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Systematic review of fondaparinux for heparin-induced thrombocytopenia: When there are no randomized controlled trials

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Abstract

Background: Fondaparinux is commonly used for treatment of heparin-induced thrombocytopenia (HIT) despite lack of approval for this indication. High quality randomized controlled trials of this agent are unlikely to be forthcoming.

Objectives: The objective of this systematic review is to update the literature on the efficacy and safety of fondaparinux for treatment of confirmed and probable HIT based on the available evidence.

Methods: Primary articles were identified using Web of Science and PubMed database searches for English-language studies from January 2006 to November 2017. Selected studies enrolled consecutive adult patients who received fondaparinux as the primary anticoagulant to treat acute HIT; confirmed the diagnosis by serological testing with a serotonin-release assay; heparin-induced platelet activation assay or enzyme-linked immunosorbent assay; provided clinical criteria used to define HIT and reported clinically important outcomes.

Results: A total of 9 studies were identified with 154 HIT positive patients. Ten experienced a new thrombotic event while receiving fondaparinux (6.5%, 95% CI, 3.4 to 11.7%) and 26 experienced major bleeding (16.9%, 95% CI, 11.7 to 23.6%). Mortality due to thrombosis or bleeding was reported in 5 patients (3.2%, 95% CI, 1.2 to 7.6%).

Conclusions: Fondaparinux appears to be an effective and safe anticoagulant for treatment of acute HIT despite the absence of randomized trials. Caution should exercised when using fondaparinux in patients with renal insufficiency.

KEYWORDS

fondaparinux, heparin, review, thrombocytopenia, thrombosis

Essentials

- Heparin-induced thrombocytopenia (HIT) can be difficult to treat.
- Fondaparinux is a parental drug that is easy to use but is not approved for treatment of HIT.
- This updated review found nine studies (154 patients) that used fondaparinux to treat HIT.
- New thrombosis (6.5%) and major bleeding (16.9%) rates were similar to approved drugs.

1 | INTRODUCTION

Heparin-induced thrombocytopenia (HIT) is an immune-mediated complication that most commonly arises five to 10 days after exposure to heparin or low-molecular-weight heparin (LMWH).[1] Heparin-dependent immunoglobulin (Ig)G antibodies bind to platelet factor 4 (PF4)/heparin complexes on platelets, leading to cross-linking of platelet FcγIIa receptors. The resulting platelet activation leads to thrombocytopenia and the potential for serious venous and arterial thromboembolic complications, including death.[1]

To confirm HIT, patients must have both a compatible clinical picture and laboratory confirmation of the presence of HIT antibodies. The 4Ts score is the most commonly used prediction rule to determine the clinical pretest probability of HIT.[2] However, the range of laboratory tests for HIT antibodies is wide with a correspondingly wide variability in sensitivity and specificity. Functional assays, such as the ^{14}C-platelet serotonin-release assay (SRA) and the heparin-induced platelet activation (HIPA) test are considered the reference standard assays; however, enzyme-linked immunoassay (ELISA), either IgG-specific or polyspecific (detecting in addition IgA and IgM class antibodies), is more commonly used because it is commercially available and technically easier to perform.[3]

If the clinical suspicion for HIT is at least moderate, it is recommended that patients be switched from heparin to an alternative nonheparin anticoagulant to reduce the likelihood of thrombosis.[4] The most commonly used drugs to treat HIT that are approved by many international health authorities are argatroban and danaparoid (danaparoid is not available in the United States). Although there is evidence showing a reduction in the risk of thromboembolic complications with these drugs, there are also negative consequences associated with their use.[1] For argatroban, there is an increased risk of bleeding and its prolongation of the INR makes transition to warfarin after platelet recovery problematic.[5] Moreover, data supporting efficacy of argatroban in patients testing positive for HIT antibodies is sparse. Danaparoid is not available in some markets and it is administered either intravenously or by multiple subcutaneous injections. Moreover, both argatroban and danaparoid are very expensive.

Over the past decade, fondaparinux has frequently been used off-label for treatment of HIT.[6] Fondaparinux is a synthetic pentasaccharide that can be administered subcutaneously and does not require intensive laboratory coagulation monitoring. It infrequently cross-reacts with HIT antibodies,[7] thus it rarely causes or exacerbates HIT[8]; however, fondaparinux has never been evaluated in a methodologically rigorous clinical trial. Instead, evidence to support its safety and effectiveness in the treatment of patients with HIT has accumulated over time, primarily in the form of case reports, case series, and small retrospective cohort studies. The most recent comprehensive systematic review of fondaparinux for treatment of adult patients with HIT was published in 2009[9] at which time, data on clinical outcomes with this agent was available for less than 30 patients. Furthermore, the accuracy of the diagnosis of HIT in some of the included reports is debatable due to failure to provide sufficient clinical details and/or results of laboratory testing for HIT antibodies.

The primary objective of this systematic review was to update the literature on the effectiveness and safety of fondaparinux in treating adult patients with confirmed or probable HIT.

2 | METHODS

2.1 | Search strategy

All English language articles from Web of Science and PubMed databases were reviewed. Search terms used included heparin-induced thrombocytopenia, HIT, fondaparinux, cohort, and prospective. Case series, clinical trials, cohort studies, case-control studies, and randomized control trials published from January 2006 to November 2017 were identified. The references of all relevant studies were checked for additional reports.

2.2 | Inclusion criteria

Studies were included if: (a) enrolled consecutive adult patients who received fondaparinux as the primary anticoagulant to treat acute HIT; (b) diagnosis of HIT was confirmed by serological testing with serotonin-release assay [SRA]; heparin-induced platelet activation assay [HIPA]) or enzyme-linked immunosorbent assay (ELISA); (c) provided clinical criteria used to define HIT (e.g, 4Ts score); and (d) reported clinically important outcomes (i.e, thrombosis, major bleeding).

We excluded patients who received greater than 24 hours of another nonheparin anticoagulant (e.g, argatroban, lepirudin, danaparoid, rivaroxaban, apixaban, dabigatran); studies that did not report the name of the diagnostic assay, included fewer than five participants (to reduce the risk of reporting bias) or limited enrollment to post cardiac surgery patients who did not have the diagnosis of HIT confirmed with a functional HIT assay (i.e, patient population with a high incidence of HIT antibodies, but a low incidence of HIT). Conference abstracts were also excluded.

2.3 | Study selection and data abstraction

From these studies, we extracted data on fondaparinux dose, duration of follow-up, incidence of new thrombotic events, major bleeding, and mortality due to thrombosis or bleeding. New thrombotic events included deep vein thrombosis (DVT), pulmonary embolism (PE), stroke (CVA), myocardial infarction (MI), and limb amputation. The definition of major bleeding was accepted as reported within the individual studies. All data was independently extracted by two authors (GH and LL). Study quality was not assessed by formal criteria due to the general low quality of studies in this field.

3 | RESULTS

A total of 290 articles were identified using the search strategy (Figure 1). After applying the inclusion/exclusion criteria as

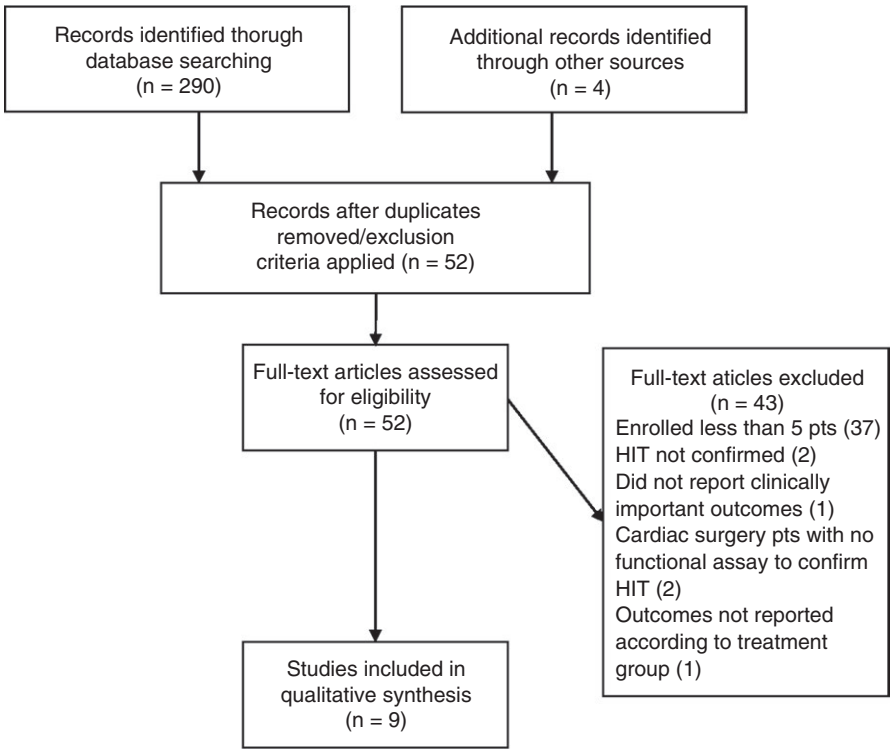

FIGURE 1 Study selection

defined above and removing duplicate studies, 48 studies remained. Hand-searching of relevant reviews identified four additional studies.

Of 52 identified articles, 37 enrolled less than five patients, two did not include patients with confirmed HIT[10,11]; one did not report clinically important outcomes,[6] two enrolled cardiac surgery patients without using a functional HIT assay,[12,13] and one did not report the outcomes according to treatment group.[14] The remaining nine studies were included in this review[15–23] (Table 1).

Of the included studies, only two were prospective yielding a combined total of 32 HIT patients.[16,17] The SRA was used to confirm HIT in all patients in two studies,[15,16] and in selected patients in three studies.[19,20,22] The HIPA was used in one study[23]; therefore, a total of 68 patients with HIT confirmed by the combination of a functional assay plus moderate/high clinical pretest probability were included in this review. All studies used either a commercial or in-house ELISA and two studies used additional HIT antibody tests (e.g, ID-PaGIA).[16,18] The dose of fondaparinux dose varied between 2.5 and 10 mg/kg each day, depending on body weight, and the presence of thrombosis. The mean duration of follow-up was 30 days in most studies.

A total of 154 HIT positive patients were identified of which 10 experienced a new thrombotic event while receiving fondaparinux (6.5%, 95% CI, 3.4%-11.7%). The types of thrombotic events were as follows: six venous, one arterial, and three both. Three of the thrombotic events were fatal (acute coronary syndrome; hypoxic brain injury in context of unwitnessed cardiac arrest; and unclear). There were 26 major bleeding events (16.9%, 95% CI, 11.7%-23.6%); however, the definition for major bleeding differed across the studies. Three of the bleeding events were fatal (ruptured abdominal aortic aneurysm, gastrointestinal bleed, and postsurgical bleed with concurrent cardiac arrest). Mortality due to thrombosis or bleeding was reported for a total of five patients (3.2%, 95% CI, 1.2%-7.6%), all from the same study.[20]

In the subgroup of patients who had HIT confirmed with the combination of a moderate/high 4Ts score and a functional assay (n = 68), the thrombotic event rate was 4.4% (95% CI, 1.0%-12.7%) and the bleeding event rate was 13.2% (95% CI, 6.9%-23.5%). Data on the complications in patients with a positive SRA from the study by Kang et al were not available and therefore not included in this subgroup.

4 | DISCUSSION

Fondaparinux is an effective and safe treatment option in patients with probable HIT. The incidence of recurrent thrombosis is low (6%) and in keeping with rates reported for anticoagulants that have been approved for the treatment of HIT. However, as with any anticoagulant, efficacy comes at the price of an increased risk of bleeding (17%).

The number of events in this review contrasts with the complete absence of events in 36 patients with probable HIT who were treated with fondaparinux in a previous narrative review by Warkentin in 2010.[8] This discrepancy is not surprising given the larger denominator of treated patients in the current analysis (additional 118 patients). Importantly, this updated review provides reassurance that a larger proportion of patients truly had HIT due to the inclusion of three studies that confirmed HIT with functional assays (64 patients)[15,16,23] and two others that used the combination

TABLE 1 Description of included studies

Author/Year	Study design	Number of HIT patients	Definition of HIT	Fondaparinux dose	Duration of follow-up	New thrombotic event	Major bleed	Mortality due to thrombosis or bleeding
Schindewolf et al, 2017[23]	Retrospective registry	23[a]	HIPA and 4Ts score	2.5-7.5 mg daily	Median 5 days (range 1-118 days)	0	3	0
Snodgrass et al, 2016[22]	Retrospective cohort	2[b]	ELISA and/or SRA + 4Ts score	Therapeutic dose	Median hospital stay 17.5 days	0	0	0
Kang et al, 2015[20]	Retrospective cohort	44	ELISA and SRA + 4Ts score	2.5 mg daily or therapeutic dose	30 days or discharge, whichever occurred last	7	16	5[c]
Linkins et al, 2015[16]	Prospective cohort	25 (12 HITT)	PF4/H-PaGIA, SRA, and/or EIA + 4Ts score	Prophylactic or therapeutic doses	30 days	3	5	0
Goldfarb et al, 2011[19]	Retrospective case series	8 (6 HITT)	HIT EIA and/or SRA + 4Ts score	7.5 mg daily	30 days	0	0	0
Warkentin et al, 2011[15]	Retrospective cohort	16 (9 HITT)	SRA or IgG-specific PF4/heparin enzyme-immunoassay + 4Ts score	5.0-10.0 mg, depending on weight daily	At least 30 days following HIT diagnosis	0	1	0
Al-Rossaies et al, 2011[21]	Retrospective cohort	5 (2 HITT)	PF4/H ELISA and met HIT definition	2.5-7.5 mg daily	30 days	0	1	0
Grouzi et al, 2010[18]	Retrospective cohort	24 (14 HITT)	PF4/H ELISA and ID-PF4/H-PaGIA and met HIT definition	5 mg subcut daily (<50 kg), 7.5 mg subcut daily (50-100 kg), 10 mg subcut daily (>100 kg)	2 years	0	0	0
Lobo et al, 2008[17]	Prospective cohort/ historic controls	7 (6 HITT)	PF4-heparin ELISA and met HIT definition	2.5-10 mg daily, depending on weight and presence of thrombosis	4 weeks after fondaparinux treatment	0	0	0
Total		154				10	26	5

ELISA, enzyme-linked immunosorbent assay; HIPA, heparin-induced platelet activation assay; SRA, serotonin release assay; subcut, subcutaneous.
[a]HIT positive patients who received fondaparinux monotherapy.
[b]Eight additional patients who received fondaparinux after an undisclosed number of days on another nonheparin anticoagulant were not included in this analysis.
[c]Three fatal bleeds: ruptured abdominal aortic aneurysm, gastrointestinal bleed and post-surgical bleed; fatal thrombosis: coronary artery disease, unwitnessed cardiac arrest (unpublished details provided by author).

of a moderate or high 4Ts score combined with a positive ELISA to confirm HIT (44 patients).[19,20]

It is noteworthy that the majority of clinical events (thrombosis, major bleeding, and associated deaths) originated from a single study.[20] Kang et al retrospectively reviewed 239 patients who received a nonheparin anticoagulant for treatment of suspected HIT at a single clinical center.[20] Out of 44 HIT positive patients who were treated with fondaparinux, seven (15.9%) experienced a thrombotic event (three fatal) and 16 had major bleeds (three fatal). The investigators reported that the thrombotic events (three venous only, one arterial only, and three both) were all objectively verified on imaging. Similarly, all bleeding events met the ISTH criteria for major bleeding.[24] Of note, approximately 60% of fondaparinux-treated patients had received only prophylactic doses (2.5 mg/d) in the study by Kang et al; however, the two fatal thrombotic events occurred while receiving therapeutic dose fondaparinux (unpublished data provided by author).

Interestingly, the same study by Kang et al is virtually the only reported study that also provided outcomes in argatroban-treated patients for whom laboratory testing supported a diagnosis of HIT. When matching patients using a propensity scoring system, these authors found a similar frequency of thrombosis in antibody-positive

patients treated with argatroban (5 of 20 = 25.0%) as they found with fondaparinux (7 of 44 = 15.9%). Kang et al concluded that fondaparinux appeared to have similar efficacy and safety as argatroban for the treatment of HIT.

With respect to bleeding, it is noteworthy that at least some of the included patients who experienced major bleeds had evidence of renal insufficiency at the time of the event.[23] Due to limited clinical details, it is not possible to provide an accurate proportion. However, given the dependence of fondaparinux on renal clearance and its long half-life, it is not surprising that renal insufficiency increases the risk of bleeding. This caveat should be kept in mind when using fondaparinux in the setting of decreased renal clearance.

This review has several limitations. First, all but two of the included studies were retrospective and therefore dependent on the quality of recorded data. Second, HIT was not confirmed with a functional assay in all patients. This limitation is difficult to overcome given that most centers do not have timely access to these assays. Lastly, the dose of fondaparinux varied from prophylactic to therapeutic across the studies and it was not always clear which dose a patient was given prior to a thrombotic or bleeding event.

It is also worthy of note that fondaparinux has been documented to cause HIT on rare occasions.[8] Further, to our knowledge, there are three reported cases in which fondaparinux was used for treatment of HIT in which the patient had persistence or worsening of HIT-associated DIC and/or symptomatic thrombosis, and in whom laboratory evidence for increased platelet activation in the presence of fondaparinux was documented.[25–27] This unusual combination of demonstrable in vitro "cross-reactivity" of HIT antibodies for fondaparinux, shown using a platelet activation assay (HIPA or SRA), together with refractory HIT, suggests that in vivo cross-reactivity may be an occasional consequence of treating HIT with fondaparinux. This phenomenon is sufficiently uncommon that it was not noted in any of the papers that met the criteria for inclusion in our review. If one assumes that none of the 154 patients identified in our review developed in vivo cross-reactivity with fondaparinux, it suggests that the upper 95% CI of this adverse event is low (2.9%).

Ideally, the efficacy and safety of fondaparinux should be established by one or more methodologically rigorous randomized controlled trials. Unfortunately, due to the difficulty in conducting HIT treatment studies[28] together with the lack of interest in the manufacturer of fondaparinux to pursue HIT as an indication, it is unlikely such a study will happen. Despite the low quality of evidence, fondaparinux has still gained wide-spread acceptance as a treatment option for HIT.[6] A similar phenomenon is currently happening with direct oral anticoagulants (DOACs).[29] Oral administration gives DOACs an advantage over fondaparinux, however, there will always be a role for a parenteral agent that can be given to HIT patients who are too sick to take oral agents. This review updates the growing body of evidence that supports fondaparinux as an effective and safe option for treatment of acute HIT despite the absence of an RCT.

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RELATIONSHIP DISCLOSURES

L. Linkins receives consultancy fees from Bayer for adjudication of a clinical trial that is not relevant to this review. T.E. Warkentin reports receiving consulting fees from Aspen Global and Octapharma; research support and consulting fees from W. L. Gore, Instrumentation Laboratory, and Medtronic Diabetes; royalties from Informa (Taylor & Francis); and consulting fees related to medical–legal testimony. G. Hu reports no relevant conflicts of interest.

AUTHOR CONTRIBUTIONS

G. Hu and L. Linkins contributed to the concept and design, analysis, and interpretation of data; critical writing and revising of the intellectual content; and final approval of the version to be published. T. Warkentin contributed to the analysis and interpretation of data; critical writing and revising of the intellectual content; and final approval of the version to be published.

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