SYSTEMATIC REVIEW

blood advances

Management of heparin-induced thrombocytopenia: systematic reviews and meta-analyses

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Heparin-induced thrombocytopenia (HIT) is a prothrombotic adverse drug reaction occurring in <0.1% to 7% of patients receiving heparin products depending on the patient population and type of heparin. Management of HIT is highly dependent on a sequence of tests for which clinicians may or may not have the results when care decisions need to be made. We conducted systematic reviews of the effects of management strategies in persons with acute HIT, subacute HIT A or B, and remote HIT. We searched Medline, EMBASE, and the Cochrane Database through July 2019 for previously published systematic reviews and primary studies. Two investigators independently screened and extracted data and assessed the certainty of the evidence using the Grading of Recommendations Assessment, Development and Evaluation approach. We found primarily noncomparative studies and case series assessing effects of treatments, which led to low to very low certainty evidence. There may be little to no difference in the effects between nonheparin parenteral anticoagulants and direct oral anticoagulants in acute HIT. The benefits of therapeutic-intensity may be greater than prophylactic-intensity anticoagulation. Using inferior vena cava filters or platelet transfusion may result in greater harm than not using these approaches. Evidence for management in special situations, such as for patients undergoing cardiovascular interventions or renal replacement therapy, was also low to very low certainty. Additional research to evaluate nonheparin anticoagulants is urgently needed, and the development of novel treatments that reduce thrombosis without increasing hemorrhage should be a priority.

Introduction

Heparin-induced thrombocytopenia (HIT) is a prothromobotic adverse drug reaction occurring in <0.1% to 7% of patients receiving heparin products, depending on the patient population, type of heparin, and duration of exposure.[1-3] One-third to one-half of cases are complicated by thromboembolism, which may be limb- or life-threatening.[4-6]

HIT may be conceptualized as occurring in 5 sequential phases: suspected HIT, acute HIT, subacute HIT A, subacute HIT B, and remote HIT (defined in Table 1).[7,8] Each phase confronts the clinician with unique management questions.

We consulted with experts in the field and patient representatives to brainstorm and prioritize 21 key questions on management of the various phases of HIT (supplemental Appendix: population, intervention, comparison, outcome questions) and to identify important outcomes (thromboembolism,

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Table 1. The 5 phases of HIT

Phase	Platelet count	Functional assay	Immunoassay
Suspected HIT	Decreased	?	?
Acute HIT	Decreased	+	+
Subacute HIT A	Normal	+	+
Subacute HIT B	Normal	–	+
Remote HIT	Normal	–	–

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 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 or anti-heparin antibodies are no longer detectable by immunoassay, the patient is said to have remote HIT. Adapted from Cuker.[8]

limb amputation, mortality, major bleeding, recurrent acute HIT, duration of hospitalization) for these questions. To determine the effects of different management strategies, we conducted systematic reviews of the literature. Here we report the findings of our systematic reviews that address the following in all HIT patients, unless specified:

- anticoagulants in patients with acute HIT, including nonheparin parenteral anticoagulants and direct oral anticoagulants (DOACs);
- inferior vena cava filters;
- platelet transfusion;
- screening limb ultrasonography in patients with acute HIT; and
- special situations in patients with acute HIT or a history of HIT including cardiac surgery, percutaneous coronary intervention, and renal replacement therapy.

Methods

This document presents the systematic reviews that were used to inform evidence-based recommendations on management of HIT in the American Society of Hematology clinical practice guidelines on venous thromboembolism.[9,10] We followed review and meta-analysis methods from the *Cochrane Handbook*[11] and reporting criteria according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[12] Our systematic review protocol is registered in the PROSPERO database (reference number CRD42020146770).

We conducted a search of the literature in OVID MEDLINE, OVID EMBASE, and Cochrane CENTRAL from database inception to July 2019. The systematic search strategy is available in supplemental Appendix II. We also reviewed reference lists of included articles. Two investigators (among R.L.M., V.A., H.B., S.R., and N.M.) independently screened titles and abstracts to identify potentially eligible references. These references were then screened in duplicate in full text to confirm eligibility.

We included reviews or studies of persons with laboratory-confirmed HIT (Table 1) who received any of the interventions in the key questions and that reported on any of the critical outcomes. We included and updated systematic reviews published after 2006 meeting modified criteria from the Risk of Bias in Systematic reviews instrument (ie, addressed the Population, Intervention, Comparison, Outcome question, included appropriate eligibility criteria, identified all relevant studies, provided study characteristics and appraisal, synthesized results correctly).[13] If a systematic review did not meet these criteria or was not available, we conducted our own systematic review of randomized controlled trials (RCTs) and comparative nonrandomized studies. If comparative studies were not available, we included case series and reports. We excluded conference abstracts. We used standardized pilot-tested forms to extract data. Pairs of reviewers extracted data independently and in duplicate. Conflicts were resolved through discussion.

We assessed the risk of bias of included studies using tools appropriate to the study design: the Cochrane Collaboration risk of bias tool[14] for RCTs; and the Risk of Bias in Nonrandomized studies of interventions tool[15] for nonrandomized comparative studies. We followed the guidance for each tool, but if a nonrandomized study did not report any adjustment for critical confounders, the study was judged to have critical bias, and we did not continue to assess the remaining risk of bias domains; however, the study was included in the review.

When pooling was possible, we calculated the pooled relative risk for dichotomous outcomes using random effects models and associated 95% confidence intervals (CIs). For continuous outcomes, we pooled the mean difference. When pooling was not possible, we described the effects narratively.

We used the Grading of Recommendations Assessment, Developing, and Evaluation (GRADE) approach and its Guideline Development Tool (www.gradepro.org) to assess the evidence across 8 domains: study limitations, inconsistency, indirectness, imprecision, publication bias, magnitude of effect, dose-response gradient, and opposing residual confounding.[16] We assessed inconsistency with the χ^2 test and I^2 statistic. Moderate heterogeneity ($I^2 > 50\%$) was explored. The certainty of evidence (ie, quality of evidence) in the effect estimates for the body of evidence of each outcome was assessed as high, moderate, low, or very low.

Results

Our search identified 9060 titles and abstracts. Of those, we screened 931 full-text papers, and 116 papers were included (supplemental Appendix: Preferred Reporting Items for Systematic Reviews and Meta-Analyses). We present the effects of different treatment strategies. Findings from additional topics are presented in the supplemental Appendix (additional systematic review results). Characteristics of eligible studies are presented in the supplemental Appendix (study characteristics).

Nonheparin parenteral anticoagulants

Our search identified 1 RCT and several nonrandomized studies comparing different nonheparin parenteral anticoagulants. Risk of bias assessments for eligible studies reporting on nonheparin parenteral anticoagulants are presented in the supplemental Appendix (risk of bias assessment).

Danaparoid. We found low to very low certainty evidence for the effects of danaparoid based on 1 RCT comparing danaparoid with dextran 70 and 1 nonrandomized study comparing danaparoid with fondaparinux (supplemental Appendix: GRADE evidence profiles).[17,18] Compared with dextran 70, danaparoid may reduce mortality, limb amputations, and thromboembolic complications

(TECs; risk ratio [RR]: 0.68; 95% CI: 0.20, 2.35; RR: 0.24; 95% CI: 0.03, 2.08; and RR: 0.30; 95% CI: 0.09, 1.01, respectively) and lead to fewer adverse events (RR: 0.71; 95% CI: 0.21, 2.44).[17] Compared with fondaparinux, it may increase the risk of thrombosis and thrombosis-related mortality (RR: 1.21; 95% CI: 0.58, 2.50) but reduce the risk of bleeding and bleeding-related mortality (RR: 0.59; 95% CI: 0.25, 1.44); however, the evidence is very uncertain.[18] We also found a case series of 1478 patients with HIT receiving danaparoid[19] that reported new thrombosis in 9.7% of patients, treatment failure (ie, developed 1 or more of the following during treatment and follow-up: new/progressive thrombosis, persistent/new platelet count reduction, unplanned amputation) in 16.4%, and major bleeding in 8.1%.

Argatroban. Despite argatroban being widely approved and available as a treatment of HIT, we found few nonrandomized studies reporting its efficacy in patients with antibody-confirmed HIT (the prospective, historically controlled studies performed for regulatory approval enrolled patients on the basis of a clinical diagnosis of HIT and did not report outcomes in the subgroup who were antibody positive). Although the evidence is of very low certainty, when comparing initiation of argatroban with a vitamin K antagonist in patients with acute HIT, argatroban may reduce thrombosis-related mortality and new TECs (RR: 0.12; 95% CI: 0.05, 0.34 and RR: 0.45; 95% CI: 0.28. 0.71, respectively), but it may increase the risk of limb amputations and major bleeds (RR: 1.26; 95% CI: 0.53, 2.99 and RR: 3.70; 95% CI: 0.52, 26.50, respectively).[20,21] Compared with danaparoid, it may increase the risk of thrombosis and thrombosis-related mortality (RR: 1.25; 95% CI: 0.47, 3.33), as well as bleeding and bleeding-related mortality (RR: 2.80; 95% CI: 1.02, 7.72).[18] In addition, compared with fondaparinux, there was very low certainty evidence that argatroban may increase the risk of thrombosis and thrombosis-related mortality, bleeding and bleeding-related mortality, and length of hospital stay (RR: 1.51; 95% CI: 0.65, 3.53; RR: 1.66; 95% CI: 0.84, 3.29; and mean difference: 14.5; 95% CI: 10.15, 18.85, respectively)[18,22]; however, the evidence is very uncertain.

Bivalirudin. No studies comparing bivalirudin with other treatment options were identified. Joseph et al[23] reported on suspected (n = 262), confirmed (n = 124), and remote (n = 75) HIT patients receiving treatment with bivalirudin. New thrombosis was identified in 21 (4.6%). No amputations were reported, but major bleeding occurred in 35 (7.6%) patients (22 with suspected HIT, 6 with confirmed HIT, and 7 with remote HIT). Additional analyses showed that critically ill patients had a greater risk of major bleeds. The study also reported 67 (14.5%) all-cause deaths at 30 days, 8 of which were HIT related.

Fondaparinux. Comparisons of fondaparinux with danaparoid and argatroban are described above.[16] In addition, of 16 patients with acute HIT treated with fondaparinux, no patient developed new or recurrent thrombosis, 1 patient experienced a major bleed (6%), and 1 patient required limb amputation (6%) related to irreversible tissue necrosis.[24]

Discontinuation of heparin and initiation of a vitamin K antagonist

Warkentin and Kelton[6] reported on 127 patients with confirmed acute HIT who were treated with either discontinuation of heparin alone or discontinuation of heparin and initiation of warfarin. Approximately 50% had a thrombotic event in the 30 days after diagnosis; the incidence of thromboembolism did not differ between the 2 treatment groups. Serious adverse events of treatment with warfarin included warfarin-induced skin necrosis and venous limb gangrene.[25,26]

Direct oral anticoagulants

Warkentin et al[27] reviewed 46 patients with confirmed or acute HIT treated with apixaban, dabigatran, edoxaban, or rivaroxaban. Only 1 patient who received rivaroxaban developed new thrombosis (2.2%; 95% CI: 0.4%, 11.3%), and no one experienced major hemorrhage. Published after 2017, we found 16 cases of acute HIT treated initially with apixaban, dabigatran, or rivaroxaban or transitioned from a nonheparin parenteral anticoagulant to a DOAC, among whom 1 event of progressive thrombosis (on rivaroxaban) was reported.[28-32] These cases provided very low certainty evidence for the effects of DOACs. As 1 study emphasized, a major limitation of these studies is that patients treated with a DOAC may represent a select subgroup of HIT patients with a particularly favorable prognosis.[27]

Therapeutic-intensity vs prophylactic-intensity dosing of nonheparin anticoagulants

One nonrandomized study with 96 patients found that there was a 50% reduction in new TECs in patients with HIT treated with therapeutic vs prophylactic doses of danaparoid (18% vs 9%, respectively).[33] However, there did not appear to be differences for therapeutic vs prophylactic doses in 172 patients with lepirudin or in 227 patients with fondaparinux.[33,34] In addition, Greinacher et al[35] found that there was little difference in the number of people who experienced death, limb amputation, or new TECs receiving (1) lepirudin 0.4 mg/kg intravenous bolus followed by 0.15 mg/kg per hour (n = 65, 33.8%) or (2) lepirudin prophylaxis 0.10 mg/kg per hour infusion (n = 43, 20.9%). There were little data for the risk of bleeding. In 1 study, bleeding occurred in 1 of 74 patients receiving a therapeutic dose of fondaparinux compared with 0 of 153 receiving prophylaxis.[34] In summary, there is very low certainty evidence for the outcomes of therapeutic- compared with prophylactic-intensity anticoagulation (supplemental Appendix: study characteristics table).

Inferior vena cava filters

There is very low certainty evidence from 1 conference abstract that reported on a case series of 69 patients receiving inferior vena cava filters, 10 of whom underwent filter insertion before or at the time of HIT diagnosis. Nine of the 10 (90%) patients developed new thrombotic events after filter insertion.[36]

Platelet transfusion

We identified 4 no-randomized studies reporting on patients with HIT who received platelet transfusions (supplemental Appendix: study characteristics table).[37-40] One nationally representative inpatient database analyzed 6332 patients with HIT International Classification of Diseases, Ninth Revision codes, 450 of whom received a platelet transfusion.[37] Those receiving platelet transfusions experienced 3.8% more arterial thromboses than patients not receiving platelet transfusions. When adjusted, the odds ratio for arterial thrombosis was 3.4 (95% CI: 1.2, 9.5) but was 0.8 (95% CI: 0.4, 0.7) for venous thrombosis. Bleeding may also be increased

in patients undergoing platelet transfusion with an adjusted odds ratio (OR) of 5.5 (95% CI: 2.3, 12.9). However, platelet count data were not available to the investigators, suggesting that the apparent increased risk of adverse outcomes with platelet transfusions could be confounded by a higher likelihood of receiving platelet transfusions because of severe thrombocytopenia (higher frequency of thrombosis associated with greater severity of thrombocytopenia); moreover, the investigators could not ascertain whether platelet transfusions preceded or followed the occurrence of thrombotic events in this study.

In contrast, a retrospective cohort of 37 HIT patients receiving at least 1 platelet transfusion reported no thrombotic events at 30 days but 6 deaths (3 within 6 days of transfusion).[39] Although no autopsies were conducted, deaths did not appear to be thrombosis related. Another series of 4 serotonin release assay (SRA)-confirmed HIT patients receiving platelet transfusions also reported no thrombotic events.[38] Finally, there was a case of an SRA-confirmed HIT patient who tested SRA negative after a medically necessitated platelet transfusion.[40] Combined, these studies provide low to very low certainty evidence for the effects of platelet transfusion in patients with acute HIT.

Limb ultrasound to detect deep vein thrombosis

There were 5 nonrandomized studies providing low to very low certainty evidence for the identification of deep vein thrombosis (DVT) in patients with confirmed HIT (supplemental Appendix: study characteristics table).[5,6,41-43] Three cohort studies suggest that symptomatic lower-extremity DVT is common in patients with HIT (26%-44%).[5,6,43] Of 434 patients with HIT (408 with HIT confirmed by heparin-induced platelet activation assay), symptomatic lower-extremity DVT (proximal) was reported in 114 (26%).[5] Symptomatic upper-extremity DVT was identified in 14 of 145 patients (9.7%) with HIT who received a central venous catheter before HIT diagnosis, but none in 115 patients without HIT.[42] In addition, in 127 patients with HIT, the following outcomes were reported: bilateral DVT (16%), proximal DVT (44%), lower limb DVT (44%), and new DVT (44%).[6]

We also identified 2 cohort studies in which HIT patients were screened for silent DVT.[41,43] Of those patients, 12% to 44% were identified with asymptomatic lower-extremity DVT. Elalamy et al[41] reported on 117 patients with confirmed HIT. Two asymptomatic DVT were identified in 18 patients with no clinically apparent thrombosis who were screened with ultrasound, and another 2 were identified in 14 patients with HIT with clinically apparent thrombosis at another site. In Hong et al,[42] among patients with HIT (SRA positive) who received a central venous catheter 2 weeks before HIT diagnosis, 9.7% (14 of 145) developed upper-extremity DVT and 33.8% (61 of 115) developed lower-extremity DVT.

Special situations: cardiovascular surgery for patients with acute HIT or subacute HIT A

Nonheparin anticoagulants. We identified 3 nonrandomized studies that reported on treatment with bivalirudin or lepirudin during cardiovascular surgery. Two studies conducted among 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 events of mortality (n = 101), and no major bleeds.[44,45] One systematic review reported on 10 studies that included 12 patients with acute HIT who received bivalirudin during cardiovascular surgery.[46] One (8%) bleeding event and no other adverse events were reported. A retrospective cohort including 57 patients with HIT receiving lepirudin reported that 4 patients (7%) with impaired renal function experienced major bleeding and required surgical exploration, but no other adverse events were reported.[47]

One case series treated 4 patients with danaparoid during cardiopulmonary bypass (CPB), and 2 died by day 45. All 4 patients had blood loss necessitating transfusion. Blood loss was high (1700-2470 mL) in comparison with 6 patients receiving heparin and epoprostenol (250-1150 mL).[48] In another 2 patients with suspected HIT who received argatroban during CPB, there was 1 bleeding event but no other adverse events.[49,50] Based on these studies in this population, there is low to very low certainty in the effects of nonheparin anticoagulants.

Heparin and perioperative plasma exchange. Four studies providing very low certainty evidence reported on patients with acute HIT treated with heparin and plasma exchange requiring urgent cardiovascular interventions.[51-54] Of the 17 patients, no adverse events were reported with the use of plasma exchange.

Heparin and antiplatelet therapy. We found 8 case studies of treatment with heparin and antiplatelet agents providing very low certainty evidence.[48,55-61] One case series followed 6 acute HIT patients who received heparin and epoprostenol during CPB and reported no adverse events.[48] Another study of 2 cases of suspected HIT who received heparin with aspirin and dipyridamole during cardiac surgery reported no thrombotic or bleeding events.[57]

Four case series reported on 59 patients with acute HIT and renal impairment or failure who received tirofiban before unfractionated heparin for CPB.[58-61] Five patients required platelet transfusions; 1 experienced bleeding; 1 had a prolonged hospitalization; and 2 patients died of heart failure. No thromboses or embolic complications were observed.

Two studies compared heparin plus iloprost for urgent CPB in patients with acute HIT with a matched control of patients treated with heparin without HIT (ie, patients testing negative for HIT or patients with normal platelet counts and without history of prolonged exposure to heparin).[55,56] In the first study, 1 patient with HIT receiving heparin plus iloprost during cardiac surgery experienced a major bleed, but none of the 10 control patients (treated with heparin) experienced a bleed.[56] In the subsequent study of 110 patients with HIT antibodies (46 thrombocytopenic) who received heparin plus iloprost during cardiac surgery matched with 118 HIT-negative patients who received heparin during surgery,[55] 6 with iloprost and 6 in the matched control group experienced thromboembolic events, and 9 in the iloprost vs 10 in the control group died during 30-day follow-up.

Special situations: cardiovascular surgery for patients with subacute HIT B or remote HIT

Eleven studies providing very low certainty evidence reported on cases of patients treated with heparin, nonheparin anticoagulants, antiplatelet agents, and plasma exchange with subacute HIT B or remote HIT requiring cardiovascular surgery (supplemental Appendix: study characteristics table).[62-72]

Heparin. Seven nonrandomized studies reported on 45 patients, 16 with subacute HIT B and 29 with remote HIT, receiving heparin during CPB.[62-67,71] No cases of thrombotic events or recurrent HIT were reported in patients with subacute HIT B.[62,64,66] However, 1 case of severe bleeding (4%) and 1 case of recurrent HIT (4%) were reported in patients with remote HIT.[63,65-67,71]

Nonheparin anticoagulants. We identified 1 case series and 2 case studies reporting on 2 patients with remote HIT receiving lepirudin, bivalirudin, and danaparoid during CPB.[68,69,71] No thrombotic events or deaths were reported in 6 patients receiving lepirudin; however, there were 3 (50%) events of bleeding leading to reoperation.[71] No adverse events were reported in a patient receiving bivalirudin.[68] A patient receiving danaparoid developed clotting of the CPB circuit, sepsis, respiratory failure, pancreatitis, and renal failure, but made a full recovery.[69]

Preoperative plasma exchange. No adverse events were reported in 1 case treated with plasma exchange until antibody clearance and then with heparin during CPB.[72]

Special situations: percutaneous cardiovascular interventions with acute HIT, subacute HIT A, subacute HIT B, or remote HIT

For patients with acute HIT or subacute HIT A. Lewis et al[73] conducted an analysis of 3 multicenter, open-label prospective studies of 91 patients with HIT, suspected HIT, or remote HIT who underwent percutaneous coronary intervention (PCI) and were treated with argatroban. One major bleeding event was reported but no deaths. In a multicenter prospective, open-label study of 50 patients with HIT or suspected HIT undergoing PCI treated with bivalirudin, there was 1 bleeding event and 1 death.[74] Magnani et al[19] included 61 patients undergoing PCI procedures (chart review and systematic review) where danaparoid was used in patients with HIT, but outcomes were not reported separately for HIT patients. Together, there is low to very low certainty evidence for the effects

For patients with subacute HIT B or remote HIT. There were no adverse events in a case report of a patient with a history of HIT treated with danaparoid during PCI[75] (supplemental Appendix: study characteristics table).

Our review also identified a systematic review and meta-analysis of treatment with bivalirudin or heparin during PCI among patients without HIT (n = 19 772).[76] 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).

Special situations: nonheparin anticoagulants for patients on renal replacement therapy with acute HIT

We identified 21 nonrandomized studies evaluating the use of argatroban, apixaban, bivalirudin, danaparoid, fondaparinux, and rivaroxaban among patients with HIT requiring renal replacement therapy (supplemental Appendix: study characteristics table). These studies provided low to very low certainty of evidence in the effects.

Argatroban. We identified 11 studies of 98 patients with HIT treated with argatroban undergoing renal replacement therapy.[77-87] Two developed minor bleeding, 19 died (18 unrelated to thrombosis and 1 unrelated to argatroban), 3 developed major bleeding, 3 developed TECs (deep vein and portal vein thromboses), and 2 required limb amputation (in 1 patient, amputation was attributed to development of gangrene before argatroban was started).

Apixaban. In 1 case of a patient with acute HIT on hemodialysis, fondaparinux was stopped after 5 days because of lack of platelet count improvement. Apixaban[88] was initiated for 10 days with platelet count recovery. No thrombotic events were reported.

Bivalirudin. Two cohort studies included 114 patients with HIT who received bivalirudin during dialysis.[23,89] Of those, 13 experienced major bleeding events (11%), 7 experienced new thromboembolic events (6%), and 32 died (28%). HIT-related mortality was not reported.

Danaparoid. We identified 3 studies that included 115 patients with suspected and confirmed HIT treated with danaparoid during continuous venovenous hemofiltration, intermittent hemodialysis, and renal replacement therapy.[90-92] Eight patients (7%) developed nonfatal thromboembolic events, of which 2 required amputation.[92] Other reported outcomes included the following: 28 deaths (25%), 12 major bleeding events (10%), 7 minor bleeding events (6%), 11 nonfatal adverse events (10%), and 14 fatal adverse events (12%; mainly sepsis/septic shock, multiorgan failure, uremia, cardio-respiratory arrest).[90-92]

Fondaparinux. We identified 3 studies including 9 patients with HIT treated with fondaparinux during chronic dialysis and hemodialysis.[93-95] Three patients (33%) developed clots (successfully managed by increasing the dose of fondaparinux), and no other adverse events were reported.

Rivaroxaban. One case report described a patient with HIT who received rivaroxaban for hemodialysis.[96] At 6-month follow-up, no new thromboembolic or bleeding events were reported.

Special situations: citrate for patients on renal replacement therapy with subacute HIT A, subacute HIT B, or remote HIT

Our search also identified a systematic review published on treatment with citrate among patients without HIT.[97] This review evaluated 14 RCTs comparing regional citrate to heparin for patients without HIT requiring continuous renal replacement therapy. The risk of mortality was similar between treatment arms (RR: 0.97; 95% CI: 0.84, 1.13). The risk of bleeding and development of HIT was lower among patients receiving regional citrate (RR: 0.3; 95% CI: 0.19, 0.49 and RR: 0.41; 95% CI: 0.19, 0.87, respectively).

Discussion

We conducted a comprehensive systematic review of the literature, including previously published systematic reviews, to determine the effects of clinically important management strategies for patients with HIT. Although evidence from well-designed large randomized controlled trials comparing different medications and strategies would be most informative, we kept our search of the literature broad and included any study design to inform our questions. As expected, most evidence came from nonrandomized studies, most of which were noncomparative or single case reports. Although a specific effect size is more informative to clinicians to communicate the effect of an intervention, we could not always

pool data statistically for a single pooled result because some data were missing from the study reports. We therefore summarized the evidence narratively providing an indication of the effects of the interventions and acknowledged the uncertainty of this evidence. As a result, there was low or very low certainty in most of the effects we found for the different strategies. The volume and quality of literature may be disappointing, but it is the best evidence available to inform decisions that must be made about how to manage patients with HIT. In fact, it was used, along with information about patients' values and preferences, resource use, health equity, acceptability, and feasibility of the strategies, to develop the current American Society of Hematology guidelines for the management of HIT.[9,10] An additional strength of this review is the application of a rigorous risk of bias instrument to assess individual nonrandomized studies, which identifies and takes into consideration the adjustment of critical confounding variables.

Although this review was conducted using gold standard methods from Cochrane and the GRADE approach to assess the certainty of the evidence, there are some limitations. The systematic review focused on the effect of different management strategies on patients with confirmed HIT, but many studies did not provide laboratory confirmation of HIT. We excluded these studies because of the potential overdiagnosis of HIT and possible overestimation of the benefits of different strategies. However, it meant that additional studies, which could have added to the precision of the results and higher certainty evidence, were not included because the evidence would have been less certain because of the potential for overestimation. We have also not included studies for lepirudin, which is no longer available, with the exception of the questions on therapeutic vs prophylactic dosing and cardiovascular surgery, for which it may provide indirect evidence for other drugs in this context. We would also caution readers about the effects found for newer medications, such as DOACs, as it is a growing research area where additional data may become available in the near future. At the time of this systematic review, we found very low certainty in the effects of DOACs, but this may change as new evidence is reported. Last, this systematic review aimed to inform the 2018 American Society of Hematology guideline for the management of HIT.[9] For this reason, the list of management strategies covered in this review were those prioritized by the guideline panel as important to cover, which means we did not review all currently used strategies to manage HIT. This systematic review was restricted to treatments identified as relevant to most clinicians in practice; however, there are other treatments that are currently being used, and systematic reviews of those treatments are still warranted. To determine the effects of the treatments we did include, we used pragmatic methodologic approaches, such as including findings from previously published systematic reviews (to not duplicate research efforts) and searching for evidence from higher-quality study designs first. This latter approach means, for example, that if we found evidence amounting to moderate certainty evidence from high-quality comparative studies, we would not look further for evidence that would likely yield lower certainty evidence. For this reason, some studies addressing the effects of an intervention may not be included.

Despite the limitations of this review, the low or very low certainty in the evidence uncovers areas for additional research. Major research priorities include the following: randomized or nonrandomized comparative studies evaluating the effects of different nonheparin anticoagulants for treatment of acute HIT; studies on the efficacy and safety of newer treatments including DOACs; and development of novel therapeutics that target pathways in the pathogenesis of HIT proximal to coagulation that could reduce thrombosis without increasing the risk of hemorrhage including intravenous immunoglobulin.

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Authorship

Contribution: All authors contributed to the review of, and critical revisions to, the manuscript; R.L.M. wrote the first draft of the manuscript and revised the manuscript based on the authors' suggestions; and A.C. and N.S. contributed sections to the first draft, revisions of subsequent drafts, and the revision after peer review.

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