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Letters

Fondaparinux and Direct Oral Anticoagulants

Promising Anticoagulant for Management of Heparin-Induced Thrombocytopenia

We read with interest the study by Schindewolf et al. (1). The investigators concluded that fondaparinux was safe and more effective than the anticoagulants that are currently Food and Drug Administration-approved for treatment of patients with suspected acute heparin-induced thrombocytopenia (HIT). Indeed, fondaparinux has emerged as one of the most widely used nonheparin anticoagulants for treatment of HIT in several jurisdictions (2).

While this retrospective study of a large patient population suggests that fondaparinux is effective and safe for treating HIT, there were a few weaknesses. First, the characteristics of the study population were not entirely comparable to those in the matched subgroups, and an analysis of statistical differences or procedure propensity score matching among subgroups was not provided. There were differences, for example, in indications for anticoagulation. The proportion of patients in the fondaparinux subgroup receiving the therapeutic agent was much lower than in other control subgroups (26.9% vs. 41.5%). Furthermore, information about the dose and route of delivery of heparin was not provided. The incidence of HIT varies based on heparin formulation (lower with low-molecular-weight than unfractionated heparin, lower with prophylactic than therapeutic doses, and lower with subcutaneous than intravenous heparin administration) (3). Last, of the 84 patients treated with fondaparinux as first-line therapy, 51 (60.7%) were double negative for PF4/H-EIA and HIPA, while only 32.4% (36 of 111) of patients were double negative in other subgroups. Thus, more obvious differences than double-positive results (32.1% vs. 21.6%) exist, which make the resulting complication rates (thromboembolic events, amputation, skin necrosis) not so convincing even though the study was based on HIT management under real-life conditions. In some ways, the results feel "too good to be true."

Despite these limitations, the report by Schindewolf et al. strengthens the case for fondaparinux as a relatively safe and effective anticoagulant for patients with HIT. These and other recent observations with fondaparinux should be considered in the context of the efficacy of direct oral anticoagulant (DOAC) therapy for patients with acute HIT (4). Given the fixed-dose oral administration of DOACs and easy transition from inpatient to longer-term outpatient anticoagulation with these agents, it seems likely that DOAC therapy, like fondaparinux, might also become an off-label treatment for HIT.

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REPLY: Fondaparinux and Direct Oral Anticoagulants

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Our retrospective registry was planned to describe treatment effects within different treatment strata and not as a comparison between them (1). Therefore, data must be interpreted with caution in regard to causality and outcome prediction by differences

TABLE 1 p Values for Differences in Baseline Characteristics Across Therapy Strata

	p Value for Comparison A vs. D vs. F (Without L Stratum)*
Sex	0.361
Age	0.066
BMI	0.463
ICD-10 code	<0.001
Previous TE (any vs. none)	0.037
Hypertension	0.031
Age >60 yrs	0.077
Immobilization	<0.001
High cholesterol	<0.001
Heart insufficiency	1.000
Diabetes	0.019
Smoking	0.004
Severe systemic infection	<0.001
Cancer	<0.001
Myocardial infarction	0.113
Obesity	0.704
PAD	0.387
Stroke	0.046
Chronic inflammatory disease	0.403
Chronic venous insufficiency	0.023
Pregnancy (women only)	1.000
Oral contraceptives (women only)	0.470
HRT (women only)	1.000
Others	<0.001
TE during preceding heparin therapy	0.014
4Ts score (<6 vs. ≥6)	<0.001
PF4/H-EIA (≥1 positive test)	0.059
HIPA (≥1 positive test)	0.169
PaGIA (≥1 positive test)	0.434

*p Values were determined using the Fisher exact test (categorical variables) or analysis of variance (continuous variables).

A = argatroban; BMI = body-mass index; D = danaparoid; EIA = enzyme immunoassay; F = fondaparinux; H = heparin; HIPA = heparin-induced platelet activation assay; HRT = hormonal replacement therapy; ICD = International Statistical Classification of Diseases and Related Health Problems; L = lepirudin; PAD = peripheral artery disease; PaGIA = particle gel immunoassay; PF4 = platelet factor 4; TE = thromboembolic event.

in baseline characteristics. The definition of universal predictive risk factors for direct matching would result in sample sizes per group that are too small to analyze. Alternative approaches, such as propensity score adjustments that would circumvent the technical problem of too-small sample sizes, would have only shifted our study aim from its descriptive focus to a more strictly comparative character. Such an undue focus is exactly what we wanted to avoid.

Nevertheless, an analysis of differences in baseline characteristics (Table 1) shows no statistical difference in the frequencies of positive laboratory heparin-Induced thrombocytopenia (HIT) diagnostics between the different anticoagulants. Thus, in regard to the aspect of the possibility of underlying HIT, the different therapy strata were comparable. Other significant baseline characteristics, for example, hypertension, venous insufficiency are rather unlikely to have a relevant influence on the assignment to one or another therapy group or even therapy outcome. Significant differences might also be due to false-positive findings when multiple subgroup comparisons are performed (the "multiplicity problem") (2). This also applies to significant baseline characteristics that might influence thrombosis/bleeding risk and therefore therapy outcome, for example, cancer, or infection.

HIT incidence is influenced by various factors (e.g., patient population, heparin formulation, and dose) (3) and have been reported previously regarding our study population (4). However, these factors do not affect the validity of our results, because patients were enrolled after HIT had already clinically been suspected. For example, heparin treatment preceding the HIT episode in fondaparinux-anticoagulated versus alternatively anticoagulated patients had only an influence on the baseline risk to develop HIT, but not after robust HIT suspicion had already been established and heparin stopped. Furthermore, fondaparinux-treated patients had on average a higher 4Ts score compared with non-fondaparinux therapy groups (6 points [high risk] vs. 5 points [intermediate risk]).

Many study patients did not have "true" HIT based on post hoc analysis of laboratory results (5). However, initially, even these patients did have a strong clinical HIT suspicion (4Ts score ≥4 points) and therefore, an indication for alternative anticoagulation before specific HIT diagnostics is available (3). Fondaparinux seems effective and safe in these patients. Another criticism of Dr. Zhu and colleagues was that outcome in fondaparinux-treated patients might be favorable due to the low likelihood of "true" HIT, which is corroborated by double-negative HIT diagnostics. In order to overcome this drawback of combining patients with different HIT likelihoods, we have identified 35 patients with "true" HIT by meticulously matching clinical parameters with laboratory HIT diagnostics. Also, in this "true" HIT subgroup, thrombotic and bleeding risk during fondaparinux treatment was low.

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