

COMMENTARY

Fondaparinux in heparin-induced thrombocytopenia: A decade's worth of clinical experience

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This is a commentary on *Linkins et al* [2018]: <https://doi.org/10.1002/rth2.12145>

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Fondaparinux is an antithrombin-dependent, synthetic anti-factor Xa-inhibitor that is used off-label as an alternative anticoagulant in the treatment of life-threatening immune heparin-induced thrombocytopenia (HIT). In their systematic review, Dr. Linkins and colleagues have summarized what is currently known on fondaparinux' safety and efficacy when used in patients with diagnosed and suspected heparin-induced thrombocytopenia.¹ The authors have performed an extensive systematic literature search on data that have been published between 2006 and 2017.

The presented data are important because the current approved alternative anticoagulants for treating this condition have clear limitations: (i) the factor Xa-inhibitor danaparoid is not available in the United States and has been subject to world-wide shortages repeatedly²; (ii) use of the thrombin inhibitor argatroban is limited in patients with hepatic insufficiency and aPTT- and INR-confounding may occur in various clinical settings, eg, disseminated intravascular coagulation, during heparin therapy, transition to vitamin K antagonist treatment³; (iii) outpatient use of argatroban and bivalirudin is precluded because these drugs require continuous IV infusion and frequent laboratory monitoring; (iv) argatroban, bivalirudin, and danaparoid use is expensive, at least in some jurisdictions⁴; and (v) last but not least, the recombinant hirudin lepirudin is not available on the market anymore since 2012.²

However, the main shortcoming of fondaparinux use in HIT is still that there has not been any randomized-controlled trial to date and authorities' approval has not been granted formally.

In order to increase the validity of their study, Dr. Linkins and colleagues have applied strict inclusion and exclusion criteria (ie, fondaparinux as primary anticoagulant with no other alternative anticoagulant allowed for >24 hours; sufficient case number (≥5 patients); laboratory confirmation of HIT (serotonin-release assay, heparin-induced platelet activation assay, or enzyme-linked immunosorbent assay), in combination with clinical symptoms consistent

with at least an intermediate pretest probability for HIT (eg, 4Ts score⁵). These rigid patient selection criteria are pivotal when drawing conclusions on general applicability when there are no high quality data from RCTs.

The question is if this has prevented or will prevent physicians in daily practice from applying the drug in patients with suspected or diagnosed heparin-induced thrombocytopenia?

The answer is no, because the users have already "voted with their feet" in favor of fondaparinux⁶ with off-label use rates of up to 50% even in patients with high clinical pretest probability of HIT.^{7,8} This—besides reports on successful fondaparinux use in HIT—may have been triggered by low therapy cost as compared to approved alternative anticoagulants, being the main cost-drivers in therapy,⁴ the ease of subcutaneous administration of the drug, and the lack of need for routine laboratory monitoring and dose adjustment.¹

Different mechanisms of action, eg, direct oral factor Xa or thrombin inhibition, could overcome the rare, but potential limitation of fondaparinux to cause HIT itself,⁹ and direct oral anticoagulants have been widely available. However, the authors of this review have already reported the same difficulties of identifying and recruiting HIT patients for a robust prospective trial using direct oral anticoagulants that already apply for fondaparinux.¹⁰ Together with the manufacturer's lack of interest in investing into research to expand indications this will pose the same problem as already observed with fondaparinux: there might be no RCTs of high quality available in the future and gathering clinical experience with direct oral anticoagulants to the same extent as for fondaparinux is expanding only slowly. Thus, the data presented by the authors of a comparable efficacy in preventing thromboembolic complications and safety with respect to bleeding complications, represent the largest body of evidence to date for an off-label alternative anticoagulant in the treatment of HIT.

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The authors' compilation of clinical data on HIT management with fondaparinux might help to harmonize current treatment recommendations. Looking at the different guideline recommendations from various professional or governmental associations reveals that these differ not only in methodological aspects but as well in their conclusions drawn.¹¹ While some guidelines recommend the use of fondaparinux,¹²⁻¹⁴ fondaparinux carries a level 2C recommendation from the American College of Chest Physicians (ACCP).¹⁵ However, ACCP held out the prospect of readjusting their recommendations once more clinical evidence has emerged. The data of Linkins and colleagues might now contribute to start this discussion and to put current fondaparinux off-label practice on a safer medico-legal level for the treating physicians. Advocacy in favor of fondaparinux already when underlying HIT is suspected and thereby "legalizing" its use might face the clinical problem that HIT diagnosis and therapy is often delayed.¹⁶ However, one must take into account that "true" HIT is still rare compared to the number of patients with HIT suspicion and that HIT is often overdiagnosed and overtreated.^{17,18} Thus, fondaparinux use will mostly concern patients with HIT suspicion.

Among numerous patients with suspected or diagnosed HIT who were treated with fondaparinux, dosing was inconsistent.^{8,19,20} This will remain a future challenge for research against the background of clinical HIT probability, thromboembolic complications, and bleeding risk.

ADDENDUM

The release of the American Society of Hematology (ASH) 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia (HIT),²¹ after this writing, recommended the use of fondaparinux in the treatment of acute HIT with thromboembolic complications. Despite the reference to the very low certainty in the evidence about effects, no preference is suggested for non-heparin anticoagulants over fondaparinux in these guidelines. However, 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, clinical stability, and need for urgent procedures), and experience of the clinician.

RELATIONSHIP DISCLOSURE

Dr. Schindewolf reports personal fees from Abbott, personal fees from Aspen, grants and personal fees from Boston Scientific, grants from Bristol-Myers Squibb, grants and personal fees from Daiichi-Sankyo, personal fees from GlaxoSmithKline, personal fees from Sanofi, grants from Bard, personal fees from Bayer Healthcare, grants from Medtronic, grants and non-financial support from Terumo, and non-financial support from Cook outside the submitted work.

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