CLINICAL GUIDELINES

blood advances

American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia

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Background: Heparin-induced thrombocytopenia (HIT) is an adverse drug reaction mediated by platelet-activating antibodies that target complexes of platelet factor 4 and heparin. Patients are at markedly increased risk of thromboembolism.

Objective: These evidence-based guidelines of the American Society of Hematology (ASH) are intended to support patients, clinicians, and other health care professionals in their decisions about diagnosis and management of HIT.

Methods: ASH formed a multidisciplinary guideline panel balanced to minimize potential bias from conflicts of interest. The McMaster University GRADE Centre supported the guideline development process, including updating or performing systematic evidence reviews. The panel prioritized clinical questions and outcomes according to their importance for clinicians and patients. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess evidence and make recommendations, which were subject to public comment.

Results: The panel agreed on 33 recommendations. The recommendations address screening of asymptomatic patients for HIT, diagnosis and initial management of patients with suspected HIT, treatment of acute HIT, and special situations in patients with acute HIT or a history of HIT, including cardiovascular surgery, percutaneous cardiovascular intervention, renal replacement therapy, and venous thromboembolism prophylaxis.

Conclusions: Strong recommendations include use of the 4Ts score rather than a gestalt approach for estimating the pretest probability of HIT and avoidance of HIT laboratory testing and empiric treatment of HIT in patients with a low-probability 4Ts score. Conditional recommendations include the choice among non-heparin anticoagulants (argatroban, bivalirudin, danaparoid, fondaparinux, direct oral anticoagulants) for treatment of acute HIT.

Summary of recommendations

These guidelines are based on updated and original systematic reviews of evidence conducted under the direction of the McMaster University Grading of Recommendations Assessment, Development and Evaluation (GRADE) Centre with international collaborators. The panel followed best practice for guideline development recommended by the Institute of Medicine and the Guidelines International Network.[1-4] The panel used the GRADE approach[5-11] to assess the certainty in the evidence and formulate recommendations.

Heparin-induced thrombocytopenia (HIT) is a prothrombotic adverse drug reaction, mediated in most cases by immunoglobulin G antibodies that target complexes of platelet factor 4 (PF4) and heparin.[12]

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Resources for implementing these guidelines, including apps, patient decision aids, and teaching slide sets, may be accessed at the ASH web page hematology.org/vte.

The full-text version of this article contains a data supplement.

Unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) are the most widely used anticoagulants in the world among hospitalized patients. Approximately 12 million inpatients in the United States alone are exposed to heparin each year.[13] The incidence of HIT among these patients ranges from <0.1% to 7%, depending on the type of heparin (UFH vs LMWH), duration of heparin exposure, and patient population (eg, surgical vs medical).[14-16] One-third to one-half of cases of HIT are complicated by thrombosis, which may be venous or arterial and may be limb- or life-threatening.[17-19] Recommendations in this guideline focus on the 5 phases of HIT (defined in Table 1) and address screening of asymptomatic patients for HIT, diagnosis and initial management of patients with suspected HIT, treatment of acute HIT, and special situations in patients with acute HIT or a history of HIT, including cardiovascular surgery, percutaneous cardiovascular intervention (PCI), renal replacement therapy, and venous thromboembolism (VTE) prophylaxis.

Interpretation of strong and conditional recommendations

The strength of a recommendation is expressed as either strong ("the guideline panel recommends…") or conditional ("the guideline panel suggests…") and has the following interpretation:

Strong recommendation

- For patients: most individuals in this situation would want the recommended course of action, and only a small proportion would not.
- For clinicians: most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.
- For policy makers: the recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.
- For researchers: the recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty in the evidence. In such instances, further research may provide important information that alters the recommendation.

Conditional recommendation

- For patients: the majority of individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences.
- For clinicians: different choices will be appropriate for individual patients, and clinicians must help each patient arrive at a management decision consistent with the patient's values and preferences. Decision aids may be useful in helping individuals make decisions consistent with their individual risks, values, and preferences.
- For policy makers: policy making will require substantial debate and involvement of various stakeholders. Performance measures about the suggested course of action should focus on whether an appropriate decision-making process is duly documented.
- For researchers: this recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help identify possible research gaps.

Recommendations

Screening asymptomatic patients for HIT

Recommendation 1.1.a. For patients receiving heparin in whom the risk of HIT is considered low (<0.1%), the American Society of Hematology (ASH) guideline panel *suggests against* platelet count monitoring to screen for HIT (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Recommendation 1.1.b. For patients receiving heparin in whom the risk of HIT is considered intermediate (0.1%-1.0%) or high (>1.0%), the ASH guideline panel *suggests* platelet count monitoring to screen for HIT. If the patient has received heparin in the 30 days before the current course of heparin, the ASH guideline panel *suggests* platelet count monitoring beginning on day 0 (the day heparin is initiated). If the patient has not received heparin in the 30 days before the current course of heparin, the ASH guideline panel *suggests* monitoring the platelet count from day 4 until day 14 or until heparin is stopped, whichever occurs first, if practicable. In high-risk patients, the ASH guideline panel *suggests* monitoring the platelet count at least every other day. In intermediate-risk patients, the ASH guideline panel *suggests* monitoring the platelet count every 2 to 3 days (conditional recommendations, very low certainty in the evidence about effects ⊕◯◯◯). **Remarks:** Low-risk patients include medical and obstetrical patients receiving LMWH, patients receiving LMWH after minor surgery or minor trauma, and any patients receiving fondaparinux. Intermediate-risk patients include medical and obstetrical patients receiving UFH and patients receiving LMWH after major surgery or major trauma. High-risk populations include surgical and trauma patients receiving postoperative UFH. Some patients may receive a combination of UFH and LMWH or UFH and fondaparinux; these patients should be considered to belong to the UFH group.

In patients at intermediate or high risk for HIT who have not received heparin in the 30 days prior to the current course of heparin, some clinicians may choose to begin monitoring the platelet count before day 4, because platelet count values before day 4 may aid in the interpretation of platelet count values beyond day 4.

Diagnosis and initial management of patients with suspected HIT

Recommendations 2.1 to 2.10 should be considered together when patients with suspected HIT are being tested and treated. The recommendations and sequence of tests and treatment are illustrated in Figure 1.

Recommendation 2.1. In patients with suspected HIT, the ASH guideline panel *recommends* using the 4Ts score to estimate the probability of HIT rather than a gestalt approach. If there is an intermediate- or high-probability 4Ts score, the ASH guideline panel *recommends* an immunoassay (strong recommendations, moderate certainty in the evidence about effects ⊕⊕⊕◯). If the immunoassay is positive and a functional assay is available (either locally or as a send-out test to a reference laboratory), the ASH guideline panel *suggests*

Table 1. The 5 phases of HIT

Phase	Platelet count	Functional assay	Immunoassay	Recommendations
Suspected HIT	Decreased	?	?	2.1-2.10
Acute HIT	Decreased	+	+	3.1-3.8, 4.1, 5.1, 6.1, 8.1.a
Subacute HIT A	Normal	+	+	3.9, 4.1, 5.1, 6.2, 8.1.a
Subacute HIT B	Normal	−	+	4.2, 5.2, 6.2, 8.1.a
Remote HIT	Normal	−	−	4.2, 5.2, 6.2, 7.1, 8.1.b

Patients with suspected HIT are those who are thought to have HIT on clinical grounds but for whom confirmatory laboratory test results are not yet available. Once the diagnosis is confirmed, the patient is labeled as having acute HIT, a highly prothrombotic phase which persists until platelet count recovery. Subacute HIT A is the phase following platelet count recovery but before the functional assay becomes negative. Subacute HIT B is the interval after the functional assay becomes negative but before the immunoassay becomes negative. Finally, once anti-PF4 or anti-heparin antibodies are no longer detectable by immunoassay, the patient is said to have remote HIT. Applicable recommendations are listed for each of the 5 phases of HIT. Adapted from Cuker.[41]

a functional assay (conditional recommendation, moderate certainty in the evidence about effects ⊕⊕⊕◯).

Remarks: Missing or inaccurate information may lead to a faulty 4Ts score and inappropriate management decisions. Every effort should be made to obtain accurate and complete information necessary to calculate the 4Ts score. If key information is missing, it may be prudent to err on the side of a higher 4Ts score. Patients should be reassessed frequently. If there is a change in the clinical picture, the 4Ts score should be recalculated.

Different immunoassays and functional assays are available. The choice of assay may be influenced by diagnostic accuracy, availability, cost, feasibility, and turnaround time. If an enzyme-linked immunoassay (ELISA) is used, a low threshold is preferred over a high threshold. In some settings, a functional assay may not be available, and decisions may need to be made on the basis of the results of the 4Ts score and immunoassay. In general, the likelihood of HIT increases with a higher 4Ts score and a higher ELISA optical density (OD). A functional assay may not be necessary for patients with a high-probability 4Ts score and very strongly positive immunoassay (eg, an ELISA value of >2.0 OD units). In some centers, a functional assay may be performed in tandem with an immunoassay for quality assurance or efficiency.

Recommendation 2.2. In patients with suspected HIT and a low-probability 4Ts score, the ASH guideline panel *recommends against* HIT laboratory testing (strong recommendation, moderate certainty in the evidence about effects ⊕⊕⊕◯). **Remark:** HIT laboratory testing may be appropriate for patients with a low-probability 4Ts score if there is uncertainty about the 4Ts score (eg, because of missing data).

Recommendation 2.3. In patients with suspected HIT and a low-probability 4Ts score, the ASH guideline panel *recommends against* empiric treatment of HIT (ie, against discontinuation of heparin and initiation of a non-heparin anticoagulant) (strong recommendation, moderate certainty in the evidence about effects ⊕⊕⊕◯).

Recommendation 2.4.a. In patients with suspected HIT and an intermediate-probability 4Ts score who have no other indication for therapeutic-intensity anticoagulation, the ASH guideline panel *recommends* discontinuation of heparin (strong recommendation, moderate certainty in the evidence about effects ⊕⊕⊕◯).

Recommendation 2.4.b. The ASH guideline panel *suggests* initiation of a non-heparin anticoagulant at prophylactic intensity if the patient is at high risk of bleeding and at therapeutic intensity if the patient is not at high risk of bleeding (conditional recommendation, moderate certainty in the evidence about effects ⊕⊕⊕◯).

Recommendation 2.5.a. In patients with suspected HIT and an intermediate-probability 4Ts score who have another indication for therapeutic-intensity anticoagulation, the ASH guideline panel *recommends* discontinuation of heparin (strong recommendation, moderate certainty in the evidence about effects ⊕⊕⊕◯).

Recommendation 2.5.b. The ASH guideline panel *suggests* initiation of a non-heparin anticoagulant at therapeutic intensity (conditional recommendation, moderate certainty in the evidence about effects ⊕⊕⊕◯).

Recommendation 2.6. In patients with suspected HIT and a high-probability 4Ts score, the ASH guideline panel *recommends* discontinuation of heparin and initiation of a non-heparin anticoagulant at therapeutic intensity (strong recommendation, moderate certainty in the evidence about effects ⊕⊕⊕◯).

Recommendation 2.7. In patients with an intermediate-probability 4Ts score and a negative immunoassay, the ASH guideline panel *recommends* discontinuation of the non-heparin anticoagulant and resumption of heparin, if indicated (strong recommendation, moderate certainty in the evidence about effects ⊕⊕⊕◯).

Recommendation 2.8. In patients with a high-probability 4Ts score and a negative immunoassay, the ASH guideline panel *recommends* discontinuation of the non-heparin anticoagulant and resumption of heparin, if indicated (strong recommendation, moderate certainty in the evidence about effects ⊕⊕⊕◯). **Remark:** Rarely, patients with HIT may have a negative immunoassay, either because of a laboratory error or because the pathologic antigen involves a complex of heparin and a molecule other than PF4. Clinical reevaluation, a repeat immunoassay, a different immunoassay, and/or a functional assay may be helpful in clarifying the diagnosis.

Recommendation 2.9. In patients with an intermediate-probability 4Ts score and a positive immunoassay, the ASH guideline panel *recommends* continued avoidance of heparin and continued administration of a non-heparin anticoagulant at therapeutic intensity. For patients who were receiving prophylactic-intensity anticoagulation, the ASH guideline panel *recommends* providing therapeutic-intensity anticoagulation (strong recommendations, moderate certainty in the evidence about effects ⊕⊕⊕◯).

Recommendation 2.10. In patients with a high-probability 4Ts score and a positive immunoassay, the ASH guideline panel *recommends* continued avoidance of heparin and continued

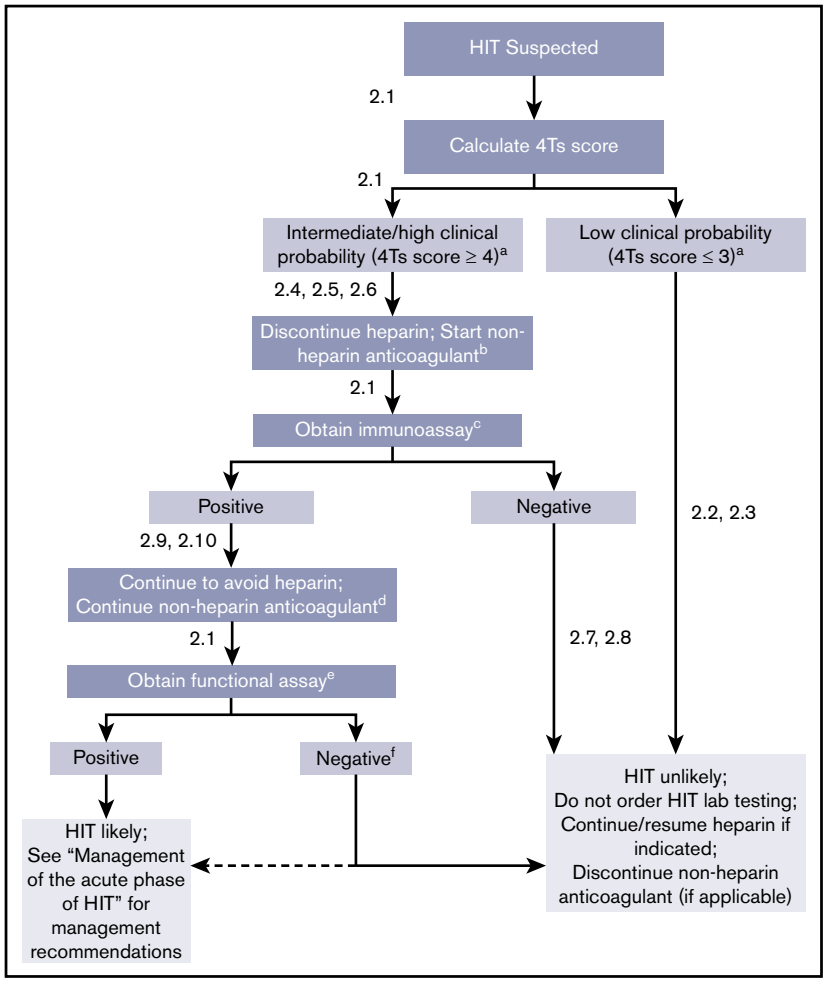

Figure 1. Algorithm for the diagnosis and initial management of patients with suspected HIT. Numbered recommendations are listed in the corresponding portion of the algorithm. Actions are in dark gray boxes; test results are in light gray boxes. [a]Missing or inaccurate information may lead to a faulty 4Ts score and inappropriate management decisions. Every effort should be made to obtain accurate and complete information necessary to calculate the 4Ts score. If key information is missing, it may be prudent to err on the side of a higher 4Ts score. HIT laboratory testing may be appropriate for patients with a low-probability 4Ts score if there is uncertainty about the 4Ts score (eg, because of missing data). Patients should be reassessed frequently. If there is a change in the clinical picture, the 4Ts score should be recalculated. [b]If the patient has an intermediate-probability 4Ts score, has no other indication for therapeutic-intensity anticoagulation, and is judged to be at high risk for bleeding, the panel suggests treatment with a non-heparin anticoagulant at prophylactic intensity rather than therapeutic intensity. If the patient has an intermediate-probability 4Ts score and is not judged to be at high risk for bleeding or has another indication for therapeutic-intensity anticoagulation, the panel suggests treatment with a non-heparin anticoagulant at therapeutic intensity rather than prophylactic intensity. In a patient with a high-probability 4Ts score, the panel recommends treatment with a non-heparin anticoagulant at therapeutic intensity. [c]Different immunoassays are available. The choice of assay may be influenced by accuracy, availability, cost, feasibility, and turnaround time. If an enzyme-linked immunoassay is used, a lower threshold is preferred over a high threshold. [d]For all patients with a positive immunoassay, including those who were receiving prophylactic-intensity treatment with a non-heparin anticoagulant before the availability of the immunoassay result, the panel recommends treatment with a non-heparin anticoagulant at therapeutic intensity. [e]Different functional assays are available. The choice of assay may be influenced by accuracy, availability, cost, feasibility, and turnaround time. In some settings, a functional assay may not be available, and decisions may need to be made on the basis of the results of the 4Ts score and immunoassay. A functional assay may not be necessary in patients with a high 4Ts score and a strongly positive immunoassay. [f]Most patients with a negative functional assay do not have HIT and may be managed accordingly. However, depending on the type of functional assay and the technical expertise of the laboratory, false-negative results are possible. Therefore, a presumptive diagnosis of HIT may be considered for some patients with a negative functional assay, especially if there is a high-probability 4Ts score and a strongly positive immunoassay (represented in the figure by a dashed line).

administration of a non-heparin anticoagulant at therapeutic intensity (strong recommendation, moderate certainty in the evidence about effects ⊕⊕⊕◯).

Management of the acute phase of HIT

Recommendation 3.1. In patients with acute HIT complicated by thrombosis (HITT) or acute HIT without thrombosis (isolated HIT), the ASH guideline panel *recommends* discontinuation of heparin and initiation of a non-heparin anticoagulant (strong recommendation, moderate certainty in the evidence about effects ⊕⊕⊕◯). When a non-heparin anticoagulant is being selected, the ASH guideline panel *suggests* argatroban, bivalirudin, danaparoid, fondaparinux, or a direct oral anticoagulant (DOAC) (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Remarks: The choice of agent may be influenced by drug factors (availability, cost, ability to monitor the anticoagulant effect, route of

administration, and half-life), patient factors (kidney function, liver function, bleeding risk, and clinical stability), and experience of the clinician.

In patients with critical illness, increased bleeding risk, or increased potential need for urgent procedures, argatroban or bivalirudin may be preferred because of shorter duration of effect. These patients may require close monitoring. In patients with moderate or severe hepatic dysfunction (Child-Pugh class B and C), it is advisable to avoid argatroban or use a reduced dose.

Fondaparinux and the DOACs are reasonable options in clinically stable patients at average risk of bleeding. The same contraindications to their use in the treatment of acute VTE should be applied in determining their appropriateness for patients with HIT.

In patients with HIT complicated by life- or limb-threatening thromboembolism (eg, massive pulmonary embolism or venous limb gangrene), a parenteral non-heparin anticoagulant may be preferred because few such patients have been treated with a DOAC.

With respect to the choice of DOAC, most of the published experience in HIT is with rivaroxaban. Various dosing regimens have been reported. For patients with acute HITT, rivaroxaban at a dose of 15 mg twice per day for 3 weeks followed by 20 mg once per day is preferred. For patients with acute isolated HIT, rivaroxaban 15 mg twice per day until platelet count recovery (usually a platelet count of $\geq 150 \times 10^9$/L) followed by 20 mg once per day is preferred if there is an indication for ongoing anticoagulation.

Recommendation 3.2. In patients with acute HITT or acute isolated HIT, the ASH guideline panel *recommends* treatment with a non-heparin anticoagulant at therapeutic-intensity dosing rather than prophylactic-intensity dosing (strong recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Recommendation 3.3. In patients with acute HITT or acute isolated HIT and no other indication for antiplatelet therapy, the ASH guideline panel *suggests* treatment with a non-heparin anticoagulant alone rather than in combination with an antiplatelet agent (conditional recommendation, low certainty in the evidence about effects ⊕⊕◯◯). **Remark:** In patients with acute HITT or acute isolated HIT and another indication for antiplatelet therapy (eg, coronary artery disease or recent coronary stent placement), the decision to continue antiplatelet therapy during treatment with a non-heparin anticoagulant may be influenced by the risk of vascular events and bleeding.

Recommendation 3.4. In patients with acute HITT or acute isolated HIT, the ASH guideline panel *recommends against* routine insertion of an inferior vena cava (IVC) filter (strong recommendation, moderate certainty in the evidence about effects ⊕⊕⊕◯).

Recommendation 3.5. In patients with acute HITT or acute isolated HIT, the ASH guideline panel *recommends against* initiation of a vitamin K antagonist (VKA) before platelet count recovery (usually a platelet count of $\geq 150 \times 10^9$/L) (strong recommendation, moderate certainty in the evidence about effects ⊕⊕⊕◯). **Remark:** This recommendation also applies to patients who are taking a VKA at the onset of acute HITT or acute isolated HITT. In these patients, the VKA would be discontinued, and intravenous vitamin K would be administered concomitant with initiation of a non-heparin anticoagulant (see recommendations 3.1, 3.2, and 3.4).

Recommendation 3.6. In patients with acute HITT or acute isolated HIT who are at average bleeding risk, the ASH guideline panel *suggests against* routine platelet transfusion (conditional recommendation, low certainty in the evidence about effects ⊕⊕◯◯). **Remark:** Platelet transfusion may be an option for patients with active bleeding or at high risk of bleeding.

Recommendation 3.7.a. In patients with acute isolated HIT, the ASH guideline panel *suggests* bilateral lower-extremity compression ultrasonography to screen for asymptomatic proximal deep vein thrombosis (DVT) (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Recommendation 3.7.b. In patients with acute isolated HIT and an upper-extremity central venous catheter (CVC), the ASH guideline panel *suggests* upper-extremity ultrasonography in the limb with the catheter to screen for asymptomatic DVT. The ASH guideline panel *suggests against* upper-extremity ultrasonography in limbs without CVCs to screen for asymptomatic DVT (conditional recommendations, very low certainty in the evidence about effects ⊕◯◯◯). **Remark:** These recommendations do not apply to patients with signs or symptoms suggestive of DVT for whom diagnostic imaging would be indicated.

Recommendation 3.8. In patients with acute isolated HIT and no asymptomatic DVT identified by screening compression ultrasonography, the ASH guideline panel *suggests* that anticoagulation be continued, at a minimum, until platelet count recovery (usually a platelet count of $\geq 150 \times 10^9$/L). The ASH guideline panel *suggests against* continuing treatment for ≥3 months unless the patient has persisting HIT without platelet count recovery (conditional recommendations, very low certainty in the evidence ⊕◯◯◯). **Remark:** These recommendations apply only to patients with isolated HIT. The ASH guideline panel did not address the duration of anticoagulation in patients with acute HITT and no other indication for anticoagulation in whom anticoagulation is typically given for 3 to 6 months.

Recommendation 3.9. In patients with subacute HIT A, the ASH guideline panel *suggests* treatment with a DOAC (eg, dabigatran, rivaroxaban, or apixaban) rather than a VKA (conditional recommendation, moderate certainty in the evidence about effects ⊕⊕⊕◯).

Remarks: The choice of agent may be influenced by drug factors (availability, cost, ability to monitor the anticoagulant effect, route of administration, and half-life), patient factors (kidney function, liver function, bleeding risk, and clinical stability), and experience of the clinician.

DOACs are preferred for clinically stable patients at average bleeding risk. The same contraindications to their use in the treatment of acute VTE should be applied in determining their appropriateness for patients with HIT.

Cardiovascular surgery

Good practice statement 4.1.a. In patients with acute HIT or subacute HIT A who require cardiovascular surgery, the ASH guideline panel agrees that surgery should be delayed until the patient has subacute HIT B or remote HIT (see recommendation 4.2), if feasible.

Recommendation 4.1.b. If delaying surgery is not feasible, the ASH guideline panel *suggests* one of the following: intraoperative anticoagulation with bivalirudin, intraoperative heparin after

treatment with preoperative and/or intraoperative plasma exchange, or intraoperative heparin in combination with a potent antiplatelet agent (eg, prostacyclin analog or tirofiban) (conditional recommendation, low certainty in the evidence about effects ⊕⊕◯◯). **Remarks:** The choice of strategy may be influenced by availability, cost, and clinician experience. Consensus protocols for the plasma exchange and intraoperative heparin strategy and for the intraoperative heparin and potent antiplatelet agent strategy have not been established. If either of these strategies is used, treatment with heparin is limited to the intraoperative setting and avoided before and after surgery.

Recommendation 4.2. In patients with subacute HIT B or remote HIT who require cardiovascular surgery, the ASH guideline panel *suggests* intraoperative anticoagulation with heparin rather than treatment with a non-heparin anticoagulant or plasma exchange and heparin or heparin combined with an antiplatelet agent (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯). **Remarks:** Treatment with heparin would be limited to the intraoperative setting and avoided before and after surgery. Postoperative platelet count monitoring for HIT may be necessary, even when postoperative heparin is not given, because delayed-onset (autoimmune) HIT beginning 5 to 10 days after the intraoperative heparin exposure has been reported.

Percutaneous cardiovascular intervention

Recommendation 5.1. In patients with acute HIT or subacute HIT A who require PCI, the ASH guideline panel *suggests* treatment with bivalirudin rather than a different non-heparin anticoagulant (conditional recommendation, low certainty in the evidence ⊕⊕◯◯). **Remarks:** If bivalirudin is not available or there is a lack of institutional experience, argatroban might be a suitable substitute. The choice of drug may be influenced by drug availability, cost, ability to monitor the anticoagulant effect, and clinician experience.

Recommendation 5.2. In patients with subacute HIT B or remote HIT who require PCI, the ASH guideline panel *suggests* treatment with bivalirudin rather than UFH (conditional recommendation, very low certainty in the evidence ⊕◯◯◯).

Remarks: Heparin is an acceptable alternative for patients with subacute HIT B or remote HIT if a suitable non-heparin anticoagulant is not available or clinician experience is lacking. If heparin is used, exposure should be limited to the intraprocedural setting and should be avoided before and after the procedure.

If bivalirudin is not available or there is a lack of institutional experience, argatroban might be a suitable substitute. The choice of drug may be influenced by drug availability, cost, ability to monitor the anticoagulant effect, and clinician experience.

Renal replacement therapy

Recommendation 6.1. In patients with acute HIT who are receiving renal replacement therapy and require anticoagulation to prevent thrombosis of the dialysis circuitry, the ASH guideline panel *suggests* treatment with argatroban, danaparoid, or bivalirudin rather than other non-heparin anticoagulants (conditional recommendation; very low certainty in the evidence about effects ⊕◯◯◯). **Remark:** The choice of agent may be influenced by drug factors (availability, cost), patient factors (liver function), and experience of the clinician.

Recommendation 6.2. In patients with subacute HIT A, subacute HIT B, or remote HIT who are receiving renal replacement therapy, are not otherwise receiving anticoagulation, and require anticoagulation to prevent thrombosis of the dialysis circuit, the ASH guideline panel *suggests* regional citrate rather than heparin or other non-heparin anticoagulants (conditional recommendation; very low certainty in the evidence about effects ⊕◯◯◯). **Remark:** Citrate is not appropriate for patients with acute HIT, who require systemic rather than regional anticoagulation (see recommendation 6.1).

VTE treatment and prophylaxis in patients with remote HIT

Recommendation 7.1. In patients with remote HIT who require VTE treatment or prophylaxis, the ASH guideline panel *recommends* administration of a non-heparin anticoagulant (eg, apixaban, dabigatran, danaparoid, edoxaban, fondaparinux, rivaroxaban, or VKA) rather than UFH or LMWH (strong recommendation, very low certainty in the evidence about effects ⊕◯◯◯). **Remarks:** For recommendations on choice of non-heparin anticoagulant for VTE prophylaxis, please refer to the *American Society of Hematology Guidelines on Prevention of Venous Thromboembolism in Surgical Hospitalized Patients* (manuscript in preparation) and *Prophylaxis for Hospitalized and Nonhospitalized Medical Patients* (Schünemann HJ et al, *Blood Advances*, in press). For recommendations on choice of agent for VTE treatment, please refer to the *American Society of Hematology Guidelines on Treatment of Acute VTE* (manuscript in preparation).

Emergency identification

Recommendation 8.1.a. In patients with a history of HIT in the past 3 months, the ASH guideline panel *suggests* carrying or wearing an emergency identifier (eg, an emergency pendant or bracelet) (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯). **Remark:** The emergency identifier should include the drug (heparin), the reaction to the drug (HIT), and the date HIT was diagnosed.

Recommendation 8.1.b. In patients with a history of HIT more than 3 months ago, the ASH panel *suggests against* carrying or wearing an emergency identifier (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Values and preferences

For most recommendations, the ASH guideline panel placed a high value on avoiding death, limb amputation, and new thrombotic events. The values were based on literature showing that most people find that DVT and pulmonary embolism likely have an impact on their lives. When considering the effects of different diagnostic strategies, the ASH guideline panel placed a higher value on avoiding false negatives (ie, missing true HIT cases) and a lower value on avoiding false positives (ie, treating patients who do not have true HIT). The high value placed on false negatives was a result of the high risk of death, limb amputation, and thrombosis associated with a delay in initiation of appropriate therapy in patients with true HIT.[17,20] The panel perceived these risks to exceed the harms of false-positive diagnosis, which are nonetheless substantial and include non-heparin anticoagulant-associated major bleeding, unnecessary suspension of heparin, and inappropriate withholding of heparin in patients who have been mislabeled as having a heparin allergy.

Explanations and other considerations

These recommendations take into consideration cost and cost-effectiveness and the impact on equity, acceptability, and feasibility.

Some recommendations address selection of a non-heparin anticoagulant among multiple options. The ASH guideline panel agreed that some agents may not be accessible in all institutions or jurisdictions and may not be affordable for all patients. In addition, experience with these medications may vary among clinicians, which may influence the choice of agent. Similar issues were considered when recommendations were made about different laboratory tests for diagnosing HIT. Although immunoassays are widely available and the turnaround time for results is relatively rapid, functional assays are not available in most institutions, and additional cost and wait time may be incurred if the test needs to be sent to a reference laboratory for analysis, thus limiting the feasibility of implementing some strategies.

Introduction

Aims of these guidelines and specific objectives

The purpose of these guidelines is to provide evidence-based recommendations about the diagnosis and management of HIT. The target audience includes patients, hematologists, internists, surgeons, hospitalists, intensivists, anesthesiologists, other clinicians, and decision makers. Policy makers interested in these guidelines include those involved in developing local, national, or international protocols with the goal of improving the diagnosis and management of patients with HIT and evaluating direct and indirect harms related to HIT. This article may also serve as the basis for adaptation by local, regional, or national guideline panels.

Description of the health problems

HIT is an iatrogenic disorder mediated in most cases by immunoglobulin G antibodies that target multimolecular complexes of PF4 and heparin.[12,21] These antibodies engender a hypercoagulable state through activation of platelets and generation of procoagulant platelet-derived microparticles as well as activation of monocytes, neutrophils, and endothelial cells, with resultant elaboration of tissue factor and proadhesive surface molecules.[22-26] The end result of these changes is a profound thrombotic tendency. Thrombosis occurs in one-third to one-half of patients with HIT and may be venous, arterial, or microvascular.[17-19] Rates of amputation are ~1% to 3%, and rates of death associated with HIT are ~5% to 10%.[17,27-31] Although HIT is associated with a decrease in platelet count, as its name implies, clinically significant bleeding at presentation is uncommon.[32]

UFH and LMWH are widely used in hospitalized patients. Approximately 12 million inpatients in the United States alone are exposed to heparin each year.[13] The incidence of HIT among these patients ranges from <0.1% to 7% depending on the type of heparin, duration of heparin exposure, and patient population. UFH is associated with an ~10-fold greater risk of HIT than LMWH,[14] whereas the risk with fondaparinux is negligible.[33,34] HIT occurs in 2% to 3% of patients who receive UFH for 6 or more consecutive days but is significantly less common with more abbreviated courses of treatment.[14,15] HIT occurs with approximately threefold-greater frequency in surgical and major trauma patients than in medical patients and is rarely observed in pediatric and obstetrical populations.[35-38]

The clinical and immunologic response to heparin in a patient with acute HIT follows a predictable pattern after discontinuation of heparin. Platelet count recovery occurs within 7 days in 90% of cases, although it may take weeks in a minority of patients.[39,40] Functional assays become negative at a median of 50 days after heparin is suspended. Circulating anti-PF4/heparin antibodies are no longer detectable by immunoassay at a median of 85 days.[39]

This stereotyped pattern of events allows HIT to be conceptually divided into 5 sequential phases (Table 1).[41] In suspected HIT, the patient is thought to have HIT on clinical grounds, but confirmatory laboratory test results are not yet available. Once the diagnosis is confirmed, the patient is labeled as having acute HIT, a highly prothrombotic phase that persists until platelet count recovery. Subacute HIT A is the phase after platelet count recovery but before the functional assay becomes negative. Subacute HIT B is the interval after the functional assay becomes negative but before the immunoassay becomes negative. Finally, once anti-PF4/heparin antibodies are no longer detectable by immunoassay, the patient is said to have remote HIT. Each phase of HIT confronts the clinician with a unique set of management questions. The terms for the various phases of HIT are used in these guidelines. Recommendations associated with each of the 5 phases are listed in Table 1.

HIT is a clinicopathologic disorder. Diagnosis rests on a careful clinical assessment of the likelihood of HIT and HIT laboratory test results. Left untreated, HIT is associated with an initial 5% to 10% daily risk of thromboembolism, amputation, and death.[17,20] Therefore, in patients in whom there is sufficient suspicion, it is often necessary to initiate empiric therapy for HIT while awaiting the results of diagnostic laboratory testing.[42] Recommendations 2.1 through 2.10 address the diagnosis and initial management of suspected HIT and are summarized in Figure 1.

Management of acute HIT involves discontinuation of heparin and administration of a non-heparin anticoagulant. Non-heparin anticoagulants acceptable for the treatment of acute HIT are listed in recommendation 3.1. Dosing and pharmacologic properties of these agents are summarized in Table 2.

Special considerations are required for patients with a history of HIT who require cardiovascular surgery, PCI, renal replacement therapy, or VTE prophylaxis. These situations are addressed in recommendations 4.1-4.2, 5.1-5.2, 6.1-6.2, and 7.1, respectively. Recommendation 8.1 addresses the use of an emergency identifier (eg, an emergency pendant or bracelet) for patients with a history of HIT.

Methods

The guideline panel developed and graded the recommendations and assessed the certainty in the supporting evidence following the GRADE approach.[5-11] The overall guideline development process, including funding of the work, panel formation, management of conflicts of interest, internal and external review, and organizational approval, was guided by ASH policies and procedures derived from the Guideline International Network (GIN)-McMaster Guideline Development Checklist (http://cebgrade.mcmaster.ca/guidecheck.html) and was intended to meet recommendations for trustworthy guidelines by the Institute of Medicine and the GIN.[1-4] An

Table 2. Non-heparin anticoagulants for treatment of acute HIT

Drug	Mechanism of action	Route of administration	Primary mechanism of elimination (half-life)	Dosing	Laboratory monitoring
Argatroban	Direct thrombin inhibitor	IV	Hepatobiliary (40-50 min)	Bolus: none Continuous infusion: Normal organ function → 2 μg/kg/min Liver dysfunction (bilirubin >1.5 mg/dL) → 0.5-1.2 μg/kg/min Heart failure, anasarca, postcardiac surgery → 0.5-1.2 μg/kg/min	Adjust to APTT 1.5-3.0 times baseline
Bivalirudin*	Direct thrombin inhibitor	IV	Enzymatic (25 min)	Bolus: none Continuous infusion: Normal organ function → 0.15 mg/kg/h Renal or liver dysfunction → dose reduction may be appropriate	Adjust to APTT 1.5-2.5 times baseline
Danaparoid	Indirect factor Xa inhibitor	IV	Renal (24 h)	Bolus: <60 kg, 1500 units 60-75 kg, 2250 units 75-90 kg, 3000 units >90 kg, 3750 units Accelerated initial infusion: 400 units/h × 4 h, then 300 units/h × 4 h Maintenance infusion: Normal renal function → 200 units/h Renal dysfunction → 150 units/h	Adjust to danaparoid-specific anti-Xa activity of 0.5-0.8 units/mL
Fondaparinux*	Indirect factor Xa inhibitor	SC	Renal (17-24 h)	<50 kg → 5 mg once per day 50-100 kg → 7.5 mg once per day >100 kg → 10 mg once per day	None
Apixaban*†	Direct factor Xa inhibitor	PO	Hepatic (8-15 h)	HITT: 10 mg twice per day × 1 week, then 5 mg twice per day Isolated HIT: 5 mg twice per day until platelet count recovery	None
Dabigatran*†	Direct thrombin inhibitor	PO	Renal (12-17 h)	HITT: 150 mg twice per day after ≥5 days of treatment with a parenteral non-heparin anticoagulant Isolated HIT: 150 mg twice per day until platelet count recovery	None
Rivaroxaban*†	Direct factor Xa inhibitor	PO	Renal (5-9 h)	HITT: 15 mg twice per day × 3 weeks, then 20 mg once per day Isolated HIT: 15 mg twice per day until platelet count recovery	None

Guidance on selecting an anticoagulant for an individual patient is provided in the remarks associated with recommendation 3.1.
APTT, activated partial thromboplastin time; IV, intravenous; PO, per os; SC, subcutaneous.
*Not approved for treatment of acute HIT.
†Dosing for treatment of acute HIT is not well established. Suggested dosing is extrapolated from venous thromboembolism and based on limited published experience in HIT.

article detailing the methods used to develop these guidelines is forthcoming.

Organization, panel composition, planning, and coordination

The work of this panel was coordinated with 9 other guideline panels (addressing other aspects of VTE) by ASH and the McMaster GRADE Centre (funded by ASH under a paid agreement). Project oversight was initially provided by a coordination panel, which reported to the ASH Committee on Quality, then by the coordination panel chair (A.C.) and vice chair (Holger Schünemann). ASH vetted and appointed individuals to the guideline panel. The McMaster GRADE Centre vetted and retained researchers to conduct systematic reviews of evidence and coordinate the guideline development process, including the use of the GRADE approach. The membership of the panel and the GRADE Centre team is described in supplement 1.

The panel included hematologists with clinical and research expertise on HIT, physicians from other disciplines with similar expertise, methodologists with expertise in evidence appraisal and guideline development, and 2 patient representatives. The panel chair was a content expert. The vice chair was a methodologist.

In addition to synthesizing evidence systematically, the McMaster GRADE Centre supported the guideline development process by determining methods, preparing agendas and meeting materials, and facilitating panel discussions. The Panel performed its work by using Web-based tools (www.surveymonkey.com and www.gradepro.org) and face-to-face and online meetings.

Guideline funding and management of conflicts of interest

Development of these guidelines was wholly funded by ASH, a nonprofit medical specialty society that represents hematologists. Most members of the guideline panel were members of ASH. ASH staff supported panel appointments and coordinated meetings but had no role in choosing the guideline questions or determining the recommendations.

Members of the guideline panel received travel reimbursement for attendance at in-person meetings, and the 2 patient representatives each received an honorarium of $200. The panelists received no other payments. Through the McMaster GRADE Centre, some researchers who contributed to the systematic evidence reviews received salary or grant support. Other researchers participated to fulfill requirements of an academic degree or program.

Conflicts of interest of all participants were managed according to ASH policies on the basis of recommendations of the Institute of Medicine[43] and the GIN.[4] At the time of appointment, a majority of the guideline panel, including the chair and the vice chair, had no conflicts of interest as defined and judged by ASH (ie, no current material interest in any commercial entity with a product that could be affected by the guidelines). Some panelists disclosed new interests or relationships during the development process, but the balance of the majority was maintained.

Before appointment to the panel, individuals disclosed both financial and nonfinancial interests. Members of the VTE Guideline Coordination Panel reviewed the disclosures and judged which interests were conflicts and should be managed. Supplement 2 provides the complete "Disclosure of Interests" forms for all panel members. In Part A of the forms, individuals disclosed material interests for 2 years before appointment. In Part B, they disclosed interests that were not mainly financial. Part C summarizes ASH decisions about which interests were judged to be conflicts. Part D describes new interests disclosed by individuals after appointment.

Recusal was also used to manage conflicts of interest. During all deliberations, panel members with a current, direct financial interest in a commercial entity with any product that could be affected by the guidelines were recused from making judgments about relevant recommendations.[4,44-46] The Evidence-to-Decision framework for each recommendation describes which individuals were recused from making judgments about each recommendation.

None of the McMaster-affiliated researchers who contributed to the systematic evidence reviews or who supported the guideline development process had any current material interest in a commercial entity with any product that could be affected by the guidelines. Supplement 3 provides the complete Disclosure of Interest forms for researchers who contributed to these guidelines.

Formulating specific clinical questions and determining outcomes of interest

The panel used the GRADEpro Guideline Development Tool (www.gradepro.org)[47] and SurveyMonkey (www.surveymonkey.com) to brainstorm and then prioritize the questions.

The ASH guideline panel selected outcomes of interest for each question a priori, following an approach described in detail elsewhere.[48] In brief, the panel first brainstormed all possible outcomes before rating their relative importance for decision-making following the GRADE approach.[48] During this rating process, the panel used definitions of the outcomes ("marker states") that were developed for these guidelines. Rating outcomes by their relative importance can help focus attention on those outcomes that are considered most important for both clinicians and patients and help to resolve or clarify potential disagreements. The outcomes rated highly by the panel and those identified as important based on the literature reviews were further refined. The panel rated the following outcomes as critical for clinical decision making across questions: thromboembolism, limb amputation, mortality, major bleeding, diagnostic accuracy, pulmonary embolism, IVC filter failure, hospitalization, and recurrent acute HIT.

Evidence review and development of recommendations

For each guideline question, the McMaster GRADE Centre prepared a GRADE Evidence-to-Decision (EtD) framework, using the GRADEpro Guideline Development Tool (www.gradepro.org).[5,6,11] The EtD table summarized the results of systematic reviews of the literature that were updated or performed for this guideline. The EtD table addressed the effects of interventions, resource use (cost-effectiveness), values and preferences (relative importance of outcomes), equity, acceptability, and feasibility. The guideline panel reviewed draft EtD tables

before, during, or after the guideline panel meeting and made suggestions for corrections and identified missing evidence. To ensure that recent studies were not missed, searches (presented in supplement 4) were updated during December 2017, and panel members were asked to suggest any studies that may have been considered missed and fulfilled the inclusion criteria for the individual questions.

Under the direction of the McMaster GRADE Centre, researchers followed the general methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions (https://training.cochrane.org/handbook) for conducting updated or new systematic reviews of intervention effects. When existing reviews were used, judgments of the original authors about risk of bias were either randomly checked for accuracy and accepted or conducted de novo if they were not available or not reproducible. For new reviews, risk of bias was assessed at the health outcome level using the Cochrane Collaboration's risk of bias tool for randomized trials or nonrandomized studies. In addition to conducting systematic reviews of intervention effects, the researchers searched for evidence related to baseline risks, values, preferences, and costs and summarized findings within the EtD frameworks.[5,6,11] Subsequently, the certainty in the body of evidence (also known as quality of the evidence or confidence in the estimated effects) was assessed for each effect estimate of the outcomes of interest following the GRADE approach. The GRADE approach was based on the following domains: risk of bias, precision, consistency, magnitude of the estimates of effects, directness of the evidence, risk of publication bias, presence of large effects, and dose-response relationship, and an assessment of the effect of residual, opposing confounding. The certainty was categorized into 4 levels ranging from very low to high.[7-9]

During a 2-day in-person meeting followed by online communication and conference calls, the panel developed clinical recommendations based on the evidence summarized in the EtD tables. For each recommendation, the panel took a population perspective and came to consensus on the following: the certainty in the evidence, the balance of benefits and harms of the compared management options, and the assumptions about the values and preferences associated with the decision. The guideline panel also explicitly took into account the extent of resource use associated with alternative management options. The panel agreed on the recommendations (including direction and strength), remarks, and qualifications by consensus or, in rare instances, by voting (an 80% majority was required for a strong recommendation) based on the balance of all desirable and undesirable consequences. The final guidelines, including recommendations, were reviewed and approved by all members of the panel.

Interpretation of strong and conditional recommendations

The recommendations are labeled as either "strong" or "conditional," according to the GRADE approach. The words "the guideline panel recommends" are used for strong recommendations and "the guideline panel suggests" for conditional recommendations. Table 3 provides GRADE's interpretation of strong and conditional recommendations by patients, clinicians, health care policy makers, and researchers.

Document review

Draft recommendations were reviewed by all members of the panel, revised, and then made available online on September 1, 2017, for external review by stakeholders including allied organizations, other medical professionals, patients, and the public. Nine individuals or organizations submitted comments. The document was revised to address pertinent comments, but no changes were made to recommendations. On July 30, 2018, the ASH Guideline Oversight Subcommittee and the ASH Committee on Quality verified that the defined guideline development process was followed, and on August 3, 2018, the officers of the ASH Executive Committee approved submission of the guidelines for publication under the imprimatur of ASH. The guidelines were then subjected to peer review by *Blood Advances*.

How to use these guidelines

ASH guidelines are primarily intended to help clinicians make decisions about diagnostic and treatment alternatives. Other purposes are to inform policy, education, and advocacy, and to state future research needs. They may also be used by patients. These guidelines are not intended to serve as or be construed as a standard of care. Clinicians must make decisions on the basis of the clinical presentation of each individual patient, ideally through a shared process that considers the patient's values and preferences with respect to the anticipated outcomes of the chosen option. Decisions may be constrained by the realities of a specific clinical setting and local resources, including but not limited to institutional policies, time limitations, and availability of treatments. These guidelines may not include all appropriate methods of care for the clinical scenarios described. As science advances and new evidence becomes available, recommendations may become outdated. Following these guidelines cannot guarantee successful outcomes. ASH does not warrant or guarantee any products described in these guidelines.

Statements about the underlying values and preferences as well as qualifying remarks accompanying each recommendation are its integral parts and serve to facilitate more accurate interpretation. They should never be omitted when recommendations from these guidelines are quoted or translated. Implementation of the guidelines will be facilitated by related interactive forthcoming decision aids. The use of these guidelines is also facilitated by the links to the EtD frameworks and interactive summary of findings tables in each section.

Recommendations

Screening asymptomatic patients for HIT

Question: Should platelet count monitoring be used to screen for HIT in patients at risk of HIT?

Recommendation 1.1.a

For patients receiving heparin in whom the risk of HIT is considered low (<0.1%), the ASH guideline panel *suggests against* platelet count monitoring to screen for HIT (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Table 3. Interpretation of strong and conditional recommendations

Implications for:	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
Clinicians	Most individuals should receive the intervention. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.	Different choices will be appropriate for individual patients; the clinician must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.
Policy makers	The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Policy-making will require substantial debate and involvement of various stakeholders.

Recommendation 1.1.b

For patients receiving heparin in whom the risk of HIT is considered intermediate (0.1% to 1.0%) or high (>1.0%), the ASH guideline panel *suggests* platelet count monitoring to screen for HIT. If the patient has received heparin in the 30 days before the current course of heparin, the ASH guideline panel *suggests* platelet count monitoring beginning on day 0 (the day heparin is initiated). If the patient has not received heparin in the 30 days before the current course of heparin, the ASH guideline panel *suggests* monitoring the platelet count from day 4 until day 14 or until heparin is stopped, whichever occurs first, if practicable. In high-risk patients, the ASH guideline panel *suggests* monitoring the platelet count at least every other day. In intermediate-risk patients, the ASH guideline panel *suggests* monitoring the platelet count every 2 to 3 days (conditional recommendations, very low certainty in the evidence about effects ⊕◯◯◯). **Remarks:** Low-risk patients include medical and obstetric patients receiving LMWH, patients receiving LMWH after minor surgery or minor trauma, and any patients receiving fondaparinux. Intermediate-risk populations include medical and obstetric patients receiving UFH and patients receiving LMWH after major surgery or major trauma. High-risk populations include surgical and trauma patients receiving postoperative UFH. Some patients may receive a combination of UFH and LMWH or UFH and fondaparinux; these patients should be considered to belong to the UFH group.

In patients at intermediate or high risk for HIT who have not received heparin in the 30 days before the current course of heparin, some clinicians may choose to begin monitoring the platelet count before day 4 because platelet count values before day 4 may aid in the interpretation of platelet count values beyond day 4.

Summary of the evidence. We did not identify any randomized or nonrandomized studies assessing platelet count monitoring to identify HIT. Instead, evidence for the importance of early recognition of HIT was used. To determine which patients are at high risk of developing HIT, a meta-analysis of 15 studies primarily in patients after orthopedic surgery and individual studies reporting the incidence of HIT by population and type of heparin were used.[14,17,20,49] Evidence for timing and frequency of platelet count monitoring was derived from individual studies that reported time intervals to diagnosis and platelet recovery.[39,49] The EtD framework is shown online at https://dbep.gradepro.org/profile/DA501AC2-CBF0-D41A-A83A-E45D3AD030D2.

Benefits. The benefit of screening would likely be greatest for patients with a high baseline risk of HIT. A meta-analysis reported that the incidence of HIT in postoperative (orthopedic and cardiac) populations receiving UFH was 2.6%, but the incidence was 0.2% in patients receiving LMWH.[14] A 14-year retrospective study of 127 patients showed that surgical patients were more likely to develop HIT than medical patients while receiving heparin thromboprophylaxis.[17] Studies demonstrated that the typical timing of the development of HIT after heparin initiation was 5 to 14 days.[17,49] Patients who had previous recent heparin exposure, generally within the last 30 days, were at risk of rapid-onset HIT with a fall in platelet count occurring within hours of heparin reexposure.[39,49] The certainty in the effects of screening is very low.

Harms and burden. Evidence for harms when treatment was delayed was found from studies reporting complications after HIT diagnosis. A retrospective study reported that 50% of patients who were treated with cessation of heparin alone or cessation of heparin and initiation of warfarin experienced a thrombotic event within 30 days after diagnosis of HIT.[17] A meta-analysis of trials to assess the value of parenteral treatment with lepirudin reported a combined event rate of death, new thromboembolic complications, and limb amputation per patient per day of 6.1% in the period between diagnosis of HIT and the start of therapy.[20] The evidence for harms related to monitoring is of very low certainty. No studies were found assessing the magnitude of overdiagnosis of HIT and subsequent treatment, although observations from the panel indicated that it may be common and the harms may be moderately large.

Other EtD criteria and considerations. Platelet count measurement is widely available. Although the cost of platelet count monitoring per patient is small, monitoring all patients receiving heparin would result in moderate costs given the frequency of heparin use. Platelet monitoring is probably acceptable to patients and physicians. For patients in the hospital, platelet count monitoring is likely to be ordered for moderate- and high-risk patients for reasons other than HIT screening. However, outpatients would need to return to the clinic for monitoring, which is less practical.

Conclusions and research needs for these recommendations. The guideline panel determined that there is very low certainty in the effects of platelet count monitoring in patients at risk of HIT. The moderate benefits from early detection of HIT among high- and moderate-risk patients would probably outweigh the harms from overdiagnosis and inappropriate treatment. The costs, acceptability, and feasibility also favored monitoring of

high- and moderate-risk patients. The harms of overdiagnosis and inappropriate treatment among low-risk patients probably outweigh the benefits of early detection.

Diagnosis and initial management of patients with suspected HIT

Recommendations 2.1 to 2.10 should be considered together when testing and treating patients with suspected HIT. The recommendations and sequence of tests and treatment are illustrated in Figure 1.

Question: In patients with suspected HIT, what is the optimal strategy for diagnosing HIT?

Recommendation 2.1

In patients with suspected HIT, the ASH guideline panel *recommends* using the 4Ts score to estimate the probability of HIT rather than a gestalt approach. If there is an intermediate- or high-probability 4Ts score, the ASH guideline panel *recommends* an immunoassay (strong recommendations, moderate certainty in the evidence about effects ⊕⊕⊕◯). If the immunoassay is positive and a functional assay is available (either locally or as a send-out test to a reference laboratory), the ASH guideline panel *suggests* a functional assay (conditional recommendations, moderate certainty in the evidence about effects ⊕⊕⊕◯).

Remarks: Missing or inaccurate information may lead to a faulty 4Ts score and inappropriate management decisions. Every effort should be made to obtain accurate and complete information necessary to calculate the 4Ts score. If key information is missing, it may be prudent to err on the side of a higher 4Ts score. Patients should be reassessed frequently. If there is a change in the clinical picture, the 4Ts score should be recalculated.

Different immunoassays and functional assays are available. The choice of assay may be influenced by diagnostic accuracy, availability, cost, feasibility, and turnaround time. If an ELISA is used, a low threshold is preferred over a high threshold. In some settings, a functional assay may not be available, and decisions may need to be made on the basis of the results of the 4Ts score and immunoassay. In general, the likelihood of HIT increases with a higher 4Ts score and a higher ELISA OD. A functional assay may not be necessary for patients with a high-probability 4Ts score and very strongly positive immunoassay (eg, an ELISA value of $>$2.0 OD units). In some centers, a functional assay may be performed in tandem with an immunoassay for quality assurance or efficiency.

Recommendation 2.2

In patients with suspected HIT and a low-probability 4Ts score, the ASH guideline panel *recommends against* HIT laboratory testing (strong recommendation, moderate certainty in the evidence about effects ⊕⊕⊕◯). **Remark:** HIT laboratory testing may be appropriate for patients with a low-probability 4Ts score if there is uncertainty about the 4Ts score (eg, because of missing data).

Summary of the evidence. We found 3 systematic reviews that assessed the accuracy of the 4Ts score and the accuracy of various immunoassays.[42,50,51] The sensitivity and specificity of each of the tests were used to model the number of true positives and true negatives and false positives and false negatives that would result from the use of different strategies: gestalt (unstructured, nonstandardized, intuition-based approach to assessing pretest probability) or 4Ts score followed by immunoassay followed by functional assay (in the setting of a negative or positive immunoassay), gestalt or 4Ts score followed by functional assay, or gestalt or 4Ts score followed by immunoassay. In the model, we assumed that the prevalence of HIT among patients with suspected HIT is 11%[42] and that the functional assay has 100% sensitivity and specificity. We used a PF4/heparin ELISA as the immunoassay in our model and assumed a delay of 1 to several days between when the test is ordered and when results are available (in contrast to rapid immunoassays, for which results may be available within minutes). We also assumed a delay of several days in obtaining functional assay results. The effects of treatment after a positive test using the optimal strategy were based on the evidence for treatments in recommendations 3.1 to 3.9. The EtD framework is shown online at https://dbep.gradepro.org/profile/883a6eac-0bee-42b7-a788-f5998a4191d7.

Benefits, harms, and burden. On the basis of the modeled effects of what happens to 1000 patients with suspected HIT who have an intermediate or high 4Ts score and who have receive the recommended strategy (Table 4, strategy 5), approximately 100 people are correctly identified as having HIT (true positives), 890 people are correctly identified as not having HIT (true negatives), and no one is incorrectly identified as having HIT (false positives), but 10 patients with HIT are missed (false negatives). The 10 missed patients may experience serious consequences of HIT if they are not treated (eg, thrombosis [30% risk], amputation [6% risk], or death [6% risk]). In total, 408 people who do not have HIT would receive non-heparin anticoagulants unnecessarily for varying periods of time depending on the timing of the follow-up tests.

If the 4Ts score is not used, and instead a decision to test with immunoassay is made using a gestalt method (Table 4, strategy 2), 5 fewer people with HIT are missed, but 478 more people receive non-heparin anticoagulants unnecessarily for varying periods of time depending on the delay in obtaining laboratory test results.

In patients with a high 4Ts score and a strongly positive immunoassay test (eg, an ELISA value of $\geq$2.0 OD units), no one is incorrectly identified as having HIT (ie, no false positives), and therefore, a follow-up functional assay is likely not necessary.

Other EtD criteria and considerations. The guideline panel placed more value on avoiding false negatives than on avoiding false positives because of the serious consequences of delays in initiation of appropriate treatment, which result in higher risks of thrombosis, amputation, and death. The panel equated 1 false negative to 10 false positives. When the relative costs of the tests and the benefits and harms are compared, the recommended optimal strategy of tests (Table 4, strategy 5; Figure 1) is probably more cost-effective than not conducting a functional assay or than testing only patients with high 4Ts scores and is more cost-effective than using a gestalt method rather than the 4Ts score. However, information to complete the 4Ts score may not always be available, and although the functional assay is available either on site or as a

Table 4. Test accuracy per 1000 patients after each strategy for diagnose (11% prevalence of HIT)

	Gestalt	4Ts	Immunoassay (based on IgG ELISA low threshold)	95% CI	Functional assay
Sensitivity	0.969	0.921	0.98	0.95-0.99	1.0
Specificity	0.004	0.542	0.85	0.78-0.91	1.0

Strategy	1. Gestalt	2. Gestalt, then IA positive, then FA	3. 4Ts score (high or intermediate)	4. 4Ts score (high or intermediate), then IA	5. 4Ts score (high or intermediate), then IA positive, then FA (recommended strategy)
True positive. Patients will be appropriately treated and/or have more testing (reduced risk of thrombosis by 55%-70%).	107	105	101*	99 (high, 48; intermediate, 51)	100
False negative. Patients will be missed and may experience serious consequences of HIT (eg, thrombosis [300 of 1000 more people with HIT if not treated], amputation [60 of 1000 more people with HIT if not treated], death [60 of 1000 more people with HIT if not treated]).	3	5	9	11 (high, 1; intermediate, 1)	10
True negative. Patients will appropriately not have more testing and will appropriately not be treated for HIT.	4	890	482	829 (high, 34; intermediate, 313)	890
False positive. Patients will continue with unnecessary testing and/or may experience serious consequences of unnecessary treatment of HIT (eg, bleeding ~8% to 35% over treatment duration) and may be falsely labeled as having HIT over the long term.	886†	0	408*†	61 (high, 6; intermediate, 55)	0
No. of immunoassay tests performed					509
No. of functional assay tests performed					160

IA, immunoassay; IgG, immunoglobulin G; FA, functional assay.
*Eighty-nine of these patients would have a high 4Ts score, and 420 would have an intermediate 4Ts score.
†When gestalt or 4Ts score is followed by IA and FA (when IA is positive), these patients would receive non-heparin anticoagulants unnecessarily for varying periods of time depending on timing of the follow-up tests.

send-out to a reference laboratory in most settings, some institutions may not have access, and equity across populations may be reduced.

Conclusions and research needs for these recommendations. This recommendation was based on moderate certainty in the evidence for the diagnostic test accuracy of the tests and management. Based on modeled effects, the recommended strategy (Table 4, strategy 5; Figure 1) likely results in few false negatives and few or no false positives. The tests that make up the recommended strategy are in current use, and therefore the strategy is feasible in most settings. Using the functional assay, however, may not be necessary for patients with a high-probability 4Ts score and a strongly positive immunoassay (eg, an ELISA value of ≥2.0 OD units). Research priorities include implementation analyses and identification of barriers to the use of the recommended strategy and in particular the use of the 4Ts score. Our modeling and recommendations apply to the PF4/heparin ELISA. Assessment of other currently available immunoassays should be conducted. Research should also include the development of novel assays that overcome the limitations of currently available assays, such as immunoassays with enhanced specificity and functional assays with enhanced feasibility.

Question: Should heparin be discontinued and non-heparin anticoagulants be initiated in patients identified as being at risk of HIT according to the 4Ts score?

Question: Should non-heparin anticoagulants be provided at therapeutic or prophylactic intensity?

Recommendation 2.3

In patients with suspected HIT and a low-probability 4Ts score, the ASH guideline panel *recommends against* empiric treatment of HIT (ie, against discontinuation of heparin and initiation of a non-heparin anticoagulant) (strong recommendation, moderate certainty in the evidence about effects ⊕⊕⊕◯).

Recommendation 2.4.a

In patients with suspected HIT and an intermediate-probability 4Ts score who have no other indication for therapeutic-intensity anticoagulation, the ASH guideline panel *recommends* discontinuation of heparin (strong recommendation, moderate certainty in the evidence about effects ⊕⊕⊕◯).

Recommendation 2.4.b

The ASH guideline panel *suggests* initiation of a non-heparin anticoagulant at prophylactic intensity if the patient is at high risk of bleeding and at therapeutic intensity if the patient is not at high risk of bleeding (conditional recommendation, moderate certainty in the evidence about effects ⊕⊕⊕◯).

Recommendation 2.5.a

In patients with suspected HIT and an intermediate-probability 4Ts score who have another indication for therapeutic-intensity anticoagulation, the ASH guideline panel *recommends* discontinuation of heparin (strong recommendation, moderate certainty in the evidence about effects ⊕⊕⊕◯).

Recommendation 2.5.b

The ASH guideline panel *suggests* initiation of a non-heparin anticoagulant at therapeutic intensity (conditional recommendation, moderate certainty in the evidence about effects ⊕⊕⊕◯).

Recommendation 2.6

In patients with suspected HIT and a high-probability 4Ts score, the ASH guideline panel *recommends* discontinuation of heparin and initiation of a non-heparin anticoagulant at therapeutic intensity (strong recommendation, moderate certainty in the evidence about effects ⊕⊕⊕◯).

Summary of the evidence. We did not find studies that assessed the outcome of patients identified at risk of HIT according to the 4Ts score. Instead, we modeled the clinical outcomes on the basis of the number of patients correctly or incorrectly identified with HIT in recommendations 2.1 and 2.2. The effects of treatment after testing positive using the recommended optimal strategy were based on the evidence for treatments in recommendations 3.1 to 3.9. The EtD framework is shown online at https://dbep.gradepro.org/profile/15d951fb-5481-492e-9518-bd44091b4198.

Benefits, harms, and burden. For patients with an intermediate or high 4Ts score (Table 4, strategy 3), discontinuing heparin and initiating a non-heparin anticoagulant would mean that 101 of 1000 patients (true positives) would be correctly treated, and the risk of new or progressive thrombosis would be reduced by 55% to 70%, but 408 of 1000 (false positives) would receive unnecessary treatment in the short term with an attendant increase in the risk of major bleeding. In contrast, if patients with a low-probability 4Ts score were all treated with discontinuation of heparin and initiation of a non-heparin anticoagulant, 9 of 1000 patients with true HIT would be treated appropriately (which is a small benefit), but 482 patients without HIT would be unnecessarily exposed to a non-heparin anticoagulant with an attendant increased risk of bleeding for a short period of time. With respect to the use of therapeutic- or prophylactic-intensity non-heparin anticoagulants in patients who have a high-probability 4Ts score, there are large benefits with reductions in thrombosis when therapeutic intensity is provided and small harms as a result of bleeding. However, among patients who have an intermediate-probability 4Ts score, there would be fewer people with true HIT (ie, more false positives) and thus less benefit associated with

treatment with therapeutic-intensity anticoagulation balanced against the high risk of bleeding, particularly for patients judged to be at high baseline bleeding risk. Conversely, with prophylactic intensity, there may be fewer bleeds.

Other EtD criteria and considerations. When considering whether to discontinue heparin and initiate non-heparin anticoagulants in patients with suspected HIT, the panel agreed that some clinicians may find it unacceptable to not treat patients suspected of HIT because of the fear of litigation. However, clinicians may need to be reminded that treating patients with a low-probability 4Ts score will result in more bleeds and greater costs and only rarely prevent adverse consequences of HIT. Although some drugs are not available in some countries, there is at least 1 non-heparin anticoagulant available in most countries.

Conclusions and research needs for this recommendation. In patients with a high- or intermediate-probability 4Ts score, the benefits and cost savings from preventing thrombosis outweigh the harms (eg, bleeds) and costs of treatment. In addition, treating for HIT is probably acceptable, feasible, and equitable. Although the difference in cost between therapeutic- and prophylactic-intensity therapy is negligible, in patients with an intermediate 4Ts score who have a high risk of bleeding, there could be greater harms with therapeutic-intensity treatment (bleeds), and the benefits are small because most patients will not have HIT. If all patients with a low-probability 4Ts score are treated, there may be greater harms as a result of bleeds in a large number of patients who do not have HIT and greater costs, and few thromboses would be prevented in the few patients with true HIT. Research could focus on the perceived barriers to managing patients according to the 4Ts score.

Question: Should non-heparin anticoagulants be continued in patients who have an intermediate or high risk of HIT according to the 4Ts score and have a positive or negative immunoassay?

Recommendation 2.7

In patients with an intermediate-probability 4Ts score and a negative immunoassay, the ASH guideline panel *recommends* discontinuation of the non-heparin anticoagulant and resumption of heparin, if indicated (strong recommendation, moderate certainty in the evidence about effects ⊕⊕⊕◯).

Recommendation 2.8

In patients with a high-probability 4Ts score and a negative immunoassay, the ASH guideline panel *recommends* discontinuation of the non-heparin anticoagulant and resumption of heparin, if indicated (strong recommendation, moderate certainty in the evidence about effects ⊕⊕⊕◯). **Remark:** Rarely, patients with HIT may have a negative immunoassay, because of a laboratory error or because the pathologic antigen involves a complex of heparin and a molecule other than PF4. Clinical reevaluation, a repeat immunoassay, a different immunoassay, and/or a functional assay may be helpful in clarifying the diagnosis.

Recommendation 2.9

In patients with an intermediate-probability 4Ts score and a positive immunoassay, the ASH guideline panel *recommends* continued avoidance of heparin and continued administration of a non-heparin anticoagulant at therapeutic intensity. For those patients who were receiving prophylactic-intensity anticoagulation, the ASH guideline panel *recommends* providing therapeutic-intensity anticoagulation (strong recommendations, moderate certainty in the evidence about effects ⊕⊕⊕◯).

Recommendation 2.10

In patients with a high-probability 4Ts score and a positive immunoassay, the ASH guideline panel *recommends* continued avoidance of heparin and continued administration of a non-heparin anticoagulant at therapeutic intensity (strong recommendation, moderate certainty in the evidence about effects ⊕⊕⊕◯).

Summary of the evidence. We did not find studies that assessed clinical outcomes (eg, thrombosis, limb amputation) in patients who were identified as being at intermediate or high risk of HIT according to the 4Ts score and who had a positive or negative immunoassay. Instead, we modeled the clinical outcomes on the basis of the number of patients correctly or incorrectly identified with HIT in recommendations 2.1 and 2.2. The effects of treatment after testing positive using the recommended optimal strategy (Table 4, strategy 5; Figure 1) were based on the evidence for treatments in recommendations 3.1 to 3.9. The EtD framework is shown online at https://dbep.gradepro.org/profile/403a664d-18cb-4f9f-a8fe-376ee77e2b0b.

Benefits, harms, and burden. For patients who have a high-probability 4Ts score (89 of 1000 patients) and a positive immunoassay, continuing treatment with a non-heparin anticoagulant would mean a reduction in thrombosis, death, and amputation for 48 patients who have true HIT; however, for 6 patients without HIT, there is a short-term risk of bleeds (Table 4, strategy 4, patients with a high-probability 4Ts score). For those with a negative immunoassay, discontinuing treatment with a non-heparin anticoagulant would be appropriate for 34 who do not have HIT, but there would be harms (possible thrombosis, amputation, or death) for the 1 patient with true HIT in whom treatment was inappropriately stopped. For patients who had an intermediate 4Ts score (420 of 1000 patients) and a positive immunoassay, continuing treatment with a non-heparin anticoagulant would mean that 51 who have true HIT would have a reduction in thrombosis, amputation, or death, but 55 patients without HIT who had continued treatment would have an increased risk of bleeds in the short term (Table 4, strategy 4, patients with an intermediate-probability 4Ts score). For patients who had a negative immunoassay, discontinuing treatment with a non-heparin anticoagulant would be appropriate for the 313 who do not have HIT, but there would be harms (possible thrombosis, amputation, or death) for the 1 patient with HIT in whom treatment was inappropriately stopped.

For patients with high risk of bleeding, no other indication for therapeutic-intensity anticoagulation, and an intermediate-probability 4Ts score who are receiving a non-heparin anticoagulant at prophylactic intensity (per recommendation 2.4.b), changing to therapeutic-intensity anticoagulation based on a positive immunoassay may be associated with small harms compared with prophylactic-intensity treatment: 55 of 106 who have a positive immunoassay test do not have HIT, and they may have more bleeds. However, for 51 of 106 people with HIT, the benefits would be large, because they may have a reduced risk of thrombosis with therapeutic-intensity non-heparin anticoagulation.

Other EtD criteria and considerations. The panel placed greater value on preventing thrombosis or clotting than major bleeding, and in principle, the panel valued false negatives 10 times more than false positives (ie, the panel was willing to accept 10 false positives for 1 false negative). The panel agreed that continuing or discontinuing non-heparin anticoagulants is feasible, and although some drugs are not available in some countries, there is at least 1 non-heparin anticoagulant available in most countries.

Conclusions and research needs for this recommendation. When non-heparin anticoagulants are continued for patients with a high- or intermediate-probability 4Ts score and a positive immunoassay, the benefits of preventing thrombosis outweigh the harms (eg, bleeds) and drug costs. In addition, continuing non-heparin anticoagulants is probably acceptable, feasible, and equitable. For patients with a high risk of bleeding, an intermediate-probability 4Ts score, and a positive immunoassay, the costs are negligible, and there may be large benefits from preventing thrombosis and small harms (bleeds) when changing from prophylactic- to therapeutic-intensity anticoagulation. The panel identified the effect of different ELISA OD thresholds on clinical outcomes as a research priority.

Management of the acute phase of HIT

Question: Should heparin be discontinued and a non-heparin anticoagulant be initiated in patients with acute HITT or acute isolated HIT?

Question: Should argatroban, bivalirudin, danaparoid, fondaparinux, or a DOAC be used to treat patients with acute HITT or acute isolated HIT?

Recommendation 3.1

In patients with HITT or acute HIT without thrombosis (isolated HIT), the ASH guideline panel *recommends* discontinuation of heparin and initiation of a non-heparin anticoagulant (strong recommendation, moderate certainty in the evidence about effects ⊕⊕⊕◯). When a non-heparin anticoagulant is being selected, the ASH guideline panel *suggests* argatroban, bivalirudin, danaparoid, fondaparinux, or a DOAC (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯). **Remarks:** The choice of agent may be influenced by drug factors (availability, cost, ability to monitor the anticoagulant effect, route of administration, and half-life), patient factors (kidney function, liver function, bleeding risk, and clinical stability), and experience of the clinician. In patients with critical illness, increased bleeding risk, or increased potential need for urgent procedures, argatroban or bivalirudin may be preferred because of shorter duration of effect. These patients may require close monitoring. In patients with moderate or severe hepatic dysfunction (Child-Pugh Class B or C), it is advisable to avoid argatroban or use a reduced dose.

Fondaparinux and the DOACs are reasonable options in clinically stable patients at average risk of bleeding. The same contraindications to their use in the treatment of acute VTE should be applied in determining their appropriateness for patients with HIT.

In patients with HIT complicated by life- or limb-threatening thromboembolism (eg, massive pulmonary embolism or venous limb gangrene), a parenteral non-heparin anticoagulant may be preferred, because few such patients have been treated with a DOAC.

With respect to the choice of DOAC, most of the published experience in HIT is with rivaroxaban. Various dosing regimens have been reported. For patients with acute HITT, rivaroxaban at a dose of 15 mg twice per day for 3 weeks followed by 20 mg once per day is preferred. For patients with acute isolated HIT, rivaroxaban 15 mg twice per day until platelet count recovery (usually a platelet count of $\geq 150 \times 10^9$/L) followed by 20 mg once per day is preferred if there is an indication for ongoing anticoagulation.

Summary of the evidence. We found 1 systematic review that included 1 case series examining the discontinuation of heparin or discontinuation of heparin and treatment with VKA and 6 studies that compared the discontinuation of heparin and initiation of non-heparin anticoagulants in patients with HIT.[52] We updated this review and found 2 additional studies. The EtD framework is shown online at https://dbep.gradepro.org/profile/86423A6B-5963-B7EC-ABE9-EC0124002ED0 and https://dbep.gradepro.org/profile/5CBFE061-894E-B073-A792-28DC54FA7F25.

One case series reported on discontinuation of heparin alone or discontinuation of heparin and treatment with a VKA.[17] One study compared treatment with danaparoid plus warfarin vs dextran 70 plus warfarin among people with acute HIT; outcomes included all-cause mortality, resolution of thromboembolic complications, serious adverse events, and major bleeds.[29] One study synthesized 3 comparisons of treatment with lepirudin vs historical controls among people with acute HIT; outcomes included all-cause mortality, thromboembolic complications, and adverse events.[30] Two studies compared treatment with argatroban vs historical controls among people with acute HIT; outcomes included all-cause mortality, thromboembolic complications, and adverse events.[28,53] One study compared treatment with argatroban, danaparoid, and fondaparinux among people with acute HIT with regard to the outcomes of thrombosis and thrombosis-related mortality and bleeding and bleeding-related mortality.[54] One study compared lepirudin vs fondaparinux among people with acute HIT with regard to the outcomes of all-cause mortality, thromboembolic complications, and adverse events.[55] One case series provided data on harms of treatment with danaparoid.[56] We identified a retrospective medical records review on the treatment of bivalirudin in 461 suspected (n = 262), confirmed (n = 124), and remote (n = 75) HIT patients.[57] No randomized trials were identified that compared DOACs in patients with acute HIT. We found 1 recently published

systematic review of 20 studies that addressed the use of rivaroxaban, apixaban, and dabigatran in patients with acute HIT.[58] This review also provided information from a cohort of individuals receiving DOACs after platelet count recovery. This review reported on the outcomes of thrombosis and bleeding.

Benefits. Discontinuation of heparin and treatment with a non-heparin anticoagulant probably results in fewer new or progressive thrombotic events (12%-25%) than discontinuation of heparin alone or discontinuation of heparin and treatment with a VKA (~50%). It was uncertain whether the benefits were different among treatments with fondaparinux, argatroban, and danaparoid.[54] There were few thrombotic events reported with DOACs (rivaroxaban, 1 of 46; apixaban, 0 of 12; dabigatran, 1 of 11), but the number of reported patients treated with these agents remains relatively small.

Harms and burden. Treatment with a non-heparin anticoagulant likely increases major bleeds (8% to 35% rate of major bleeds). In particular, critically ill patients and patients with certain comorbidities may have a greater risk of bleeds.[57] Limb amputations occurred in 13.7% of patients treated with argatroban and in 4.2% of patients treated with danaparoid.[29,53] There were fewer bleeds with DOACs (rivaroxaban, 0 of 46; apixaban, 0 of 12; dabigatran, 0 of 11). There was also very low certainty in the evidence for a difference in the risk of bleeding with fondaparinux, argatroban, and danaparoid because of the small number of patients included in the study.[54]

Other EtD criteria and considerations. The recommendation is based on greater value being placed on preventing thrombosis than on preventing major bleeding. The panel agreed that there is no reason that non-heparin anticoagulants would not be prescribed or provided to any populations, and therefore there would be no impact on equity. Starting non-heparin anticoagulants is probably more cost-effective than stopping heparin alone, because new or progressive thrombotic complications will be prevented. The direct costs of the non-heparin anticoagulants are variable in different settings and countries. The greatest cost of the non-heparin anticoagulants that require continuous infusion (eg, argatroban, bivalirudin, and danaparoid) may relate to prolonged stays in the intensive care unit and hospital because of administration and monitoring of the drug and not necessarily to the direct cost of the medication. Fondaparinux and DOACs, which do not require administration in a health care setting or routine laboratory monitoring, would therefore have lower costs. However, depending on health insurance, the costs of these agents may be a burden to some patients. Oral medications are probably both acceptable and feasible; however, the acceptability of a specific medication to a clinician is likely dependent on personal experience and would be a key factor in the choice of a specific DOAC or parenteral non-heparin anticoagulant. Although some drugs may not be available in some countries, there is at least 1 non-heparin anticoagulant available in most countries.

Conclusions and research needs for this recommendation. The benefits of discontinuing heparin and starting a non-heparin anticoagulant (compared with discontinuing heparin alone or discontinuing heparin and starting a VKA) may result in large reductions in death and thrombotic events; however, harms (such as major bleeding) may be moderate. Harms (such as major bleeding) may be greater in critically ill patients and patients with certain comorbidities. The benefits and harms of the effects of DOACs compare favorably with those associated with the use of parenteral non-heparin anticoagulants. There may be large savings with DOACs or fondaparinux as a result of reduced hospitalization periods. However, some patients may have to pay for the medications, depending on health care coverage. The oral medications are probably acceptable to patients and may become increasingly acceptable to clinicians as the evidence base and experience grow.

More research is needed on treatment of acute HIT with DOACs, including encouraging physicians to present outcome data when using DOACs, creating an international registry to capture treatment with DOACs, and conducting studies that compare DOACs and parenteral non-heparin anticoagulants.

Question: Should a non-heparin anticoagulant at therapeutic-intensity dosing rather than prophylactic-intensity dosing be provided to patients with acute HITT or acute isolated HIT?

Recommendation 3.2

In patients with acute HITT or acute isolated HIT, the ASH guideline panel *recommends* treatment with a non-heparin anticoagulant at therapeutic-intensity dosing rather than prophylactic-intensity dosing (strong recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Summary of the evidence. We did not identify any randomized controlled trials (RCTs) comparing therapeutic vs prophylactic doses of non-heparin anticoagulants for patients with confirmed diagnoses of acute HITT or acute isolated HIT. We identified 2 prospective cohorts that evaluated therapeutic and prophylactic doses of danaparoid, lepirudin (not available since 2012), and fondaparinux.[59-61] These studies reported on the outcomes of new thromboembolic events, platelet response, mortality, major and minor bleeds, and limb amputations. The EtD framework is shown online at https://dbep.gradepro.org/profile/D1230F84-C07C-BBF8-9214-2AB5D71750A3.

Benefits. The study comparing danaparoid doses found that therapeutic intensity may reduce thrombotic events by 50%; however, this outcome is uncertain because of the small number of patients.[61] The studies comparing different doses of lepirudin suggested no difference in thrombotic events or platelet response.[60,61] The study comparing fondaparinux doses also found no differences in thrombotic events or mortality.[59]

Harms and burden. The effects on harms are uncertain because of the small number of patients studied. An increase in bleeding with therapeutic compared with prophylactic dosing is probable.[59-61]

Other EtD criteria and considerations. The panel agreed that providing therapeutic-intensity dosing is feasible and acceptable and that the differences in costs of prophylactic- and therapeutic-intensity dosing would be negligible. The panel placed greater value on preventing thrombosis and death than on the risk of major bleeding.

Conclusions and research needs for this recommendation. The guideline panel recommends treatment with a non-heparin anticoagulant at therapeutic-intensity dosing rather than prophylactic-intensity dosing on the basis of very low certainty in the evidence

about effects. The strong recommendation is based on a likely large magnitude of benefit, including prevention of more life-threatening thrombotic events and death, and small known harm. No research priorities related to this question were identified.

Question: Should treatment with a non-heparin anticoagulant alone or in combination with an antiplatelet agent be provided to patients with acute HITT or acute isolated HIT and no other indication for antiplatelet therapy?

Recommendation 3.3

In patients with acute HITT or acute isolated HIT and no other indication for antiplatelet therapy, the ASH guideline panel *suggests* treatment with a non-heparin anticoagulant alone rather than in combination with an antiplatelet agent (conditional recommendation, low certainty in the evidence about effects ⊕⊕◯◯). **Remark:** In patients with acute HITT or acute isolated HIT and another indication for antiplatelet therapy (eg, coronary artery disease or recent coronary stent placement), the decision to continue antiplatelet therapy during treatment with a non-heparin anticoagulant may be influenced by the risk of vascular events and bleeding.

Summary of the evidence. We did not identify any RCTs or non-randomized studies comparing non-heparin anticoagulants alone to non-heparin anticoagulants plus antiplatelet agents in patients with acute HITT or acute isolated HIT. We identified 2 studies that compared heparin plus iloprost for urgent cardiopulmonary bypass (CPB) in patients with acute HIT with a matched control of patients without HIT.[62,63] These studies reported on the outcomes of thromboembolic events, mortality, and bleeding. The EtD framework is shown online at https://dbep.gradepro.org/profile/da74ffb6-d628-4392-9509-be7652f5ab4a.

Benefits. There are no studies in patients with HIT to confirm whether adding antiplatelet therapy to treatment with a non-heparin anticoagulant reduces thromboembolic events.

Harms and burden. In the 2 studies of 142 patients with HIT who received heparin plus iloprost for CPB, 30-day mortality was reported in 9 patients, thromboembolism in 3 patients, and moderate bleeding in 9 patients.[62,63] In other populations (eg, patients with atrial fibrillation), bleeding risk was increased with the addition of antiplatelet therapy to anticoagulation.

Other EtD criteria and considerations. Most clinicians and other stakeholders are likely not currently providing antiplatelet therapy, and therefore providing a non-heparin anticoagulant alone is probably acceptable. Although there are negligible costs associated with adding antiplatelet therapy, adding this therapy may increase bleeds.

Conclusions and research needs for this recommendation. The guideline panel suggests treatment with a non-heparin anticoagulant alone rather than in combination with an antiplatelet agent on the basis of low certainty in the evidence. The benefits of adding antiplatelet therapy are unknown, and there is evidence from other populations of an increased risk of bleeding. Future research may be needed to identify whether there are benefits of combining antiplatelet therapy and anticoagulation among patients with HIT.

Question: Should routine insertion of an IVC filter be provided to patients with acute HITT or acute isolated HIT?

Recommendation 3.4

In patients with acute HITT or acute isolated HIT, the ASH guideline panel *recommends against* routine insertion of an IVC filter (strong recommendation, moderate certainty in the evidence about effects ⊕⊕⊕◯).

Summary of the evidence. We did not identify any randomized or nonrandomized comparative studies that evaluated IVC filter insertion vs no insertion in patients with acute HIT or HITT. We found 1 case series of 10 patients with HIT who received IVC filters that reported thrombotic events.[64] We identified 1 study of 260 HIT patients receiving a different vascular intervention, CVC insertion, in which the outcome of upper-extremity CVC-associated DVT was reported.[65] We found indirect evidence from 2 RCTs of patients without HIT who received IVC filters in addition to anticoagulant therapy.[66,67] These trials reported on the outcomes of mortality, pulmonary embolism, DVT, and major bleeding. The EtD framework is shown online at https://dbep.gradepro.org/profile/306AE83F-E6BE-7B4C-984C-211A8AB2C807.

Benefits. Indirect evidence from RCTs of patients without HIT shows that trivial reductions in pulmonary embolisms (relative risk [RR], 0.54; 95% confidence interval [CI], 0.22-1.33) and major bleeding (RR, 0.81; 95% CI, 0.51-1.28) are likely with the insertion of IVC filters.[66,67] In 1000 people receiving an IVC filter, there are likely 2 fewer pulmonary embolisms (from 4 fewer to 2 more) and 9 fewer major bleeds (from 25 fewer to 14 more). The certainty in these effects is moderate.

Harms and burden. There are likely large harms with the insertion of IVC filters (9 of 10 patients with acute HIT and an IVC filter developed a new thromboembolic event).[64] In addition, indirect evidence demonstrates a risk of HIT-associated thrombosis at sites of vascular injury. Upper-extremity DVT occurred more frequently in HIT patients with a CVC (14 of 145 [9.7%]) than in patients without a CVC (0 of 115 [0%]).[65] The indirect evidence from RCTs of patients without HIT is consistent, with a potential increase in mortality (RR, 1.15; 95% CI, 0.83-1.60) and new proximal DVT (RR, 1.64; 95% CI, 0.93-2.90) associated with IVC filter insertion.[66,67] The evidence for harms is of moderate certainty.

Other EtD criteria and considerations. Complications and requirements for additional medical interventions (eg, removal of a fractured filter) would also be increased with IVC filters. Patients may find that insertion of IVC filters is invasive and not acceptable.

Conclusions and research needs for this recommendation. The guideline panel determined that there is moderate certainty in the effects of IVC filter placement for people with HIT. Although trivial benefits are likely with IVC filter placement, there are likely large harms in the form of increased thromboembolic complications. Despite the feasibility of placing IVC filters, it would probably reduce equity and not be acceptable to some patients. Given the balance of large harms, trivial benefits, and other

considerations, the guideline panel recommended against IVC filter placement. No research priorities related to this recommendation were identified.

Question: Should a VKA be initiated before platelet count recovery in patients with acute HITT or acute isolated HIT?

Recommendation 3.5

In patients with acute HITT or acute isolated HIT, the ASH guideline panel *recommends against* initiation of a VKA before platelet count recovery (usually a platelet count of $\geq 150 \times 10^9$/L) (strong recommendation, moderate certainty in the evidence about effects ⊕⊕⊕◯). **Remark:** This recommendation also applies to patients who are taking a VKA at the onset of acute HITT or acute isolated HITT. In these patients, the VKA would be discontinued and intravenous vitamin K would be administered concomitant with initiation of a non-heparin anticoagulant (see recommendations 3.1, 3.2, and 3.4).

Summary of the evidence. We found 3 studies of patients with HIT who received a VKA before platelet recovery.[17,68,69] One study reported on 6 patients with HIT with regard to the outcomes of skin necrosis, limb gangrene, amputations, and death; 1 study involved a retrospective medical record review of patients with HIT who experienced venous limb gangrene; and 1 study reported on the outcome of thrombosis in 21 patients with isolated HIT.[68-70] The EtD framework is shown online at https://dbep.gradepro.org/profile/2EDAF7FC-665F-302A-97CA-ED3B70A9A133.

Benefits. There are likely no demonstrated benefits of initiating a VKA before platelet count recovery.

Harms and burden. There are probably large harms with the initiation of a VKA before platelet count recovery, including an increased risk of new or progressive thrombosis and venous limb gangrene. Among 6 patients with HIT, 5 events of skin necrosis and 2 events of limb gangrene were reported.[69] Warfarin was withdrawn in 2 patients. One patient required limb amputation. One patient died. Of 66 patients with HIT and DVT who received warfarin, 8 developed venous limb gangrene.[68] Of 21 patients with HIT treated with warfarin before platelet count recovery, 10 developed thrombosis.[17]

Other EtD criteria and considerations. Although early initiation of a VKA may lead to moderate savings because of earlier hospital discharge, it may result in greater costs as a result of thrombosis and limb loss. The cost-effectiveness probably favors not administering a VKA before platelet recovery.

Conclusions and research needs for this recommendation. The guideline panel determined that initiation of a VKA before platelet count recovery is associated with trivial benefit and large harm based on moderate certainty in the evidence about effects. The recommendation to avoid treatment with a VKA before platelet count recovery also applies to patients who are taking a VKA at the onset of acute HITT or acute isolated HITT. In these patients, the VKA would be discontinued and vitamin K would be administered. No research priorities related to this recommendation were identified.

Question: Should routine platelet transfusion be administered in patients with acute HITT or acute isolated HIT who are at average risk of bleeding?

Recommendation 3.6

In patients with acute HITT or acute isolated HIT who are at average risk of bleeding, the ASH guideline panel *suggests against* routine platelet transfusion (conditional recommendation, low certainty in the evidence about effects ⊕⊕◯◯). **Remark:** Platelet transfusion may be an option for patients with active bleeding or at high risk of bleeding.

Summary of the evidence. We found 4 nonrandomized studies of patients with HIT receiving platelet transfusions. One nationally representative inpatient database analyzed 6332 patients with HIT International Classification of Diseases, Ninth Revision (ICD-9) codes, of whom 450 received a platelet transfusion.[71] We identified 1 retrospective cohort of 37 HIT patients, 1 cohort of 4 HIT patients, and 1 case study of a HIT patient who received platelet transfusions.[72-74] The EtD framework is shown online at https://dbep.gradepro.org/profile/0B5351AD-4CFF-7A8F-8E7E-F9B9307A1441.

Benefits. There may be situations of substantial bleeding or high risk of bleeding in which platelet transfusions would provide a benefit to the patient. In the inpatient database study, platelet transfusion was associated with an adjusted odds ratio (OR) for venous thrombosis of 0.8 (95% CI, 0.4-0.7).[71] In the 37-patient cohort, no thrombotic events at 30 days were reported.[72] In the 4-patient cohort, no thrombotic events were reported.[73] One HIT patient with a positive serotonin release assay (SRA) tested SRA negative after platelet transfusion.[74]

Harms and burden. There may be increased harms of arterial thrombotic events with the addition of platelet transfusion. In the inpatient database study, those receiving platelet transfusions experienced 3.8% more arterial thromboses than patients not receiving platelet transfusions.[71] The adjusted OR for arterial thrombosis was 3.4 (95% CI, 1.2-9.5). The adjusted OR for venous thrombosis was 0.8 (95% CI, 0.4-0.7). The adjusted OR for any bleeding event was 5.5 (95% CI, 2.3-12.9), although the panel recognized that increased bleeding among patients who received platelet transfusion was likely the result of confounding by indication. Among the 37 HIT patients, 6 deaths were reported.[73]

Other EtD criteria and considerations. Special situations may necessitate the use of platelet transfusions. For HIT patients at average risk of bleeding, the harms associated with routine platelet transfusions seem to outweigh the benefits.

Conclusions and research needs for this recommendation. The guideline panel determined that there is low certainty in the evidence of effects against routine platelet transfusions for people with HIT at average risk of bleeding. Platelet transfusion may be an option for patients with active bleeding or those who are at high risk of bleeding. No research priorities related to this recommendation were identified.

Question: Should routine limb ultrasonography be used to screen for asymptomatic DVT in patients with acute isolated HIT?

Recommendation 3.7.a

In patients with acute isolated HIT, the ASH guideline panel *suggests* bilateral lower-extremity compression ultrasonography to screen for asymptomatic proximal DVT (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Recommendation 3.7.b

In patients with acute isolated HIT and an upper-extremity CVC, the ASH guideline panel *suggests* upper-extremity ultrasonography in the limb with a catheter to screen for asymptomatic DVT. The ASH guideline panel *suggests against* upper-extremity ultrasonography in limbs without CVCs to screen for asymptomatic DVT (conditional recommendations, very low certainty in the evidence about effects ⊕◯◯◯). **Remark:** These recommendations do not apply to patients with signs or symptoms suggestive of DVT in whom diagnostic imaging would be indicated.

Summary of the evidence. We found 5 nonrandomized studies that reported on DVT outcomes in patients with confirmed HIT.[17,19,65,75,76] Three cohort studies reported on symptomatic lower-extremity proximal DVT.[17,19,75] One study reported on symptomatic upper-extremity DVT.[19] Two cohort studies reported on asymptomatic HIT patients who were screened for silent DVT.[65,76] The EtD framework is shown online at https://dbep.gradepro.org/profile/52FE6F09-0233-F65B-BA7A-5ADB96E1007D.

Benefits. There may be benefits of screening for silent DVTs when the findings would change clinical practice; however, this is uncertain. Ultrasound studies identified silent lower-extremity DVT in 12% to 44% of asymptomatic HIT patients.[65,76] The panel agreed that the benefits of lower-extremity screening in patients with acute isolated HIT are moderate because of the high prevalence of silent DVT and the high risk of pulmonary embolism with proximal DVT.

Although no study reported on the prevalence of silent upper-extremity DVT among people with HIT, symptomatic upper-extremity DVT is common in HIT patients with a CVC (14 of 145) and uncommon in those without a CVC (0 of 115).[65] The panel agreed that there may be benefit to screening patients with CVC for upper-extremity DVT in the limb where the CVC has been placed because of the high baseline prevalence of CVC-associated upper-extremity DVT and the moderate risk of pulmonary embolism associated with upper-extremity DVT. The panel agreed that the benefit of screening for upper extremity DVT in the absence of a CVC is likely to be trivial because of the low baseline prevalence of symptomatic DVT.

Harms and burden. There may be harms of unnecessary treatment, such as major bleeds, with the detection and treatment of silent DVT for both upper and lower extremities, but this is uncertain.

Other EtD criteria and considerations. The cost of ultrasound screening is negligible given the restricted patient population (ie, patients with acute isolated HIT), and the screening is probably cost-effective with regard to screening for lower-extremity DVT or upper-extremity CVC-associated DVT. Ultrasound is probably not cost-effective for upper-extremity DVT screening in the absence of a CVC.

Conclusions and research needs for this recommendation. The guideline panel determined that there is very low certainty in the evidence of effects for bilateral lower-extremity compression ultrasonography to screen for asymptomatic DVT. The guideline panel determined that there is very low certainty in the evidence of effects for upper-extremity ultrasonography to screen for CVC-associated DVT. The guideline panel determined that there is very low certainty in the evidence of effects for upper-extremity ultrasonography to screen for DVT in the absence of a CVC.

Research is needed to determine whether a strategy of screening and treatment of asymptomatic DVT in patients with acute isolated HIT influences outcomes important to patients such as symptomatic thromboembolism, major bleeding, and death.

Question: Should anticoagulation be continued until platelet count recovery or for a longer period of time in patients with acute isolated HIT and no asymptomatic DVT by screening ultrasonography?

Recommendation 3.8

In patients with acute isolated HIT and no asymptomatic DVT identified by screening compression ultrasonography, the ASH guideline panel *suggests* that anticoagulation be continued, at a minimum, until platelet count recovery (usually a platelet count of $\geq 150 \times 10^9$/L). The ASH guideline panel *suggests against* continuing treatment of ≥3 months unless the patient has persisting HIT without platelet count recovery (conditional recommendations, very low certainty in the evidence ⊕◯◯◯). **Remark:** These recommendations apply only to patients with isolated HIT. The ASH guideline panel did not address the duration of anticoagulation in patients with acute HITT and no other indication for anticoagulation in whom anticoagulation is typically given for 3 to 6 months.

Summary of the evidence. We found 1 cohort study that followed the progression of platelet counts and thrombotic events of 62 untreated patients with isolated HIT.[17] The EtD framework is shown online at https://dbep.gradepro.org/profile/154EF022-9F75-AB97-A89A-1B0CFABAF906.

Benefits. The cohort study found that thromboembolic events occurred in 52% of patients within 30 days after discontinuation of heparin. Most events occurred within the first 10 days, corresponding to the period of platelet count recovery. There may be an additional benefit of prolonged treatment beyond platelet count recovery, but this is uncertain.

Harms and burden. The cumulative risk of bleeding with anticoagulant therapy increases with treatment duration.

Other EtD criteria and considerations. The costs of treatment beyond platelet count recovery are likely to be negligible because the patient would be transitioned to an oral agent, and oral anticoagulants are relatively inexpensive. However, the costs of

increased bleeds with extended anticoagulant therapy may outweigh reduction in thromboembolic events, thus potentially favoring a shorter course of treatment.

Conclusions and research needs for this recommendation. The guideline panel determined that there is evidence of high thrombotic risk in patients with isolated HIT during the period of platelet count recovery. The benefits of a longer course of treatment are trivial (as a result of a low risk of thromboembolic events after platelet recovery), and the harms (cumulative risk of bleeding) with greater (but limited) duration of therapy are small. Although some clinicians provide treatment of 4 to 6 weeks, the panel could not agree on a specific duration of therapy on the basis of current evidence and therefore provided a minimum (until platelet count recovery) and maximum (<3 months) duration of treatment. The panel agreed that studies comparing different lengths of therapy would be useful for determining the optimal duration of treatment in patients with isolated HIT.

Question: Should a DOAC (eg, dabigatran, rivaroxaban, or apixaban) rather than a VKA be provided to patients with subacute HIT A?

Recommendation 3.9

In patients with subacute HIT A, the ASH guideline panel *suggests* treatment with a DOAC (eg, dabigatran, rivaroxaban, or apixaban) rather than a VKA (conditional recommendation, moderate certainty in the evidence about effects ⊕⊕⊕◯).

Remarks: The choice of agent may be influenced by drug factors (availability, cost, ability to monitor the anticoagulant effect, route of administration, and half-life), patient factors (kidney function, liver function, bleeding risk, and clinical stability), and experience of the clinician.

DOACs are preferred in clinically stable patients at average risk of bleeding. The same contraindications to their use in the treatment of acute VTE should be applied in determining their appropriateness for patients with HIT.

Summary of the evidence. We found a systematic review of case series of 11 patients with HIT who received DOACs after platelet count recovery.[58] The systematic review reported on outcomes of thrombotic events and major bleeding. Indirect evidence comparing DOACs with a VKA in patients with VTE (without HIT) was also used to inform this recommendation. The EtD framework is shown online at https://dbep.gradepro.org/profile/39E8D89A-A33A-28E1-B5F9-809F7FB7BA27.

Benefits. Indirect evidence in patients with VTE (without HIT) shows that DOACs likely lead to a lower risk of bleeding than a VKA and to a risk of thrombotic events similar to that associated with a VKA.[77] Among 11 patients with HIT who were transitioned to DOACs after platelet count recovery, there were no thrombotic events.[58]

Harms and burden. Indirect evidence in patients with VTE (without HIT) shows that there are likely fewer bleeds with DOACs than with a VKA. Among 11 patients with probable HIT who were transitioned to DOACs, 1 patient had a major hemorrhage secondary to known varices.[58]

Other EtD criteria and considerations. DOACs are more expensive than VKAs. Out-of-pocket costs for patients will depend on insurance coverage. The potential greater out-of-pocket costs of DOACs may reduce equity. However, VKAs come with additional costs, including those associated with prolonged hospitalization and monitoring. DOACs may be more acceptable to patients because they do not require routine laboratory monitoring and dietary restrictions.

Conclusions and research needs for this recommendation. The guideline panel suggests treatment with a DOAC rather than a VKA for patients with subacute HIT A based on moderate certainty in the evidence of effects. The particular choice of agent may be influenced by drug factors (availability, cost, ability to monitor the anticoagulant effect, route of administration, and half-life), patient factors (kidney function, liver function, bleeding risk, and clinical stability), and experience of the clinician. The panel agreed that an international registry of patients with subacute HIT A treated with a DOAC would provide important information.

Cardiovascular surgery

Question: Should intraoperative anticoagulation with (1) heparin or (2) treatment with a non-heparin anticoagulant or (3) plasma exchange and heparin or (4) heparin and an antiplatelet agent be provided to patients with acute HIT or subacute HIT A who require cardiovascular surgery?

Good practice statement 4.1.a

In patients with acute HIT or subacute HIT A who require cardiovascular surgery, the ASH guideline panel agrees that surgery should be delayed until the patient has subacute HIT B or remote HIT (see recommendation 4.2), if feasible.

Recommendation 4.1.b

If delaying surgery is not feasible, the ASH guideline panel *suggests* one of the following: intraoperative anticoagulation with bivalirudin, intraoperative heparin after treatment with preoperative and/or intraoperative plasma exchange, or intraoperative heparin in combination with a potent antiplatelet agent (eg, prostacyclin analog or tirofiban) (conditional recommendation, low certainty in the evidence about effects ⊕⊕◯◯). **Remarks:** The choice of strategy may be influenced by availability, cost, and clinician experience. Consensus protocols for the plasma exchange and intraoperative heparin strategy and for the intraoperative heparin and potent antiplatelet agent strategy have not been established. If either of these strategies is used, treatment with heparin is limited to the intraoperative setting and avoided before and after surgery.

Summary of the evidence. We did not identify any RCTs comparing non-heparin anticoagulants, preoperative or intraoperative plasma exchange with heparin, or heparin and an antiplatelet agent for use in patients with acute HIT or subacute HIT A. No nonrandomized comparison studies of interventions were identified.

We identified 2 prospective cohort studies, 1 case series, 1 case report of a single patient with HIT, and indirect evidence in the form of small randomized trials in patients without HIT who received a non-heparin anticoagulant (ie, bivalirudin, danaparoid, and argatroban).[78-80] The 3 studies conducted among patients with HIT reported on outcomes of procedural success, mortality, and major bleeding. One systematic review reported on 10 studies of 12 patients with acute HIT who received bivalirudin during cardiovascular surgery.[81] The systematic review reported on outcomes of bleeding and adverse events. Indirect evidence among patients without HIT treated with bivalirudin vs heparin undergoing cardiovascular surgery reported on the outcomes of procedural success, myocardial infarction, stroke, major bleeding, and mortality.[82-85] Indirect evidence among patients without HIT treated with danaparoid vs heparin undergoing cardiovascular surgery reported on the outcomes of myocardial infarction, reoperation for bleeding, and mortality.[86,87]

We identified 4 studies that reported on cases of patients with acute HIT undergoing cardiovascular surgery who were treated with heparin and plasma exchange.[88-91] These studies reported on the outcomes of HIT-related thrombosis, mortality, amputation, and other adverse events.

We identified 6 studies that reported on cases of patients with HIT undergoing cardiovascular surgery who were treated with heparin and antiplatelet agents, specifically, prostacyclin analogs or tirofiban.[62,63,92-95] These studies reported on the outcomes of thrombotic events, bleeding, and adverse events. The EtD framework is shown online at https://dbep.gradepro.org/profile/5A998D17-1484-A5FC-ABD7-D817503963DC.

Benefits. For patients with HIT undergoing cardiovascular surgery, thrombotic events and procedural success may be similar across interventions and comparators (ie, non-heparin anticoagulants, heparin with plasma exchange, and heparin with potent antiplatelet agents), but this is uncertain because there are no direct comparisons. The 3 studies of patients with HIT who received bivalirudin for either on-pump or off-pump surgery reported rates of 94% and 92% for procedural success (defined as absence of death, Q-wave myocardial infarction, repeat operation for coronary revascularization, or stroke), 4 deaths (n = 155), and no major bleeds.[78-80]

Harms and burden. For patients with HIT undergoing cardiovascular surgery, the risk of bleeding may be similar across treatment options, but this is uncertain. However, treatment with danaparoid may increase the risk of bleeding. In 1 case series of 4 patients treated with danaparoid during CPB, all 4 experienced blood loss requiring transfusion.[92] In addition, the panel agreed that the half-life of danaparoid and fondaparinux is inappropriately long for cardiac surgery and may therefore lead to increased risk of bleeding. Certain antiplatelet agents (eg, iloprost) may have additional harms, such as hypotension. Plasma exchange also carries potential harms, including procedural risk and adverse effects associated with receipt of donor plasma.

Other EtD criteria and considerations. Costs, availability, and clinical experience may vary with each treatment strategy.

Conclusions and research needs for this recommendation. The guideline panel recommended delaying cardiovascular surgery until the patient has subacute HIT B or remote HIT so that intraoperative heparin can be used. However, if delaying surgery is not feasible, the panel determined that there is very low certainty in the evidence of effects for treatment with intraoperative anticoagulation with bivalirudin, for preoperative and/or intraoperative plasma exchange and heparin, and for treatment with heparin and a potent antiplatelet agent such as a prostacyclin analog or tirofiban. The benefits and harms of these options may be similar. Among non-heparin anticoagulants, there is more evidence and experience with bivalirudin than other agents. There may be more bleeding with danaparoid. Costs, availability, and clinical experience may vary with each treatment strategy.

Direct comparison of treatment options for intraoperative anticoagulation in patients with HIT is an important research priority. Anticoagulation in HIT patients with ventricular assist devices or those who use extracorporeal membrane oxygenation is also worthy of investigation.

Question: Should intraoperative anticoagulation with heparin or treatment with a non-heparin anticoagulant or plasma exchange and heparin or heparin and an antiplatelet agent be provided to patients with subacute HIT B or remote HIT who require cardiovascular surgery?

Recommendation 4.2

In patients with subacute HIT B or remote HIT who require cardiovascular surgery, the ASH guideline panel suggests intraoperative anticoagulation with heparin rather than treatment with a non-heparin anticoagulant, plasma exchange and heparin, or heparin combined with an antiplatelet agent (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯). **Remarks:** Treatment with heparin would be limited to the intraoperative setting and avoided before and after surgery. Postoperative platelet count monitoring for HIT may be necessary, even when postoperative heparin is not given, because delayed-onset (autoimmune) HIT beginning 5 to 10 days after the intraoperative heparin exposure has been reported.

Summary of the evidence. We did not identify any RCTs comparing non-heparin anticoagulants, plasma exchange with heparin, or heparin and an antiplatelet agent for use in patients with subacute HIT B or remote HIT. No nonrandomized comparison studies of interventions were identified.

We identified 10 studies that reported patients with subacute HIT B or remote HIT requiring cardiovascular interventions who received heparin, non-heparin anticoagulants, antiplatelet agents, or plasma exchange.[39,96-104] The studies reported on outcomes of thrombotic events, bleeding, adverse events, mortality, and recurrent HIT. The EtD framework is shown online at https://dbep.gradepro.org/profile/DA1DC8AA-C703-3D20-8DEC-32208503CEED.

Benefits. Six studies reported on 39 patients with subacute HIT B or remote HIT undergoing cardiovascular surgery who received intraoperative heparin.[39,96-100] Among the sixteen patients with subacute HIT B, no thrombotic events were reported.[96,98,100] Among the 23 patients with remote HIT, no new thrombotic events were reported.[39,97,99,100]

Two studies reported on 2 patients undergoing cardiovascular surgery with remote HIT who received non-heparin anticoagulants (bivalirudin and danaparoid).[101,102] No events were reported for the patient treated with bivalirudin.[101] The patient treated with danaparoid developed thrombosis of the CPB circuit.[88]

Two studies reported on 8 patients with remote HIT undergoing cardiovascular surgery who received antiplatelet agents.[103,104] No thrombotic events or deaths were reported. One study reported on 6 patients with subacute HIT B who received antiplatelet agents.[104] No thrombotic events or deaths were reported.

One study reported on 1 patient undergoing cardiovascular surgery who was treated with plasma exchange until antibody clearance, and heparin was used during CPB.[105] No events were reported.

Harms and burden. For patients with subacute HIT B or remote HIT undergoing cardiovascular surgery, the risk of recurrence of acute HIT may be low with all interventions, but this is uncertain. There may be greater risk of bleeding with treatments other than heparin. The risk of bleeding is likely to be lower with heparin than with a non-heparin anticoagulant or with heparin and an antiplatelet agent, in part because of greater familiarity with heparin dosing and monitoring. Heparin-associated bleeding may be easier to manage because of the availability of a reversal agent (protamine). Antiplatelet agents may have additional harms, such as hypotension with iloprost. Plasma exchange carries additional harms, including procedural risk and adverse effects associated with receipt of donor plasma.

Six studies reported on 39 patients with subacute HIT B or remote HIT undergoing cardiovascular surgery who received heparin.[39,96-100] For the 23 patients with remote HIT, 1 case of recurrent HIT and 1 case of severe bleeding were reported.[39,97,99,100]

Two studies reported on 2 patients undergoing cardiovascular surgery with remote HIT who received non-heparin anticoagulants (bivalirudin and danaparoid).[101,102] The patient who received danaparoid developed thrombosis of the CPB circuit, sepsis, respiratory failure, pancreatitis, and renal failure but made a full recovery.[102]

Two studies reported on 8 patients with remote HIT who received heparin with an antiplatelet agent. One bleeding event leading to reoperation was reported.[103,104] One study reported on 6 patients with subacute HIT B who received heparin with an antiplatelet agent.[104] Three events of bleeding leading to reoperation were reported.

Other EtD criteria and considerations. There are additional costs and possible adverse events associated with using a non-heparin anticoagulant, preoperative plasma exchange and heparin, or heparin and an antiplatelet agent; adverse events include bleeding and hypotension and the procedural risk and adverse effects of receiving donor plasma.

Conclusions and research needs for this recommendation. The guideline panel suggests intraoperative anticoagulation with heparin rather than treatment with a non-heparin anticoagulant, plasma exchange and heparin, or heparin and an antiplatelet agent on the basis of very low certainty in the evidence of effects. Heparin is the standard of care for cardiovascular surgery and has several advantages in this context, including familiarity, measurability, and reversibility. However, there was very low-quality evidence of the risk of recurrence of HIT when heparin is used. There are additional costs and possible adverse events associated with using a non-heparin anticoagulant, plasma exchange and heparin, or heparin and an antiplatelet agent. Overall, the desirable consequences of using heparin and the undesirable consequences of using the other treatment strategies probably favor use of heparin.

Research priorities include development of a registry on the use of heparin during cardiac surgery among patients with subacute HIT B or remote HIT.

Percutaneous cardiovascular intervention

Question: Should bivalirudin, argatroban, danaparoid, or fondaparinux be provided to patients with acute HIT or subacute HIT A who require PCI?

Recommendation 5.1

In patients with acute HIT or subacute HIT A who require PCI, the ASH guideline panel *suggests* treatment with bivalirudin rather than a different non-heparin anticoagulant (conditional recommendation, low certainty in the evidence ⊕⊕◯◯). **Remarks:** If bivalirudin is not available or there is a lack of institutional experience, argatroban might be a suitable substitute. The choice of drug may be influenced by drug availability, cost, ability to monitor the anticoagulant effect, and clinician experience.

Summary of the evidence. We did not identify any RCTs comparing different non-heparin anticoagulants for use during PCI in patients with acute HIT or subacute HIT A. We identified 3 studies evaluating the use of non-heparin anticoagulants (bivalirudin and argatroban) during PCI among patients with suspected or confirmed HIT.[56,106,107] These studies reported on the outcomes of mortality and bleeding. We identified 2 studies reporting indirect evidence on treatment with non-heparin anticoagulants during PCI among patients without HIT.[108,109] These studies reported on the outcomes of bleeding, ischemic adverse events, and composite outcomes of death, myocardial infarction, or urgent revascularization. The EtD framework is shown online at https://dbep.gradepro.org/profile/8BC628BF-6464-8F9C-A540-E848F59ACFB0.

Benefits. Among 91 patients with HIT, suspected HIT, or remote HIT treated with argatroban during PCI, no deaths were reported.[107] For 61 PCI procedures in which danaparoid was used, no adverse outcomes were reported.[56] Among 19 772 patients without HIT, bivalirudin demonstrated a lower risk of major bleeding than heparin (OR, 0.55; 95% CI, 0.44-0.69) and a similar risk of ischemic adverse events (OR, 1.07; 95% CI, 0.96-1.19).[108]

Harms. For patients with HIT undergoing PCI, there is concern that non-heparin anticoagulants could increase bleeding compared with heparin (although this was not observed in a meta-analysis comparing UFH and bivalirudin in patients without HIT). Among 50 patients with suspected or confirmed HIT receiving bivalirudin, 1 death and 1 bleeding event were reported.[106] Among 91 patients with suspected or confirmed HIT who received argatroban, 1 bleeding event was reported.[107] Among 152 patients without HIT who received argatroban or abciximab or eptifibatide

during PCI, 4 composite outcomes of death, myocardial infarction, or urgent revascularization (no deaths, 4 myocardial infarctions, and 2 revascularizations) and 2 major bleeds were reported at 30 days.[109]

Other EtD criteria and considerations. Clinicians have more experience in treating patients without HIT with bivalirudin during PCI.

Conclusions and research needs for this recommendation. The guideline panel suggests treatment with bivalirudin during PCI for patients with acute HIT or subacute HIT A on the basis of low certainty in the evidence about effects. This recommendation is based primarily on favorable evidence and extensive experience with bivalirudin in patients without HIT. If bivalirudin is not available or there is a lack of institutional experience, argatroban might be a suitable substitute. The choice of drug may be influenced by drug availability, cost, ability to monitor the anticoagulant effect, and clinician experience. There was much less data on the use of bivalirudin, argatroban, or other non-heparin anticoagulants in patients with HIT. No research priorities related to this recommendation were identified.

Question: Should bivalirudin, argatroban, danaparoid, fondaparinux, or heparin be provided to patients with subacute HIT B or remote HIT who require PCI?

Recommendation 5.2

In patients with subacute HIT B or remote HIT who require PCI, the ASH guideline panel *suggests* treatment with bivalirudin rather than UFH (conditional recommendation, very low certainty in the evidence ⊕◯◯◯).

Remarks: Heparin is an acceptable alternative for patients with subacute HIT B or remote HIT if a suitable non-heparin anticoagulant is not available or clinician experience is lacking. If heparin is used, exposure should be limited to the intraprocedural setting and should be avoided before and after the procedure.

If bivalirudin is not available or if there is a lack of institutional experience, argatroban might be a suitable substitute. Choice of drug may be influenced by drug availability, cost, ability to monitor the anticoagulant effect, and clinician experience.

Summary of the evidence. We did not identify any RCTs comparing non-heparin anticoagulants and UFH for use in patients with subacute HIT B or remote HIT who require PCI. We identified 1 case study that reported on the use of danaparoid for a patient with remote HIT requiring PCI.[110] This study reported on the outcomes of thrombotic and bleeding events. Two studies reported indirect evidence of treatment with non-heparin anticoagulants during PCI among patients without HIT.[108,109] These studies reported on the outcomes of bleeding, ischemic adverse events, mortality, myocardial infarction, and urgent revascularization. Two studies reported indirect evidence of treatment with non-heparin anticoagulants (bivalirudin and danaparoid) among people with subacute HIT B and remote HIT undergoing cardiac surgery.[101,102] These studies reported on the outcomes of transfusions and adverse events. Six studies reported indirect evidence of treatment with heparin among people with subacute HIT B and remote HIT undergoing cardiac surgery.[39,96-100] These studies reported on the outcomes of thrombotic and bleeding events and recurrent HIT. The EtD framework is shown online at https://dbep.gradepro.org/profile/505C2564-BBEA-0CCE-BB2D-5D3961D8CAD4.

Benefits. There may be benefits among patients with subacute HIT B or remote HIT undergoing PCI who are treated with non-heparin anticoagulants. In 1 patient with remote HIT undergoing PCI who received danaparoid, no thrombotic or bleeding events were reported. Among 19 772 patients without HIT undergoing PCI, bivalirudin demonstrated a lower risk of major bleeding than heparin (OR, 0.55; 95% CI, 0.44-0.69) and a similar risk of ischemic adverse events (OR, 1.07; 95% CI, 0.96-1.19).[108] Among 152 patients without HIT undergoing PCI, 4 composite outcomes of death, myocardial infarction, or urgent revascularization (no deaths, 4 myocardial infarctions, and 2 revascularizations) and 2 major bleeds were reported at 30 days.[109] For 16 patients with subacute HIT B undergoing CPB who received heparin, no thrombotic events were reported. Among 23 patients with remote HIT undergoing CPB who received heparin, 1 case of recurrent HIT was reported; however, no other thrombotic events were reported.[39,97,99,100]

Harms. There may be harms from treatment with non-heparin anticoagulants for patients with subacute HIT B or remote HIT undergoing PCI, but this is uncertain. One patient with remote HIT undergoing CPB who received bivalirudin required red blood cell and fresh frozen plasma transfusions, but no other outcomes were reported.[101] One patient with remote HIT undergoing CPB who received danaparoid developed thrombosis of the CPB circuit, sepsis, respiratory failure, pancreatitis, and renal failure but made a full recovery.[102] Among 23 patients with remote HIT undergoing CPB who received heparin, 1 case of severe bleeding was reported.[39,97,99,100]

Other EtD criteria and considerations. Alternative anticoagulants probably require specialized clinical experience. Bivalirudin is widely used for PCI in the United States but not internationally. Heparin could be used in areas where alternative non-heparin anticoagulants are unavailable or clinical staff are unfamiliar with treating patients with non-heparin anticoagulants.

Conclusions and research needs for this recommendation. The guideline panel suggests treatment with bivalirudin rather than unfractionated heparin for patients with subacute HIT B or remote HIT requiring PCI on the basis of low certainty in the evidence of effects. This recommendation is based on evidence that bivalirudin reduces bleeding risk compared with heparin in patients without HIT and that use of a non-heparin anticoagulant may avoid the small risk of HIT recurrence with use of heparin. Heparin is an acceptable alternative in patients with subacute HIT B or remote HIT if a suitable non-heparin anticoagulant is not available or clinician experience is lacking. If heparin is used, exposure should be limited to the intraprocedural setting and should be avoided before and after the procedure. If bivalirudin is not available or there is a lack of institutional experience, argatroban might be a suitable substitute. The choice of drug may be influenced by drug availability, cost, ability to monitor the anticoagulant effect, and clinician experience. No research questions related to this recommendation were identified.

Renal replacement therapy

Question: Should argatroban, danaparoid, bivalirudin, fondaparinux, or a DOAC be provided to patients with acute HIT who are receiving renal replacement therapy and require anticoagulation to prevent thrombosis of the dialysis circuitry?

Recommendation 6.1

In patients with acute HIT who are receiving renal replacement therapy and require anticoagulation to prevent thrombosis of the dialysis circuitry, the ASH guideline panel *suggests* treatment with argatroban, danaparoid, or bivalirudin rather than other non-heparin anticoagulants (conditional recommendation; very low certainty in the evidence about effects ⊕◯◯◯). **Remark:** The choice of agent may be influenced by drug factors (availability and cost), patient factors (liver function), and experience of the clinician.

Summary of the evidence. We did not identify any RCTs comparing non-heparin anticoagulants for use in patients with acute HIT who require renal replacement therapy. We identified nonrandomized studies evaluating the use of argatroban, danaparoid, fondaparinux, bivalirudin, and rivaroxaban. Ten studies reported on treatment with argatroban,[111-120] 3 studies reported on treatment with danaparoid,[70,121,122] 3 studies reported on treatment with fondaparinux,[123-125] 2 studies reported on treatment with bivalirudin,[57,126] and 1 study reported on treatment with rivaroxaban.[127] These studies reported on the outcomes of bleeding, thromboembolic events, mortality, and serious adverse events.

Indirect evidence was identified on the use of argatroban and danaparoid among patients without HIT. One RCT evaluated 13 patients with end-stage renal disease without HIT who received argatroban during intermittent hemodialysis.[128] Two RCTs compared danaparoid and heparin or LMWH during hemodialysis in patients without HIT.[129,130] These studies reported on the outcomes of bleeding, thromboembolic events, serious adverse events, and laboratory measures. The EtD framework is shown online at https://dbep.gradepro.org/profile/948a7b63-bf96-41ec-8e18-ae25298b9836.

Benefits. There may be moderate benefits associated with the treatment of patients with HIT undergoing renal replacement therapy with selected non-heparin anticoagulants (eg, argatroban, danaparoid, or bivalirudin) compared with others (eg, fondaparinux and rivaroxaban) for which there is little data and greater dependence on the kidneys for clearance. Among 13 patients without HIT who received argatroban, no thrombosis, bleeding, serious adverse events, or clinically significant changes in vital signs or routine laboratory measures were reported.[128] Among 62 patients without HIT who received danaparoid, no events were reported.[129,130] Among 9 patients with HIT who received fondaparinux, no bleeding or other adverse events were reported.[123-125] Among 114 patients with HIT who received bivalirudin during dialysis, no amputations were reported, 7 had new thromboembolic events, and 32 died.[57,126] For the 1 patient who received rivaroxaban, no thromboembolic or bleeding events were reported.[127]

Harms and burden. Among 97 patients with HIT who received argatroban, 18 deaths were reported; however, none were the result of thrombosis.[111-120] One patient with peripheral vascular disease underwent amputation, and 3 patients developed thrombotic events. Major bleeding occurred in 3 of 50 treatment courses in 1 study and in 2 of 30 patients in another study. One patient required co-intervention with aspirin. Among 115 patients with HIT receiving danaparoid during hemodialysis, 8 patients developed nonfatal thromboembolic events (of which 2 required amputation), 28 died, 11 had nonfatal major bleeding events, 7 had minor bleeding events, 11 had nonfatal adverse events, and 14 had fatal adverse events.[70,121,122] Among 9 patients with HIT who received fondaparinux, 3 patients developed thromboses that were managed by increasing the dose.[123-125] Among 114 patients with HIT who received bivalirudin during dialysis, 13 experienced major bleeding events.[57,126]

Other EtD criteria and considerations. Compared with fondaparinux and rivaroxaban, argatroban, danaparoid, and bivalirudin are less dependent on the kidneys for clearance. Non-heparin anticoagulants are probably feasible to provide. However, there may be some jurisdictions in which specific non-heparin anticoagulants are not available. At least 1 non-heparin anticoagulant is probably available, acceptable, and feasible to provide in most jurisdictions.

Conclusions and research needs for this recommendation. The guideline panel suggests treatment with argatroban, danaparoid, or bivalirudin rather than other non-heparin anticoagulants on the basis of very low certainty in the evidence of effects. The choice of agent may be influenced by drug factors (availability and cost), patient factors (liver function), and experience of the clinician. There may be moderate benefits with select non-heparin anticoagulants (such as argatroban, danaparoid, or bivalirudin) compared with others (such as fondaparinux and rivaroxaban) for which there is little data and greater dependence on the kidneys for clearance. No research questions related to this recommendation were identified.

Question: Should argatroban, danaparoid, bivalirudin, fondaparinux, regional citrate, heparin, or a DOAC be provided to patients with subacute HIT A, subacute HIT B, or remote HIT who are receiving renal replacement therapy, are not otherwise receiving anticoagulation, and require anticoagulation to prevent thrombosis of the dialysis circuit?

Recommendation 6.2

In patients with subacute HIT A, subacute HIT B, or remote HIT who are receiving renal replacement therapy, are not otherwise receiving anticoagulation, and require anticoagulation to prevent thrombosis of the dialysis circuit, the ASH guideline panel *suggests* regional citrate rather than heparin or other non-heparin anticoagulants (conditional recommendation; very low certainty in the evidence about effects ⊕◯◯◯). **Remark:** Citrate is not appropriate for patients with acute HIT who require systemic rather than regional anticoagulation (see recommendation 6.1).

Summary of the evidence. We did not identify any RCTs comparing non-heparin anticoagulants for use in patients with

subacute HIT A, subacute HIT B, or remote HIT who require renal replacement therapy. We identified nonrandomized studies evaluating the use of argatroban, danaparoid, fondaparinux, bivalirudin, and rivaroxaban. Ten studies reported on treatment with argatroban,[111-120] 3 studies reported on treatment with danaparoid,[70,121,122] 3 studies reported on treatment with fondaparinux,[123-125] 2 studies reported on treatment with bivalirudin,[57,126] and 1 study reported on treatment with rivaroxaban.[127] These studies reported on the outcomes of bleeding, thromboembolic events, mortality, and serious adverse events.

Indirect evidence was identified on the use of argatroban and danaparoid among patients without HIT. One RCT evaluated 13 patients with end-stage renal disease without HIT who received argatroban during intermittent hemodialysis.[128] Two RCTs compared danaparoid and heparin or LMWH during hemodialysis in patients without HIT.[129,130] One systematic review evaluated 14 RCTs comparing regional citrate to heparin for patients without HIT who required continuous renal replacement therapy.[131] One case series reported on 3 patients with remote HIT who received a second course of heparin for various indications more than 100 days after the initial episode of HIT.[39] These studies reported on the outcomes of bleeding, thromboembolic events, serious adverse events, and laboratory measures. The EtD framework is shown online at https://dbep.gradepro.org/profile/1553EA74-7DB0-1209-84EB-DF6DBC3DA805.

Benefits. Patients with HIT and end-stage renal disease may benefit from treatment with argatroban, danaparoid, bivalirudin, or citrate, but the relative benefits are uncertain. Among 13 patients without HIT who received argatroban, no thrombosis, bleeding, serious adverse events, or clinically significant changes in vital signs or routine laboratory measures were reported.[128] Among 62 patients without HIT who received danaparoid, no events were reported.[129,130] Among 9 patients with HIT who received fondaparinux, no bleeding or other adverse events were reported.[123-125] Among 114 patients with HIT who received bivalirudin during dialysis, no amputations were reported, 7 had new thromboembolic events, and 32 died.[57,126] For the 1 patient who received rivaroxaban, no thromboembolic or bleeding events were reported.[127]

Among patients without HIT receiving either citrate or heparin, the risk of mortality was similar between treatment arms (RR, 0.97; 95% CI, 0.84-1.13).[131] The risk of bleeding was lower among patients receiving regional citrate (RR, 0.3; 95% CI, 0.19-0.49). The risk of development of HIT was lower among the patients receiving regional citrate (RR, 0.41; 95% CI, 0.19-0.87). Among 3 patients who received a second course of heparin more than 100 days after an episode of acute HIT, none developed recurrent HIT.

Harms and burden. Patients may experience some harms (eg, mortality and bleeding) from treatment with argatroban, danaparoid, or bivalirudin, but this is uncertain. Among 97 patients with HIT who received argatroban, 18 deaths were reported; however, none were the result of thrombosis.[111-120] One patient with peripheral vascular disease underwent amputation, and 3 patients developed thrombotic events. Major bleeding occurred in 3 of 50 treatment courses in 1 study and in 2 of 30 patients in another study. One patient required co-intervention with aspirin. Among patients without HIT receiving danaparoid during hemodialysis, 2 of 25 developed nonfatal thromboembolic events, none required amputation, 1 had minor bleeding, and 2 reported nonfatal adverse events.[70,121,122] Among 9 patients with HIT who received fondaparinux during hemodialysis, 3 developed thromboses that were managed by increasing the dose.[123-125] Among 114 patients with HIT who received bivalirudin during dialysis, 13 experienced major bleeding events, 7 experienced new thromboembolic events, and 32 died (HIT-related mortality was not disaggregated from all-cause mortality).[57,126]

Other EtD criteria and considerations. Compared with fondaparinux and rivaroxaban, argatroban, danaparoid, and bivalirudin are less dependent on the kidneys for clearance. Citrate may have similar efficacy and superior safety (reduced bleeding and reduced HIT) compared with heparin in patients without a history of HIT. Citrate is acceptable to clinicians and inexpensive compared with other non-heparin anticoagulants (eg, argatroban, danaparoid, fondaparinux, bivalirudin, and rivaroxaban) and therefore probably increases equity.

Conclusions and research needs for this recommendation. The guideline panel suggests regional citrate rather than heparin or other non-heparin anticoagulants on the basis of very low certainty in the evidence. Citrate has similar efficacy and superior safety (reduced bleeding and reduced HIT) compared with heparin in patients without a history of HIT. It is familiar to clinicians and is inexpensive compared with other non-heparin anticoagulants (eg, argatroban, danaparoid, fondaparinux, bivalirudin, and rivaroxaban). No research questions related to this recommendation were identified.

VTE and prophylaxis in patients with remote HIT

Question: Should a non-heparin anticoagulant (eg, apixaban, dabigatran, danaparoid, edoxaban, fondaparinux, rivaroxaban, or a VKA) or heparin be administered to patients with remote HIT who require VTE treatment or prophylaxis?

Recommendation 7.1

In patients with remote HIT who require VTE treatment or prophylaxis, the ASH guideline panel *recommends* administration of a non-heparin anticoagulant (eg, apixaban, dabigatran, danaparoid, edoxaban, fondaparinux, rivaroxaban, or a VKA) rather than UFH or LMWH (strong recommendation, very low certainty in the evidence about effects ⊕◯◯◯). **Remarks:** For recommendations on the choice of non-heparin anticoagulant for VTE prophylaxis, please refer to *American Society of Hematology Guidelines on Prevention of Venous Thromboembolism in Surgical Hospitalized Patients* (manuscript in preparation) and *Prophylaxis for Hospitalized and Nonhospitalized Medical Patients* (Schünemann HJ et al, *Blood Advances*, in press). For recommendations on the choice of agent for VTE treatment, please refer to *American Society of Hematology Guidelines on Treatment of Acute VTE* (manuscript in preparation).

Summary of the evidence. We did not identify any RCTs comparing heparin to non-heparin anticoagulants for treatment of patients with remote HIT who require VTE prophylaxis or treatment. We identified 1 study that reported on development of thrombosis and likelihood of recurrence of thrombocytopenia among patients re-exposed to heparin.[39] The study reported on the outcome of

recurrent HIT. The EtD framework is shown online at https://dbep.gradepro.org/profile/7B9F1760-2AC7-D97B-BAC8-680F1B04A2EA.

Benefits. Similar benefits may be experienced by patients with remote HIT who receive non-heparin anticoagulants or heparin for the prevention or treatment of VTE; however, this is uncertain. Three patients with serologically confirmed HIT received a second course of heparin more than 100 days after an episode of acute HIT.[39] None developed recurrent HIT.

Harms and burden. The incidence of recurrent HIT in patients with remote HIT treated with a course of heparin or LMWH for VTE prophylaxis or treatment is not known. However, cases highlighting the harms of recurrent HIT have been reported. The panel agreed that HIT recurrence would be a serious consequence. Apart from the prospect of recurrent HIT, adverse events associated with heparin and non-heparin anticoagulants would be expected to be similar for patients without HIT and with remote HIT.

Other EtD criteria and considerations. The panel placed a high value on avoiding recurrent HIT and related serious consequences, therefore favoring treatment with non-heparin anticoagulants even though heparin is less expensive than non-heparin anticoagulants. In addition, there are several non-heparin anticoagulants available for VTE prophylaxis and treatment with comparable benefits and harms in patients without a history of HIT. Stakeholders would not find the treatment of patients with remote HIT with heparin instead of non-heparin anticoagulants acceptable, even though it would be feasible.

Conclusions and research needs for this recommendation. The guideline panel recommends administration of a non-heparin anticoagulant (eg, apixaban, dabigatran, danaparoid, edoxaban, fondaparinux, rivaroxaban, or a VKA) rather than UFH or LMWH on the basis of very low certainty in the evidence about effects. Apart from the recommendation to avoid heparin anticoagulants, these patients should be treated similarly to those without a history of HIT. For recommendations on choice of non-heparin anticoagulant for VTE prophylaxis, please refer to *American Society of Hematology Guidelines on Prevention of Venous Thromboembolism in Surgical Hospitalized Patients* and *American Society of Hematology Guidelines on Prevention of Venous Thromboembolism in Medical Hospitalized Patients*. For recommendations on choice of agent for VTE treatment, please refer to *American Society of Hematology Guidelines on Treatment of Acute VTE*. No research priorities related to this recommendation were identified.

Emergency identification

Question: Should patients with a history of HIT carry or wear an emergency identifier (eg, an emergency pendant or bracelet)?

Recommendation 8.1.a

In patients with a history of HIT in the last 3 months, the ASH guideline panel *suggests* carrying or wearing an emergency identifier (eg, an emergency pendant or bracelet) (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯). **Remark:** The emergency identifier should include the drug (heparin), the reaction to the drug (HIT), and the date HIT was diagnosed.

Recommendation 8.1.b

In patients with a history of HIT more than 3 months ago, the ASH panel *suggests against* carrying or wearing an emergency identifier (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Summary of the evidence. No RCTs were identified that compared carrying vs not carrying an emergency identifier for patients with a history of HIT. We identified 1 study that reported on development of thrombosis and the likelihood of recurrence of thrombocytopenia among patients re-exposed to heparin.[39] One study reported on current practices among children with hemophilia who wore or did not wear an emergency identifier.[132] The EtD framework is shown online at https://dbep.gradepro.org/profile/4136F0E9-871F-A458-A526-FE3BF6DEF8E8.

Benefits. The risk of HIT recurrence or exacerbation with heparin re-exposure is greatest in the first 3 months after diagnosis of acute HIT. Therefore, for patients with HIT diagnosed less than 3 months ago, there may be large potential benefits to wearing an emergency identifier, including a decreased risk of recurrent HIT and a reduction in patient anxiety about the risk of recurrent HIT.

There may be small benefit for patients with a history of HIT diagnosed more than 3 months ago, but this is uncertain. Among patients with remote HIT, 3 patients with serologically confirmed HIT received a second course of heparin more than 100 days after the initial episode of HIT, and none developed recurrent HIT.[39]

Harms and burden. Among patients diagnosed with HIT less than 3 months ago, there may be a small risk of inappropriate avoidance of heparin as a result of wearing an emergency identifier, but this is uncertain. For patients diagnosed with HIT more than 3 months ago, there are situations where heparin re-exposure may be appropriate (eg, cardiac surgery), and avoidance of heparin could result in inferior treatment. Indirect evidence from patients without HIT (with hemophilia) suggests that 3% to 6% experience adverse events from wearing a medical bracelet (rashes and bruising).[132]

Other EtD criteria and considerations. There is possibly important uncertainty or variability in how much patients value the main outcomes. The panel placed greater weight on avoidance of recurrent HIT through use of an emergency identifier than on the potential for inappropriate avoidance of heparin in the first 3 months, when the risk of HIT recurrence with heparin re-exposure is relatively high. The panel placed greater weight on the potential harms of inappropriate avoidance of heparin than on the potential risk of recurrent HIT after 3 months, when the risk of HIT recurrence with heparin re-exposure is relatively low. The costs of an emergency identifier are negligible. Wearing an emergency identifier may not be acceptable to some patients because of experienced or anticipated stigma. However, for some patients, wearing an emergency identifier may decrease anxiety. Emergency identifiers are feasible and acceptable to clinicians.

Conclusions and research needs for this recommendation. The guideline panel suggests carrying or wearing an emergency identifier (eg, an emergency pendant or bracelet) for patients with a

history of HIT in the last 3 months. The emergency identifier should include the drug (heparin), the reaction to the drug (HIT), and the date HIT was diagnosed. The guideline panel suggests against carrying or wearing an emergency identifier for patients with a history of HIT diagnosed more than 3 months ago. No research priorities related to this recommendation were identified.

What are others saying and what is new in these ASH guidelines?

This guideline differs from previously published guidelines on HIT in a number of respects. Two key differences are highlighted here.

Although other recent guidelines have included individual recommendations on diagnosing suspected HIT,[52,133,134] our guideline is the first to integrate multiple recommendations regarding diagnosis and initial management of patients with suspected HIT into an algorithm for clinicians (see recommendations 2.1 through 2.10 and Figure 1). The recommendations that make up the algorithm are based on a novel modeling strategy that incorporated not only the diagnostic accuracy of various tests for HIT but also the impact of those tests on patient-important outcomes, such as thrombosis, amputation, major bleeding, and mortality.

Other guidelines either do not recommend fondaparinux[52] or suggest a preference for conventional non-heparin anticoagulants (eg, danaparoid or argatroban) over fondaparinux[133] for the treatment of acute HIT. Those guidelines do not address the use of DOACs in the management of acute HIT. In contrast, our guideline suggests that danaparoid, argatroban, bivalirudin, fondaparinux, and DOACs are all potentially suitable for the treatment of acute HIT and provides guidance on selecting anticoagulants for individual patients (see recommendation 3.1. and accompanying remarks).

Limitations of these guidelines

The limitations of these guidelines are inherent in the low or very low certainty in the evidence we identified for many of the questions. For most recommendations, there were few to no comparative studies in patients with a confirmed diagnosis of HIT. For some recommendations, studies of patients without HIT were used as indirect evidence. For this reason, the certainty in the evidence was often down-rated for indirectness. When searching for evidence for the diagnosis of HIT and subsequent management while awaiting a confirmed diagnosis, we also found no studies assessing the impact of different diagnostic strategies on outcomes important to patients such as mortality and thrombotic events. Instead, we modeled the outcomes on the basis of the numbers of true positives and false positives and true negatives and false negatives. When modeling, we assumed that the gold standard for confirmation of HIT was a functional assay such as the SRA or heparin-induced platelet activation assay. Although diagnostic test accuracy of the functional assay is not 100%, this assumption was consistently applied across models for all tests. Finally, nonfinancial conflicts of interest, such as intellectual conflicts, were declared and reviewed but did not result in recusal during the decision process.

Revision or adaptation of the guidelines

Plans for updating these guidelines

After these guidelines are published, ASH will maintain them through surveillance for new evidence, ongoing review by experts, and regular revisions.

Updating or adapting recommendations locally

Adaptation of these guidelines will be necessary in many circumstances. These adaptations should be based on the associated EtD frameworks.[135]

Priorities for research

On the basis of gaps in evidence recognized during the guideline development process, the panel identified a number of priorities for future research. Specific suggestions are detailed with each recommendation. Key research priorities with respect to diagnosis include integration of emerging rapid immunoassays into diagnostic algorithms, identification of barriers to adherence to and implementation analyses of evidence-based diagnostic algorithms, and development of novel laboratory assays that overcome limitations of currently available assays (ie, immunoassays with enhanced specificity and functional assays with enhanced practicability). Key research priorities with respect to management include direct comparisons of non-heparin anticoagulants for treatment of acute HIT, obtaining more data on the efficacy and safety of DOACs in this setting, elucidation of the role of intravenous immunoglobulin in acute HIT, and development of novel therapeutics that target pathways in the pathogenesis of HIT proximal to coagulation that could be effective in reducing thrombosis without increasing the risk of hemorrhage.

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Authorship

Contribution: A.C., R.L.M., and N.S. wrote the manuscript; guideline panel members A.C., G.M.A., B.H.C., D.B.C., A.G., Y.J.G., L.A.L., S.B.R., S.S., T.E.W., A.W., and N.S. critically reviewed the manuscript and provided suggestions for improvement; members of the knowledge synthesis team R.A.M., R.L.M., and N.S. contributed evidence summaries to the guidelines; all authors approved of the content; and A.C. was chair and N.S. was vice chair of the panel and led the panel meeting.

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