiving fondaparinux in the Organization for the Assessment of Strategies for Ischemic Syndromes (OASIS)-6 trial raises concern about the efficacy of this agent in interventional settings.[146]

In summary, although the level of evidence supporting the use of bivalirudin during PCI in patients with HIT is limited to a small prospective cohort, the data in patients without HIT is high quality (RCTs summarized in meta-analyses). The use of lepirudin is supported by data from studies with patients without HIT; however, there is concern about an associated increased risk of bleeding with this agent. The highest level of evidence supporting argatroban for PCI in patients with HIT comes from a subgroup analysis of the prospective, historical controlled HIT treatment trials. There is no evidence to support the use of fondaparinux in this setting.

Recommendation

5.2. In patients with acute HIT or subacute HIT who require PCI, we suggest the use of bivalirudin (Grade 2B) **or argatroban** (Grade 2C) **over other nonheparin anticoagulants.**

Remarks: Other factors, such as drug availability, cost, and ability to monitor the anticoagulant effect, may influence the choice of agent.

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Table 17—*[Section 5.2] Studies Evaluating Nonheparin Anticoagulants During PCI in Patients With HIT*

Study/Year	Type of Study	Participants	Intervention	Outcomes	Follow-up	Results
Mahaffey et al[139]/2003	Cohort without internal controls, prospective, multicenter	52 patients with HIT or suspected HIT undergoing PCI, (testing for HIT Ab was not required)	Bivalirudin 1 mg/kg bolus then 2.5 mg/kg/h for 4 h; after year 2002 changed to 0.75 mg/kg bolus followed by 1.75 mg/kg/h for up to 4 h	Procedural success: TIMI grade 3 flow and final lesion stenosis < 50%	48 h after drug administration or hospital discharge (whichever came first)	Procedural success: 49 of 50 (98%)
				Clinical success: absence of death, requirement for emergent bypass or Q-wave MI		Clinical success: 48 of 50 (96%)
				Major bleeding: ICH, RPH, hemodynamic compromise, bleeding with ≥ 3 U PRBC transfusion or Hb < 3 g/dL or Hct ≥ 9%)		MI: 0 CVA: 0 Major bleeding event: 1 of 50 (2%) Death: 1 of 50 (2%)[a]
Cochran et al[140]/2003	Cohort without internal controls, prospective, single center	25 patients with suspected or confirmed HIT who underwent PCI or peripheral interventions (20 patients HIT Ab-positive at time of procedure; 11 patients had HITT)	Lepirudin 0.1-0.8 mg/kg alone (ACT > 300 s) (n = 4) OR	Angiographic success: post angioplasty stenosis < 50%; post stent stenosis < 20%	Hospital discharge	Angiographic success: 100%
			Lepirudin AND eptifibatide 180 μg/kg bolus × 2 then 2 μg/kg/min OR Tirofiban 10 μg/kg bolus then 0.15 μg/kg/min (ACT > 250 s) (n = 21)	Clinical success: angiographic success and freedom from MACE		Clinical success: 23 of 25 (92%)
				Major bleeding[b]		MI: 0 CVA: 0 Major bleeding events: 2 of 25 (8%) both received lepirudin + GP Death: 2 of 25 (8%)[c]
Lewis et al[141]/2002	Post hoc subgroup analysis of ARG-216, ARG-310, ARG-311	91 patients with HIT or suspected HIT or past history of HIT who underwent PCI (this table includes data on initial PCI only for 21 patients who underwent > 1 PCI)	Argatroban 350 μg/kg bolus then 25 μg/kg/min (30 μg/kg/min in ARG-216) and adjusted to maintain ACT 300-450 s	Angiographic success: final stenosis < 50% in ≥ 1 lesion attempted	For 24 h after drug cessation or until hospital discharge (whichever came first)	Angiographic success: 86 of 88 (98%)
				Clinical success: absence of death, emergent bypass, Q-wave infarction		Clinical success: 86 of 88 (98%)
				Major bleeding: overt and associated with drop in Hb > 5 g/dL and transfusion ≥ 2 units PRBC or ICH, RPH, or into a prosthetic joint		MI: 4 of 91 (4%) Emergent bypass: 2 of 91 (2%) Major bleeding: 1 of 91 (1%) Death: 0 of 91

ACS = acute coronary syndrome; GP = glycoprotein IIb/IIIa inhibitor; Hct = hematocrit; MACE = composite of death, nonfatal MI, stroke and target vessel revascularization.

[a]Asystolic arrest.

[b]Defined as requiring transfusion > 2 units PRBC or ICH or RPH.

[c]One death was determined to be related to the procedure (retroperitoneal hemorrhage).

5.3 Patients Who Require Renal Replacement Therapy

5.3.1 Patients With Acute HIT: Renal replacement therapy is a term that encompasses a large number of different procedures in patients with renal failure (eg, intermittent hemodialysis, continuous venovenous hemofiltration, continuous venovenous hemodialysis, continuous arteriovenous hemodialysis). Heparin is the anticoagulant most commonly used to maintain patency of the filter and extracorporeal circuit during these procedures. Although hemodialysis can be performed without anticoagulant therapy,[147] we do not recommend this approach for patients with acute or subacute HIT because of the prothrombotic nature of HIT (high risk of thrombosis within the renal replacement circuit and the patient).[148]

There are no head-to-head studies comparing the efficacy and safety of nonheparin anticoagulants during renal replacement therapy in patients with HIT. Caution must be exercised when comparing the results of different studies using nonheparin anticoagulants because of the large variety of procedures and significant interstudy differences with respect to type of hemofilter membrane, blood flow rates, dialysate flow rates, and other specific aspects of renal replacement therapy. For a more comprehensive review, including dosing information, see Davenport and Davenport[148]).

Argatroban: Argatroban has two properties that make it ideal for renal replacement therapy: (1) it is not renally cleared, and (2) dialytic clearance by high-flux membranes is considered clinically insignificant.[149] The evidence for the use of argatroban during renal replacement therapy in patients with HIT comes from one small prospective, dose-finding study in patients undergoing continuous renal replacement therapy (n = 30)[150] and a secondary analysis of the prospective, historical controlled treatment studies (47 patients who received seven different methods of renal replacement therapy).[151] The incidence of new thrombosis (0%-4%) and major bleeding (0%-6%) while on argatroban in these studies was low. An RCT evaluating three different doses of argatroban during intermittent hemodialysis in patients without HIT (n = 13) showed similar results.[149]

Danaparoid: Danaparoid has been successfully used during renal replacement therapy despite its dependence on renal clearance. The highest level of evidence supporting the use of danaparoid during renal replacement therapy in patients with HIT comes from one small pilot study (five patients with continuous venovenous hemofiltration)[152] and a retrospective review of cases and comparative studies of HIT and patients without HIT who underwent intermittent hemodialysis (n = 122).[153] In the review, thrombosis of either the patient or the hemodialysis circuit occurred in 7% of the 97 patients with HIT, and major bleeding occurred in 6%.[153] Only one-third of the patients in this study had the diagnosis of HIT confirmed with a functional assay. Small RCTs that compared danaparoid with heparin or LMWH during hemodialysis in patients without HIT have also shown it to be effective and safe.[154,155]

Lepirudin and Fondaparinux: Lepirudin is dependent on renal clearance and antihirudin antibodies may develop that further reduce renal clearance.[156,157] Because of the prolonged half-life of this agent in renal failure, intermittent doses of lepirudin prior to dialysis may continue to exert an anticoagulant effect between dialysis sessions. Small studies evaluating hirudin during continuous venovenous hemofiltration, predominantly in patients without HIT, have reported an increased risk of hemorrhagic complications.[158-160] The evidence regarding the use of fondaparinux is limited to case reports.[161,162]

In summary, there is no direct evidence supporting the use of one alternative nonheparin anticoagulant over another in patients with acute HIT who require renal replacement therapy. There has been more experience with danaparoid than argatroban for this indication; however, although the highest level of evidence supporting the use of danaparoid comes from comparative studies in patients without HIT, the use of argatroban is supported by prospective data (albeit limited) and pharmacokinetics (ie, lack of renal clearance). Although successful use of lepirudin has been reported, an increased risk of bleeding has been raised as a concern.

Recommendation

5.3.1. In patients with acute or subacute HIT who require renal replacement therapy, we suggest the use of argatroban or danaparoid over other nonheparin anticoagulants (Grade 2C)**.**

Remarks: We acknowledge that the cost of argatroban may be prohibitive at some clinical centers. We further suggest that if the prothrombotic state of HIT appears to have resolved (as seen by normalization of the platelet count), saline flushes during dialysis would be a reasonable option. This suggestion is based on the presumed pathogenesis of thrombosis in this condition and not on the results of clinical trials.

5.3.2 Patients With a Past History of HIT: Citrate has been evaluated as a substitute for heparin during renal replacement therapy in patients who are unable to receive heparin because of a high risk of bleeding.[163-165] Citrate acts as a regional anticoagulant by

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chelating ionized calcium. However, it requires special dialysates and careful monitoring for metabolic derangements. Citrate has also been used for catheter locking, although the evidence to support its efficacy is not as high quality as for heparin.[166] Although it has not been evaluated in patients with acute HIT, citrate for renal replacement and catheter locking appears to be a reasonable alternative for patients with a past history of HIT.

Recommendation

5.3.2. In patients with a past history of HIT who require ongoing renal replacement therapy or catheter locking, we suggest the use of regional citrate over the use of heparin or LMWH (Grade 2C)**.**

5.4 Pregnant Patients

The incidence of HIT during pregnancy is lower than in the nonpregnant population, especially when LMWH is used (at either prophylactic or therapeutic doses [one in 1,167 pregnancies[21,22,34] and zero in 2,777 pregnancies[35]]). When it does occur, however, heparin should be discontinued and treatment with a nonheparin anticoagulant initiated. The quality of evidence on the efficacy and safety of nonheparin anticoagulants in this patient population is very low.

Danaparoid: The highest level of evidence for danaparoid comes from a retrospective case series[167] in which 30 women with acute HIT (28 with VTE) received danaparoid (at various doses) during pregnancy. Five of the patients (17%) developed recurrent VTE and three (10%) developed major bleeding during treatment. There was no evidence of anti-Xa activity due to danaparoid in the umbilical cord blood of the six infants who were checked after delivery.

Lepirudin, Argatroban, and Fondaparinux: Data supporting the use of lepirudin,[168-170] argatroban,[171,172] and fondaparinux[173-175] to treat HIT during pregnancy are limited to case reports. The advantage of lepirudin is that it can be administered SC (it has been given in doses ranging from 25 mg bid to 125 mg bid; monitored by aPTT 2 h post injection).[170,176] However, long-term administration has been associated with the development of antilepirudin antibodies that prolong the drug's effective half-life. Consequently, a patient who develops HIT in the first trimester and is treated with lepirudin will be at higher risk for developing antilepirudin antibodies than a patient who is diagnosed with HIT in the third trimester.[176] One proposed strategy for reducing the duration of exposure to lepirudin in a patient diagnosed with HIT during the first trimester of pregnancy is to use SC lepirudin during the first two trimesters and then switch to warfarin in the last trimester when the risk of teratogenicity secondary to warfarin is lower (assuming the patient's platelet count has fully recovered). Investigators recommend that lepirudin be started intravenously with a switch to SC administration once platelet counts have recovered (overlapping with IV lepirudin by 1 hour).[170,176]

Argatroban cannot be given SC and has only been evaluated in pregnancy in case reports. Fondaparinux can be given SC, but unlike lepirudin, the effectiveness of fondaparinux for treating HIT is still uncertain (see section 3.2). Indirect support for the safety of fondaparinux during pregnancy in patients without HIT is derived from one small prospective cohort study without internal controls in which women who developed hypersensitivity skin reactions while receiving LMWH for a history of VTE or recurrent fetal loss were treated with fondaparinux.[177] In this study, 10 patients (during 12 pregnancies) received fondaparinux 2.5 mg bid until the start of spontaneous labor. None of the 13 infants had any congenital abnormalities and no major bleeding occurred during the pregnancies (three patients had > 1,000 mL blood loss at delivery). A retrospective case series of 29 pregnant women who received fondaparinux 2.5 mg daily (staring in the first trimester) for infertility and unexplained recurrent fetal loss reported similar results.[178] However, fondaparinux crosses the human placenta, as shown in a case report of four patients who had elevated anti-Xa activity in umbilical cord blood (approximately one-tenth the concentration in the maternal plasma).[179] Further studies on the safety and efficacy of this drug in context of pregnancy are needed.

Despite the low quality of evidence supporting the use of danaparoid for treatment of HIT during pregnancy, the number of patients who have been exposed to this agent compared with the alternatives and the lack of placental transfer make it the current best choice.

Recommendation

5.4. In pregnant patients with acute or subacute HIT, we suggest danaparoid over other nonheparin anticoagulants (Grade 2C)**. We suggest the use of lepirudin or fondaparinux only if danaparoid is not available** (Grade 2C)**.**

Remarks: Other factors, such as drug availability, cost, and ability to monitor the anticoagulant effect, may influence the choice of agent.

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6.0 Management of Patients With a Past History of HIT

With certain procedures (eg, surgery requiring CPB, hemodialysis), the properties of heparin make it preferable to alternative nonheparin anticoagulants (eg, short half-life, reversibility, readily available assays for monitoring the anticoagulant effect, low cost). The risk of giving heparin to patients with acute or subacute HIT is too high (ie, risk of fatal thrombosis); hence, our recommendations for management of patients who require these procedures are given in section 5.0. This section will address patients who have a past history of HIT (> 3 months previous) for whom re-exposure to heparin (or LMWH) is being considered.

Patients with a past history of HIT can theoretically be re-exposed to heparin, in specific circumstances, because of several unique properties of HIT antibodies. First, the HIT antibody is known to be transient, with a median time to disappearance of 50 to 80 days (depending on the assay performed).[36] Second, there is no evidence to suggest that patients with a prior history of HIT (who are currently HIT antibody negative) will have an amnestic immune response on re-exposure to heparin (ie, sensitization does not occur with < 4 days of exposure to heparin and the level of response is not stronger than with the initial episode of HIT).[36] Patients who have developed rapid-onset HIT (within 24 h of heparin exposure) have been found to have residual HIT antibodies in their blood from their initial heparin exposure (typically within the past 100 days).[36,37] These observations suggest that it may be possible to re-expose a patient with a previous history of HIT to heparin for < 4 days without precipitating a second episode of acute HIT. Because there are no clinical trials evaluating the safety of this premise, our recommendations are based on the incidence of recurrent HIT or re-emergence of HIT antibodies following intentional (or accidental) re-exposure to heparin or LMWH in observational studies.

Five studies have reported outcomes in patients who were re-exposed to heparin or LMWH in the context of a past history of HIT[6,37,132,180,181] (Table 18). Three studies including a total of 20 patients who were re-exposed to heparin during cardiac or vascular surgery reported no episodes of recurrent HIT and only one episode of re-emergence of HIT antibodies.[6,132,180] Similar results were seen in the case series by Wanaka et al,[181] in which five patients were re-exposed to heparin during multiple episodes of intermittent hemodialysis (see section 5.3 for patients with a past history of HIT who require hemodialysis). The registry by Lubenow et al[37] included the largest number of patients who were re-exposed to heparin (n = 45), but the proportion of patients who were re-exposed > 3 months after their episode of acute HIT is not available, nor was the incidence of re-emergence of HIT antibodies; however, 91% of the re-exposed patients developed thrombocytopenia by day 15 of re-exposure.

6.1 Patients With a History of HIT Who Require Cardiac Surgery

Although the evidence is very limited, the combination of the unique properties of HIT antibodies as previously described, and the serious difficulties that may be encountered using nonheparin anticoagulants during procedures such as CPB, lead us to conclude that the risk of short-term re-exposure may be justified in specific circumstances.[76] In these cases, the use of heparin should be restricted to the time of surgery, and other heparin exposure before and after the procedure should be scrupulously avoided. Patients with recent HIT whose platelet count has recovered but who still have detectable HIT antibodies are at risk for developing rapid-onset HIT with heparin re-exposure unless a washed platelet activation assay (eg, SRA or HIPA) is negative and the ELISA is negative or only weakly positive.[76]

Recommendations

6.1.1. In patients with a history of HIT in whom heparin antibodies have been shown to be absent who require cardiac surgery, we suggest the use of heparin (short-term use only) over nonheparin anticoagulants (Grade 2C)**.**

6.1.2. In patients with a history of HIT in whom heparin antibodies are still present who require cardiac surgery, we suggest the use of nonheparin anticoagulants (see Recommendation 5.1.1) over heparin or LMWH (Grade 2C)**.**

6.2 Patients Who Require PCI

In theory, the same approach described for re-exposure to heparin for patients with a past history of HIT who require cardiac surgery could be used for patients who require PCI. However, there are two reasons we would favor the use of nonheparin anticoagulants over re-exposure to heparin for PCI: (1) the risk for recurrent immunization that could present as acute HIT if heparin is then used for cardiac surgery in the same patient, and (2) the favorable experience with bivalirudin during PCI (as compared with the difficulties of using bivalirudin and other nonheparin anticoagulants during cardiac surgery).[76]

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Table 18—*[Section 6.0] Studies of Patients With a Past History of HIT Who Were Re-exposed to Heparin*

Study/Year	Type of Study	Participants	Intervention	Outcomes	Follow-up	Results
Wanaka et al[181]/2010	Case series, retrospective, single center (letter)	5 patients with laboratory-confirmed HIT (PAT-positive ELISA) who required hemodialysis	Re-exposure to heparin (after initial treatment with argatroban and confirmed HIT Ab- negative > 100 d later)	Thrombocytopenia HIT antibodies Clotting of dialyzer	1-6 yr	Thrombocytopenia: 0 HIT antibodies: 0 Clotting in dialyzer: 2 of 5 (both resolved with aspirin)
Nuttall et al[132]/2003	Cohort with concurrent controls, prospective, single center	12 cardiac surgery patients with a previous clinical diagnosis of HIT[a] who required CPB	Heparin during CPB only (HIT Ab-negative)[b] r-hirudin 0.25 mg/kg bolus, 0.20 mg/kg in CPB pump prime, 0.5 mg/min infusion (ECT) (HIT Ab-positive)	Volume of allogenic blood products Blood loss Need for reoperation Thrombotic events Death	Not prespecified	Recurrence of thrombocytopenia or HIT antibodies not reported Volume of allogenic blood products and blood loss: higher in r-hirudin group Need for reoperation: Heparin 1 of 6 (17%) r-Hirudin 3 of 6 (50%) Thrombotic events: 0 Death: 0
Lubenow et al[37]/2002	Registry, retrospective, multicentre	45 patients with laboratory-confirmed HIT (HIPA)	Re-exposure to heparin	Relation of the time interval to previous heparin exposure and onset of platelets < 100 x 10^9/L	Until development of thrombocytopenia (platelet count < 100 × 10^9/L)	Interval between heparin exposures: 1 d to 21 y Onset of thrombocytopenia if re-exposure within 3 mo: Day 4.9 ± 4.4 (mean ± SD) Onset of thrombocytopenia if re-exposure after 3 mo:[c] day 11.5 ± 5.5 (mean ± SD) Likelihood of thrombocytopenia (n = 45) Day 5 (45%) Day 8 (54%) Day 15 (91%)
Potzsch et al[180]/2000	Case series, retrospective, single center (letter)	10 patients with history of confirmed HIT (HIPA-positive) who required CPB surgery[d]	Re-exposure to heparin	Prolonged thrombocytopenia[e] HIT antibodies	10 d after surgery	No prolonged thrombocytopenia or increase in HIT antibodies

(Continued)

Table 18—*Continued*

Study/Year	Type of Study	Participants	Intervention	Outcomes	Follow-up	Results
Warkentin et al[6]/1996	Case series, retrospective, multicenter	7 patients with laboratory-confirmed HIT (SRA) over 14-y period	Re-exposure to heparin	New thrombosis	Until end of treatment in pts re-exposed to full heparin treatment (n = 3)[f]	No decrease in platelet count or new thrombosis in any of the patients
				Decrease in platelet count	Until discharge in patients re-exposed to heparin during cardiac or vascular surgery only (n = 4)	HIT antibodies positive in 1 patient with short-term exposure and testing not done in 1 patient with longer exposure

See Table 1, 2, 8, 10, 12, 15, and 16 for expansion of abbreviations.
[a]Six were PF4-ELISA positive immediately prior to surgery.
[b]Only one patient who was PF4-ELISA negative prior to study had a positive PF4-ELISA with HIT in past; therefore, five patients may never have had HIT.
[c]Proportion of patients in this category was not provided (author was contacted and no further details available).
[d]Negative for HIT antibodies at time of surgery.
[e]Not defined.
[f]Duration of follow-up was 8 d, 11 d, and 19 d in the pts who received more than a short term re-exposure to heparin.

Recommendation

6.2. In patients with a history of HIT who require cardiac catheterization or PCI, the recommended treatment is the same as in Recommendation 5.2.

6.3 Patients Who Require Prophylaxis or Treatment of Thrombosis

In contrast to the situation with cardiac surgery or PCI, re-exposure to heparin or LMWH in patients with a past history of HIT who require anticoagulant therapy for prophylaxis or treatment of venous or arterial thrombosis is unlikely to be limited to < 4 days. The limited available evidence suggests that the longer the re-exposure to heparin, the higher the likelihood of re-emergence of HIT antibodies and, potentially, acute HIT.[37] Furthermore, 25% of patients with HIT will present with thrombosis before their platelet count drops. Therefore, relying on platelet count monitoring alone to watch for sensitization may not be safe.[3,5] Given the established efficacy and safety of alternative anticoagulants, such as warfarin, danaparoid, fondaparinux, and the new oral anticoagulants, dabigatran and rivaroxaban, for thromboprophylaxis, re-exposure to heparin/LMWH should be avoidable in most cases.

The options for treatment of acute thrombosis are more limited. Warfarin will not inhibit active thrombin and should not be used alone to treat acute thrombosis. A recent secondary analysis of two large RCTs comparing heparin or LMWH with fondaparinux for treatment of VTE showed that fondaparinux was less likely to exacerbate HIT in patients who had preexisting platelet-activating antibodies than patients who received heparin or LMWH (zero out of 10 patients who received fondaparinux went on to develop clinical HIT compared with four out of four patients who received heparin or LMWH).[182] This suggests that fondaparinux may be safe to use in patients with a previous history of HIT.

Recommendation

6.3. In patients with a past history of HIT who have acute thrombosis (not related to HIT) and normal renal function, we suggest the use of fondaparinux at full therapeutic doses until transition to VKA can be achieved (Grade 2C)**.**

Conclusions

The diagnosis and treatment of HIT is an ongoing challenge. Studies evaluating the efficacy and safety of fondaparinux and new anticoagulants in the treatment of HIT would be of tremendous value to the medical community.

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Author Contributions: As Topic Editor, Dr Linkins oversaw the development of this article, including the data analysis and subsequent development of the recommendations contained herein.
Dr Linkins: contributed as Topic Editor.
Dr Dans: contributed as panelist.
COL Moores: contributed as panelist.
Dr Bona: contributed as frontline clinician.
Dr Davidson: contributed as panelist.
Dr Schulman: contributed as panelist.
Dr Crowther: contributed as panelist.

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Endorsements: This guideline is endorsed by the American Association for Clinical Chemistry, the American College of Clinical Pharmacy, the American Society of Health-System Pharmacists, the American Society of Hematology, and the International Society of Thrombosis and Hematosis.

Additional information: The supplement Tables can be found in the Online Data Supplement at http://chestjournal.chestpubs.org/content/141/2_suppl/e495S/suppl/DC1.

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