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Use of Fondaparinux Off-Label or Approved Anticoagulants for Management of Heparin-Induced Thrombocytopenia

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ABSTRACT

BACKGROUND Life-threatening heparin-induced thrombocytopenia (HIT) is treated with the alternative nonheparin anticoagulants argatroban, lepirudin, or danaparoid. Frequently, the pentasaccharide fondaparinux is used off-label.

OBJECTIVES The authors sought to investigate the safety and efficacy of the different anticoagulants for treating HIT.

METHODS In a national, multicenter registry study, hospitalized patients who were diagnosed with HIT, an at least intermediate clinical HIT-risk (4Ts score ≥4 points), and received treatment with ≥1 dose of the aforementioned anticoagulants were included. Main outcome measures were the incidences of HIT-specific complications (thromboembolic venous/arterial events, amputations, recurrent/persistent thrombocytopenia, skin lesions) and bleedings.

RESULTS Of 195 patients, 46 (23.6%), 4 (2.1%), 61 (31.3%), and 84 (43.1%) had been treated first-line with argatroban, lepirudin, danaparoid, and fondaparinux, respectively. The composite endpoint of HIT-specific complications (thromboembolic events, amputation, skin necrosis) occurred in 11.7% of patients treated with approved alternative anticoagulation and in 0.0% of fondaparinux-treated patients. The all-cause in-hospital mortality rates were 14.4% during approved alternative anticoagulation and 0.0% during fondaparinux treatment. Bleeding complications occurred in alternatively anticoagulated patients and in fondaparinux-treated patients in 6.3% and 4.8%, respectively. Post hoc analysis of clinical and laboratory features confirmed "true" HIT in at least 74 of 195 (38.0%) patients; 35 of 74 (47.3%) were treated with fondaparinux.

CONCLUSIONS Fondaparinux is effective and safe in suspected acute HIT; no HIT-specific complications occurred in the fondaparinux-treated patients, even among those with a high clinical HIT probability. Further data from randomized controlled trials are urgently needed because lepirudin was recalled from the market; danaparoid access has been limited and is not approved in the United States; and argatroban is contraindicated in patients with impaired liver function, and activated partial thromboplastin time confounding may interfere with monitoring. (Retrospective Registry of Patients With Acute Heparin-induced Thrombocytopenia Type II; NCT01304238) (J Am Coll Cardiol 2017;70:2636–48) © 2017 by the American College of Cardiology Foundation.

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Immune heparin-induced thrombocytopenia (HIT) is caused by an antibody formation-triggering complex of heparin and the positively charged, tetrameric platelet factor 4 (PF4) (1). Cross-linking between antibody/PF4/heparin complexes and FcγRIIa receptors on platelets (2) enhances platelet activation and aggregation. The clinical sequelae include thrombocytopenia, potentially life-threatening venous and/or arterial thromboembolism, and skin lesions (3,4). The mortality rate is up to 30% (5). Switching to a nonheparin anticoagulant is mandatory for patients with strongly suspected (or serologically confirmed) HIT (5).

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The approved alternative non-heparin anticoagulants are the antithrombin-dependent factor Xa inhibitor danaparoid (only approved outside the United States) and the direct thrombin inhibitors lepirudin, argatroban, and (with limitations) bivalirudin (5). The successful off-label use of the synthetic, ultra-low-molecular-weight (1.728 kDa) pentasaccharide fondaparinux, an antithrombin-dependent, selective factor Xa inhibitor, has been described in limited case series (6,7). Nevertheless, the possibility that fondaparinux with its active pentasaccharide sequence, derived from the natural antithrombin binding pentasaccharide structure of heparin, may cause HIT (8–12) has not been confirmed and remains controversial (13–15). Furthermore, even if fondaparinux rarely did induce HIT antibodies and cause HIT, this is a different clinical scenario than in a patient who already has HIT antibodies, and where fondaparinux is proposed as a treatment; in this situation, fondaparinux has been proven to have low in vitro and in vivo cross-reactivity versus heparin (16–19). However, the possibility of a low frequency (1% or less) of clinically relevant cross-reactivity with fondaparinux does exist (18,19). Fondaparinux is currently not approved in any jurisdiction for therapy in patients with suspected or confirmed acute HIT.

The aim of this registry study of patients with suspected acute HIT who had been treated with argatroban, danaparoid, lepirudin, or fondaparinux was to obtain additional "real-life" data concerning their therapeutic efficacy and safety.

METHODS

STUDY DESIGN. We performed a retrospective, national, multicenter, noninterventional, observational registry study (NCT01304238). The Ethics Committee of the State Chambers of Physicians Bavaria confirmed that neither ethics approval nor written informed consent was required due to the complete data anonymization. Patients at 9 hospitals throughout Germany hospitalized between January 2005 and October 2009 were screened via the electronically registered International Statistical Classification of Diseases and Related Health Problems (ICD-10) discharge diagnosis codes D68.53 (immune HIT) or D68.52 (erroneously coded as nonimmune HIT type I). Potentially eligible patients were double-checked by comparison with the list of ordered specific laboratory diagnostics. For each of these 261 pre-selected patients, the pre-test probability score for HIT (4Ts score) (20) was determined on the basis of the medical

ABBREVIATIONS AND ACRONYMS

EIA^+/EIA^- = positive/negative platelet factor 4-dependent enzyme immunoassay

HIPA = heparin-induced platelet activation assay

$HIPA^+/HIPA^-$ = heparin-induced platelet activation assay with/without heparin-induced thrombocytopenia antibodies

HIT = heparin-induced thrombocytopenia

ICD-10 = International Statistical Classification of Diseases and Related Health Problems

OD = optical density

PF4 = platelet factor 4

PF4/H-EIA = platelet factor 4/heparin-dependent enzyme immunoassay

SRA = serotonin release assay

compensation for data acquisition and data management from GlaxoSmithKline. The sponsor had no influence on the study design, the collection, the analysis, and the interpretation of data, in the writing of the manuscript, and in the decision to submit the manuscript for publication. There were no agreements concerning confidentiality of the data between the sponsor and the authors or the institutions named in the credit lines; all collected data were fully disclosed. Dr. Schindewolf has received speaker fees from Abbott, Aspen, Boston Scientific, Bristol-Myers Squibb, Daiichi-Sankyo, GlaxoSmithKline, and Sanofi; travel grants from Bard, Bayer Healthcare, Bristol-Myers Squibb, and Terumo; research grants from Cook, Daiichi-Sankyo, and Terumo; and is a member of the advisory boards of and a consultant for Bayer Healthcare, Bristol-Myers Squibb, Daiichi-Sankyo, and Sanofi. Dr. Beyer-Westendorf has received honoraria from Bayer Healthcare, Boehringer Ingelheim, GlaxoSmithKline, Bristol-Myers Squibb/Pfizer, LEO Pharma, and Mitsubishi Pharma. Dr. Schellong has received speaker fees from Aspen, Bayer Healthcare, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, GlaxoSmithKline, and Pfizer; has received consulting fees from Aspen; and is on the advisory boards of Bayer Healthcare, Boehringer Ingelheim, Daiichi-Sankyo, GlaxoSmithKline, and Pfizer. Dr. Brachmann has received consultant fees from Biotronik and Medtronic. Dr. Madlener has received lecture fees from Bayer Healthcare, Boehringer Ingelheim, CSL-Behring, GlaxoSmithKline, Mitsubishi Pharma, Roche, Sanofi, Pfizer, and Bristol-Myers Squibb. Dr. Pötzsch has received lecture fees from Amgen, Boehringer Ingelheim, CSL-Behring, and Roche-Diagnostics. Dr. Hankowitz has received consultant fees from Aspen, Bayer Healthcare, Bristol-Myers Squibb, Daiichi-Sankyo, and Sanofi; speaker fees from Sanofi; and has received a research grant from Daiichi-Sankyo. Dr. Müller is an employee of and holds shares in GlaxoSmithKline. Drs. Banik and Eberle are past employees of GlaxoSmithKline. Dr. Kropff is a past employee of and holds shares in GlaxoSmithKline. Dr. Lindhoff-Last has received speakers fees from Bayer Healthcare, Boehringer Ingelheim, GlaxoSmithKline, and Sanofi; and is a member of the advisory boards of Bayer Healthcare, Boehringer, and GlaxoSmithKline. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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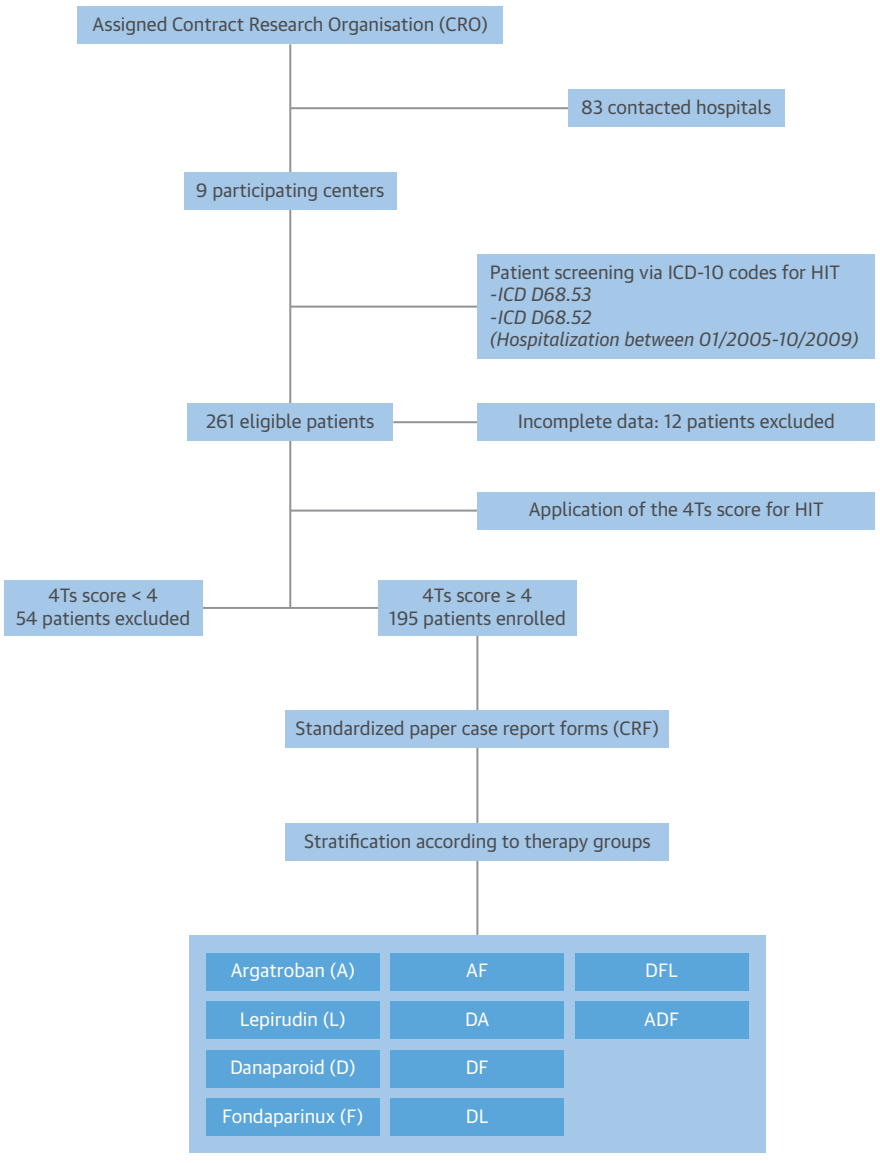
FIGURE 1 Study Protocol



Patient selection, enrollment, and therapy stratification of alternative anticoagulation in patients with suspected acute heparin-induced thrombocytopenia (HIT) in the GerHIT (German HIT) registry study. Reproduced with permission from Schindewolf et al. (51). A = argatroban; D = danaparoid; F = fondaparinux; ICD-10 = International Statistical Classification of Diseases and Related Health Problems; L = lepirudin.

records. Ultimate enrollment criteria were a 4Ts score ≥4 points and prior treatment with at least 1 dose of at least 1 of the commercially available anticoagulants fondaparinux, argatroban, danaparoid, and lepirudin. The study protocol is shown in **Figure 1**.

CASE REPORT FORMS. Case report forms for data documentation included 4Ts scores, ICD-10 codes for HIT, sex, age, weight, height, thrombophilic risk factors, date of HIT suspicion/diagnosis, prior heparin therapy, alternative anticoagulant regimens (dosage, duration, alterations of therapy), complications, and laboratory data (serum creatinine levels, hemoglobin, platelet counts; specific HIT diagnostics: PF4/heparin-dependent enzyme immunoassay [PF4/H-EIA] specific for anti-PF4/heparin IgG or IgG/IgM/IgA class antibodies; particle gel immunoassay; functional heparin-induced platelet activation assay [HIPA]; serotonin release assay [SRA]).

TABLE 1 Therapy Strata After Suspicion of HIT

Treatment Group (N = 195)	
Monotherapy	160 (82.1)
A	32 (16.4)
L	4 (2.1)
D	46 (23.6)
F	78 (40.0)
Sequential therapy	35 (17.9)
AF	11 (5.6)
DA	11 (5.6)
DF	5 (2.6)
DL	4 (2.1)
DFL	1 (0.5)
ADF	3 (1.5)

Values are n (%).
A = argatroban; D = danaparoid; F = fondaparinux; L = lepirudin; HIT = heparin-induced thrombocytopenia.

TABLE 2 Treatment Regimens and the Duration of Therapy With Alternative Anticoagulants

Treatment Group*	Number of Patients	Treatment Duration (Days)
A monotherapy	31	9.0 (2.0–191.0)
A per sequential therapy group		
AF	11	5.0 (1.0–10.0)
DA	11	6.0 (3.0–21.0)
ADF	3	9.0 (3.0–10.0)
L monotherapy	3	10.0 (6.0–19.0)
L per sequential therapy group		
DL	4	42.0 (2.0–1,116.0)
DFL	1	60.0†
D monotherapy	42	12.5 (1.0–61.0)
D per sequential therapy group		
DA	11	3.0 (1.0–26.0)
DF	5	2.0 (1.0–23.0)
DL	4	7.0 (1.0–57.0)
DFL	1	1.0†
ADF	3	5.0 (3.0–26.0)
F monotherapy	72	5.0 (1.0–118.0)
F per sequential therapy group		
AF	10	9.0 (1.0–91.0)
DF	5	10.0 (5.0–91.0)
DFL	1	211.0†
ADF	3	15.0 (3.0–30.0)

Values are n or median (range). *Differences to numbers of therapy strata (see Table 1) are explained by missing data regarding treatment duration. †Range not applicable.
Abbreviations as in Table 1.

PRIMARY AND SECONDARY STUDY OUTCOMES. Because of the noninterventional study design, no formal efficacy criterion was defined. The primary outcome measures were the incidences of arterial and venous (deep vein thrombosis/pulmonary embolism) thromboembolic complications during alternative anticoagulation. The secondary outcome measures were further HIT- and therapy-associated complications (amputations, recurrent/persistent thrombocytopenia, skin lesions, bleedings, and fatal complications measured as in-hospital mortality).

DEFINITION OF PATIENTS WITH "TRUE" HIT. Diagnosis of "true" HIT was based on the combination of 4 to 8 points in the 4Ts score (intermediate to high clinical HIT probability) and presence of HIT antibodies in the functional HIPA ($HIPA^+$), classically in conjunction with a positive PF4-dependent EIA (EIA^+). Possible exceptions were $HIPA^+/EIA^-$ status, for example, non-PF4-associated HIT (21), or $HIPA^-/EIA^+$ status with strong positive EIA results (22,23), for example, missing or false-negative HIPA results. In concordance with previous studies detecting platelet-activating antibodies in about 50% of the patients with EIA^+ (24), we considered $HIPA^-/EIA^+$ status as "true" HIT in one-half of the patients. This reflects a prudent approach, because values of optical density (OD) measurements using PF4-dependent EIAs, which significantly increase the probability of "true" HIT at ODs >1.2 (25), were not available for all the patients with $HIPA^-/EIA^+$ status.

DATA MANAGEMENT. All the data were recorded in a validated database using single data entry and reviewed by the contract research organization data management and the principal investigators for plausibility and completeness. No imputation of missing values was performed. To safeguard anonymization, no queries to the investigators regarding missing or implausible data were allowed.

STATISTICAL ANALYSIS. Data analysis was based on a pre-specified analysis plan (Online Appendix). Due to the retrospective study design, no confirmatory analyses were performed; all the statistics were solely descriptive and presented as absolute and relative frequencies (categorical data), standard deviations, medians, minimums and maximums, and quartiles (numerical data). The results were categorized according to the type of anticoagulant treatment. The statistical analyses were performed using SAS software (version 9.1, SAS Institute, Cary, North Carolina).

RESULTS

CHARACTERISTICS OF THE STUDY POPULATION AND STRATIFICATION ACCORDING TO ALTERNATIVE ANTICOAGULATION. In total, 195 of 261 (74.7%) patients with a D69.53 or D69.52 ICD-10 code discharge diagnosis and a 4Ts score ≥4 points were enrolled in the study (intermediate clinical HIT probability [4 to 5 points]: 96 of 195 [49.2%] patients; high clinical HIT probability [6 to 8 points]: 94 of 195 [48.2%] patients) (missing but ≥4 points: 4 patients; 3

TABLE 3 Stratified Basic Characteristics of the Study Population

	Therapy strata										
	Total	**A**	**L**	**D**	**F**	**AF**	**DA**	**DF**	**DL**	**DFL**	**ADF**
Number of patients	195/195 (100.0)	32/195 (16.4)	4/195 (2.1)	46/195 (23.6)	78/195 (40.0)	11/195 (5.6)	11/195 (5.6)	5/195 (2.6)	4/195 (2.1)	1/195 (0.5)	3/195 (1.5)
Sex											
Female	84/195 (43.1)	10/32 (31.3)	1/4 (25.0)	21/46 (45.7)	35/78 (44.9)	5/11 (45.5)	5/11 (45.5)	2/5 (40.0)	2/4 (50.0)	1/1 (100.0)	2/3 (66.7)
Male	110/195 (56.4)	22/32 (68.8)	2/4 (50.0)	25/46 (54.3)	43/78 (55.1)	6/11 (54.5)	6/11 (54.5)	3/5 (60.0)	2/4 (50.0)	0/1 (0.0)	1/3 (33.3)
Age, yrs	193	31	4	45	78	11	11	5	4	1	3
Mean ± SD	68.5 ± 12.5	66.4 ± 12.3	61.8 ± 13.7	67.8 ± 13.0	71.7 ± 11.4	71.5 ± 12.1	60.0 ± 14.0	71.0 ± 8.6	55.3 ± 16.0	56.0	63.7 ± 7.5
Range	24–92	41–86	43–76	29–88	24–92	44–86	32–77	64–86	35–74	n.a.	55–68
BMI, kg/m^2	27.2 ± 5.5	26.4 ± 4.2	22.6 ± 6.7	28.5 ± 7.0	27.1 ± 4.8	25.9 ± 3.3	28.4 ± 6.6	28.9 ± 5.6	25.6 ± 4.4	19.5	31.7 ± 14.0
ICD-10 diagnosis code											
Immune HIT, D69.53	157/195 (80.5)	23/32 (71.9)	1/4 (25.0)	26/46 (56.5)	77/78 (98.7)	11/11 (100.0)	8/11 (72.7)	4/5 (80.0)	3/4 (75.0)	1/1 (100.0)	3/3 (100.0)
Nonimmune HIT, D69.52	12/195 (6.2)	4/32 (12.5)	0/4 (0.0)	6/46 (13.0)	0/78 (0.0)	0/11 (0.0)	1/11 (9.1)	1/5 (20.0)	0/4 (0.0)	0/1 (0.0)	0/3 (0.0)
Missing	26/195 (13.3)	5/32 (15.6)	3/4 (75.0)	14/46 (30.4)	1/78 (1.3)	0/11 (0.0)	2/11 (18.2)	0/5 (0.0)	1/4 (25.0)	0/1 (0.0)	0/3 (0.0)
Previous TE, before current suspected HIT episode											
Arterial	17/195 (8.7)	2/32 (6.3)	0/4 (0.0)	6/46 (13.0)	4/78 (5.1)	2/11 (18.2)	0/11 (0.0)	1/5 (20.0)	1/4 (25.0)	0/1 (0.0)	1/3 (33.3)
Venous	12/195 (6.2)	3/32 (9.4)	0/4 (0.0)	2/46 (4.3)	2/78 (2.6)	3/11 (27.3)	0/11 (0.0)	0/5 (0.0)	0/4 (0.0)	1/1 (100.0)	1/3 (33.3)
Combined	4/195 (2.1)	2/32 (6.3)	0/4 (0.0)	0/46 (0.0)	1/78 (1.3)	0/11 (0.0)	0/11 (0.0)	0/5 (0.0)	1/4 (25.0)	0/1 (0.0)	0/3 (0.0)
None	144/195 (73.8)	17/32 (53.1)	3/4 (75.0)	32/46 (69.6)	70/78 (89.7)	5/11 (45.5)	11/11 (100.0)	3/5 (60.0)	2/4 (50.0)	0/1 (0.0)	1/3 (33.3)
Missing	18/195 (9.2)	8/32 (25.0)	1/4 (25.0)	6/46 (13.0)	1/78 (1.3)	1/11 (9.1)	0/11 (0.0)	1/5 (20.0)	0/4 (0.0)	0/1 (0.0)	0/3 (0.0)
Reason for anticoagulation*											
Prophylactic	155/195 (51.8)	24/32 (75.0)	2/4 (50.0)	39/46 (84.8)	66/78 (84.6)	9/11 (81.8)	8/11 (72.7)	2/5 (40.0)	3/4 (75.0)	0/1 (0.0)	2/3 (66.7)
Therapeutic	76/195 (39.0)	14/32 (43.8)	2/4 (50.0)	18/46 (39.1)	21/78 (26.9)	6/11 (54.5)	6/11 (54.5)	3/5 (60.0)	2/4 (50.0)	1/1 (100.0)	3/3 (100.0)
Area of anticoagulation*											
Surgery	112/195 (57.4)	13/32 (40.6)	2/4 (50.0)	11/46 (23.9)	68/78 (87.2)	8/11 (72.7)	6/11 (54.5)	0/5 (0.0)	3/4 (75.0)	1/1 (100.0)	0/3 (0.0)
Cardiac surgery	77/195 (39.5)	6/32 (18.8)	0/4 (0.0)	2/46 (4.3)	66/78 (84.6)	3/11 (27.3)	0/11 (0.0)	0/5 (0.0)	0/4 (0.0)	0/1 (0.0)	0/3 (0.0)
Other surgery	35/195 (17.9)	7/32 (21.9)	2/4 (50.0)	9/46 (19.6)	2/78 (2.6)	5/11 (45.5)	6/11 (54.5)	0/5 (0.0)	3/4 (75.0)	1/1 (100.0)	0/3 (0.0)
Medicine	93/195 (47.7)	20/32 (62.5)	2/4 (50.0)	42/46 (91.3)	11/78 (14.1)	3/11 (27.3)	6/11 (54.5)	5/5 (100.0)	1/4 (25.0)	0/1 (0.0)	3/3 (100.0)
MICU and SICU	46/195 (23.6)	14/32 (43.8)	0/4 (0.0)	20/46 (21.7)	3/78 (3.9)	1/11 (9.1)	5/11 (0.0)	1/5 (20.0)	1/4 (25.0)	0/1 (0.0)	1/3 (33.3)
Unspecified	5/195 (2.6)	3/32 (9.4)	0/4 (0.0)	0/46 (0.0)	0/78 (0.0)	0/11 (0.0)	1/11 (9.1)	0/5 (0.0)	1/4 (25.0)	0/1 (0.0)	0/3 (0.0)
Thromboembolic events during preceding heparin therapy											
Number of patients	195/195 (100.0)	32/195 (16.4)	4/195 (2.1)	46/195 (23.6)	78/195 (40.0)	11/195 (5.6)	11/195 (5.6)	5/195 (2.6)	4/195 (2.1)	1/195 (0.5)	3/195 (1.5)
Thromboembolic events, total	47/195 (24.1)	8/32 (25.0)	3/4 (75.0)	11/46 (23.9)	6/78 (7.7)	5/11 (45.5)	9/11 (81.8)	2/5 (40.0)	1/4 (25.0)	0/1 (0.0)	2/3 (66.7)
Arterial	19/195 (9.7)	1/32 (3.1)	2/4 (50.0)	2/46 (4.4)	3/78 (3.9)	1/11 (9.1)	6/11 (54.6)	2/5 (40.0)	1/4 (25.0)	0/1 (0.0)	1/3 (33.3)
Venous	25/195 (12.8)	7/32 (21.9)	0/4 (0.0)	8/46 (17.4)	3/78 (3.9)	3/11 (27.3)	3/11 (27.3)	0/5 (0.0)	0/4 (0.0)	0/1 (0.0)	1/3 (33.3)
Combined	3/195 (1.5)	0/32 (0.0)	1/4 (25.0)	1/46 (2.2)	0/78 (0.0)	1/11 (9.1)	0/11 (0.0)	0/5 (0.0)	0/4 (0.0)	0/1 (0.0)	0/3 (0.0)

Values are n/N (%), n, mean ± SD, or range. Missing or undeterminable results were counted as negative. *Multiple responses possible.

BMI = body mass index; ICD = International Statistical Classification of Diseases and Related Health Problems; MICU = medical intensive care unit; n.a. = not applicable; SICU = surgical intensive care unit; TE = thromboembolic event; other abbreviations as in Table 1.

points: 1 patient) and assigned to 10 different therapy strata (monotherapy or sequential therapy groups, regardless of sequence. During antecedent heparin therapy, 79 of 195 (40.5%) complications occurred (24 hemoglobin-relevant bleedings, 47 thromboembolic events, 5 skin lesions, 1 amputation, 2 fatalities). Of note, 112 of 195 (57.4%) patients had previously had post-surgical prophylaxis. Remarkably, 64 of 91 (70.3%) of the patients with cardiac or vascular procedures were in the fondaparinux monotherapy group. Details on therapy strata, 4Ts score distribution, and basic patient characteristics are listed in Tables 1 to 4. Thromboembolic and bleeding complications are plotted against 4Ts scores and laboratory HIT results in Online Tables 1 to 3.

LABORATORY TESTING FOR HIT STRATIFIED ACCORDING TO ALTERNATIVE TREATMENT REGIMENS. Laboratory testing for HIT was performed using at least 2 assays for 189 of 195 (96.9%) patients. The test results, stratified according to treatment regimens, are summarized in Table 5.

TABLE 4 4Ts Scores Stratified According to Treatment Regimen

	Therapy Strata										
4Ts scores	All	A	L	D	F	AF	DA	DF	DL	DFL	ADF
Number of patients	195/195 (100.0)	32/195 (16.4)	4/195 (2.1)	46/195 (23.6)	78/195 (40.0)	11/195 (5.6)	11/195 (5.6)	5/195 (2.6)	4/195 (2.1)	1/195 (0.5)	3/195 (1.5)
3 points	1/195 (0.5)	0/32 (0.0)	0/4 (0.0)	0/46 (0.0)	1/78 (1.3)	0/11 (0.0)	0/11 (0.0)	0/5 (0.0)	0/4 (0.0)	0/1 (0.0)	0/3 (0.0)
4 points	46/195 (23.6)	10/32 (31.3)	0/4 (0.0)	22/46 (47.8)	10/78 (12.8)	3/11 (27.3)	0/11 (0.0)	1/5 (20.0)	0/4 (0.0)	0/1 (0.0)	0/3 (0.0)
5 points	50/195 (25.6)	13/32 (40.6)	2/4 (50.0)	11/46 (23.9)	16/78 (20.5)	0/11 (0.0)	3/11 (27.3)	2/5 (40.0)	0/4 (0.0)	1/1 (100.0)	2/3 (66.7)
6 points	74/195 (38.0)	7/32 (21.9)	2/4 (50.0)	8/46 (17.4)	44/78 (56.4)	5/11 (45.5)	3/11 (27.3)	1/5 (20.0)	3/4 (75.0)	0/1 (0.0)	1/3 (33.3)
7 points	13/195 (6.7)	0/32 (0.0)	0/4 (0.0)	4/46 (8.7)	3/78 (3.9)	2/11 (18.2)	3/11 (27.3)	1/5 (20.0)	0/4 (0.0)	0/1 (0.0)	0/3 (0.0)
8 points	7/195 (3.6)	2/32 (6.3)	0/4 (0.0)	1/46 (2.2)	1/78 (1.3)	0/11 (0.0)	2/11 (18.2)	0/5 (0.0)	1/4 (25.0)	0/1 (0.0)	0/3 (0.0)
Missing	4/195 (2.1)	0/32 (0.0)	0/4 (0.0)	0/46 (0.0)	3/78 (3.9)	1/11 (9.1)	0/11 (0.0)	0/5 (0.0)	0/4 (0.0)	0/1 (0.0)	0/3 (0.0)

Values are n/N (%).
Abbreviations as in Table 1.

COURSE OF PLATELET COUNTS. The course of platelet counts during heparin therapy and alternative anticoagulation are shown in the **Central Illustration**.

CLINICAL COMPLICATIONS DURING ALTERNATIVE ANTICOAGULATION. For outcome analysis, initial therapy strata were ungrouped, and complications were analyzed per single first-line anticoagulant. Regarding thromboembolic complications, 9 of 111 (8.1%) events were reported (4 deep vein thromboses, 2 pulmonary embolisms, and 3 arterial events), which occurred within a median time span of 4 days (range 1 to 21 days) after the start of approved alternative therapy. Two arterial events resulted in lower limb amputations. According to the first-line therapy stratification, all thromboembolic events and amputations occurred during argatroban and danaparoid therapy (Table 6). Skin necroses due to HIT (as attributed by the treating physicians on the basis of temporal, clinical, and laboratory aspects) occurred in 2 of 111 (1.8%) patients despite approved anticoagulation with danaparoid. Of note, none of these specific HIT-associated complications occurred during fondaparinux use (0 of 84; 0.0%). Therapy-resistant recurrent or persistent thrombocytopenia was documented in 8 of 195 (4.1%) patients; of these, only 1 patient was treated with fondaparinux, but was also refractory to argatroban and danaparoid.

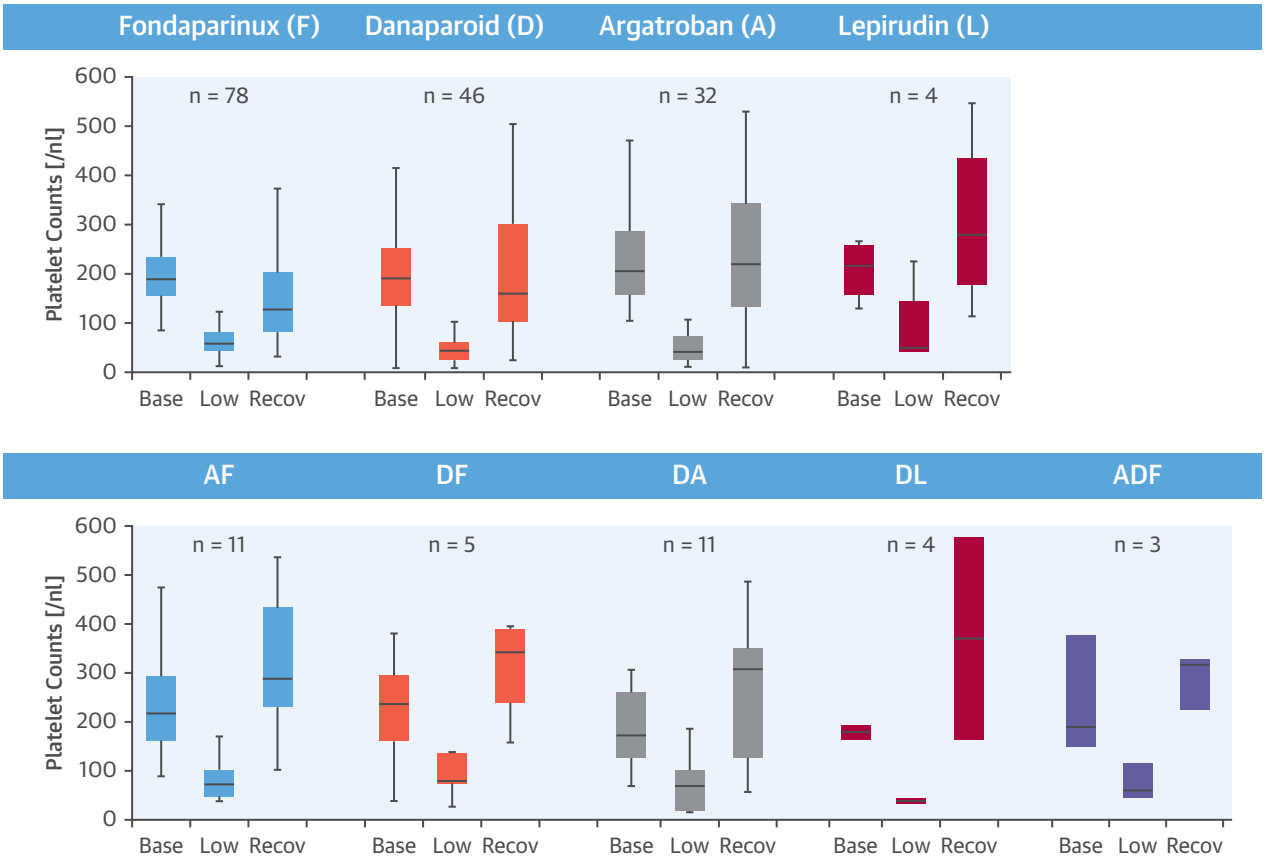
In total, 7 of 111 (6.3%) hemoglobin-relevant bleeding complications were reported with a median onset time of 7.5 days (range 1 to 27 days) after the start of approved alternative anticoagulation (argatroban 3 patients, danaparoid 4). Bleedings occurred in 4 of 84 (4.8%) of fondaparinux-treated patients. In Table 7 thromboembolic and bleeding complications per treatment day are shown. Measurements of blood concentrations of anticoagulants were not reported.

TABLE 5 Laboratory Diagnostics for HIT

	Therapy Strata										
	Total	A	L	D	F	AF	DA	DF	DL	DFL	ADF
Number of patients	195/195 (100.0)	32/195 (16.4)	4/195 (2.1)	46/195 (23.6)	78/195 (40.0)	11/195 (5.6)	11/195 (5.6)	5/195 (2.6)	4/195 (2.1)	1/195 (0.5)	3/195 (1.5)
PF4/H-EIA											
Total	174/195 (89.2)	27/32 (84.4)	1/4 (25.0)	40/46 (87.0)	76/78 (97.4)	11/11 (100.0)	9/11 (81.8)	4/5 (80.0)	2/4 (50.0)	1/1 (100.0)	3/3 (100.0)
≥1 positive test	89/174 (51.2)	13/27 (48.2)	1/1 (100.0)	24/40 (60.0)	28/76 (36.8)	7/11 (63.6)	8/9 (88.9)	3/4 (75.0)	2/2 (100.0)	1/1 (100.0)	2/3 (66.7)
HIPA											
Total	189/195 (96.9)	31/32 (96.9)	4/4 (100.0)	43/46 (93.5)	78/78 (100.0)	11/11 (100.0)	9/11 (81.8)	5/5 (100.0)	4/4 (100.0)	1/1 (100.0)	3/3 (100.0)
≥1 positive test	61/189 (32.3)	8/31 (25.8)	1/4 (25.0)	16/43 (37.2)	23/78 (29.5)	4/11 (36.4)	1/9 (11.1)	4/5 (80.0)	2/4 (50.0)	1/1 (100.0)	1/3 (33.3)
PaGIA											
Total	24/195 (12.3)	11/32 (34.4)	4/4 (100.0)	4/46 (8.7)	2/78 (2.6)	1/11 (9.1)	1/11 (9.1)	1/5 (20.0)	0/4 (0.0)	0/0 (0.0)	0/0 (0.0)
≥1 positive test	19/24 (79.2)	9/11 (81.8)	3/4 (75.0)	4/4 (100.0)	1/2 (50.0)	1/1 (100.0)	1/1 (100.0)	0/1 (0.0)	0/0 (0.0)	0/0 (0.0)	0/0 (0.0)
SRA											
Total	0/195 (0.0)	0/32 (0.0)	0/4 (0.0)	0/46 (0.0)	0/78 (0.0)	0/11 (0.0)	0/11 (0.0)	0/5 (0.0)	0/4 (0.0)	0/1 (0.0)	0/3 (0.0)

Values are n/N (%). Missing or undeterminable results were counted as negative.
EIA = enzyme immunoassay; H = heparin; HIPA = heparin-induced activation assay; PaGIA = particle gel immunoassay; PF4 = platelet factor 4; SRA = serotonin-release assay; other abbreviations as in Table 1.

CENTRAL ILLUSTRATION **Extent of Thrombocytopenia During Suspected HIT**



Schindewolf, M. et al. J Am Coll Cardiol. 2017;70(21):2636–48.

Courses of platelet counts are presented as median levels during heparin treatment before (Base) and at onset (Low) of HIT and after (Recov) start of alternative anticoagulation. The data were stratified according to the different alternative treatment groups. A = argatroban; D = danaparoid; F = fondaparinux; HIT = heparin-induced thrombocytopenia; L = lepirudin.

Furthermore, 16 of 111 (14.4%) fatalities occurred during approved alternative anticoagulation, none with fondaparinux (0 of 84; 0.0%) (**Table 6**). In order to capture more remote events as well, that is, during second- and third-line therapy, data were analyzed as per single anticoagulant exposure (Online Table 4).

Graphically, thromboembolic and bleeding complications during alternative anticoagulation are plotted against 4Ts scores and laboratory HIT results (Online Tables 2 and 3). Because fondaparinux and danaparoid can be applied in prophylactic as well as therapeutic doses, the association of administered doses with thromboembolic and bleeding outcomes is listed in Online Tables 5 and 6.

DISCUSSION

The aim was to obtain data on the therapeutic efficacy and safety of approved alternative treatment options and, notably, of the off-label-used pentasaccharide fondaparinux in patients with suspected acute HIT (4Ts score ≥4 points) under real-world clinical practice conditions.

THERAPEUTIC EFFICACY AND SAFETY OF FONDAPARINUX COMPARED WITH APPROVED ALTERNATIVE ANTICOAGULATION. In the 84 first-line and 14 second-line fondaparinux-treated patients, there were no HIT-specific complications (i.e., arterial and venous thromboembolic events, amputations, skin necroses, and recurrent thrombocytopenia) (0.0%)

TABLE 6 Complications During Alternative Anticoagulation Stratified per First-Line Anticoagulant

	Therapy Strata				
	Total	A	L	D	F
Number of anticoagulant exposures	195/195 (100.0)	46/195 (23.6)	4/195 (2.1)	61/195 (31.3)	84/195 (43.1)
Complications during alternative anticoagulation	51/195 (26.2)	17/46 (34.8)	1/4 (25.0)	31/61 (50.8)	6/84 (7.1)
Thromboembolic events	9/195 (4.6)	4/46 (8.7)	0/4 (0.0)	5/61 (8.2)	0/84 (0.0)
Arterial*	3/195 (1.5)	1/46 (2.2)	0/4 (0.0)	2/61 (3.3)	0/84 (0.0)
Venous	6/195 (3.1)	3/46 (6.5)	0/4 (0.0)	3/61 (4.9)	0/84 (0.0)
DVT	4/195 (2.1)	2/46 (4.4)	0/4 (0.0)	2/61 (3.3)	0/84 (0.0)
PE	2/195 (1.0)	1/46 (2.2)	0/4 (0.0)	1/61 (1.6)	0/84 (0.0)
Amputations	2/195 (1.0)	1/46 (2.2)	0/4 (0.0)	1/61 (1.6)	0/84 (0.0)
Thrombocytopenia, recurrent	4/195 (2.1)	0/46 (0.0)	0/4 (0.0)	4/61 (6.6)	0/84 (0.0)
Thrombocytopenia, persistent†‡	4/195 (2.1)	2/46 (4.4)	0/4 (0.0)	3/61 (4.9)	1/84 (1.2)
Skin reactions, necrotic	2/195 (1.0)	0/46 (0.0)	0/4 (0.0)	2/61 (3.3)	0/84 (0.0)
Bleeding complications	11/195 (5.6)	3/46 (6.5)	0/4 (0.0)	4/61 (6.6)	4/84 (4.8)
Fatalities‡§	16/195 (8.2)	5/46 (10.9)	1/4 (25.0)	12/61 (19.7)	0/84 (0.0)
Other	3/195 (1.5)	2/46 (4.4)	0/4 (0.0)	0/61 (0.0)	1/84 (1.2)

Values are n/N (%). *Arterial events resulted in 2 amputations. †Persistent thrombocytopenia in 1 patient was attributed to 3 anticoagulants (ADF). ‡Complications caused by several anticoagulants were counted as 1 event for each anticoagulant and as 1 event in the column "Total." §Two fatal outcomes were attributed to 2 anticoagulants (DA and DL, respectively) by the treating physician.

DVT = deep vein thrombosis; PE = pulmonary embolism; other abbreviations as in Table 1.

and no deaths (**Table 6,** Online Table 4). As a further sign of successful HIT treatment, full platelet recovery was observed in patients treated with fondaparinux (**Central Illustration**). The lower median platelet increase in the fondaparinux monotherapy group (61.5 platelets/nl) compared with the other treatment groups might be attributable to the shorter median treatment duration (5.0 days vs. 8.0 days). The only unsuccessful efficacy outcome in regard to fondaparinux treatment was persistent thrombocytopenia in 1 patient. However, this was also not resolved by switching anticoagulation to danaparoid and argatroban. Because HIT diagnostics were negative, the most probable cause for thrombocytopenia was an underlying endocarditis, but not HIT.

By comparison, the composite endpoint of HIT-specific complications (thromboembolic events, amputation, skin necrosis) occurred in 11.7% of patients treated with the approved alternative anticoagulants (**Table 6**). However, these high complication rates compare well to a pooled analysis of data in the published reports (26-30) (Online Table 7).

Regarding safety outcomes, bleeding complications occurred in 4.8% of fondaparinux-treated patients and in 6.3% of alternatively anticoagulated patients. However, due to the large variation of treatment durations, bleeding risk per day has been considered to be a more meaningful parameter (31). Although argatroban and dabigatran bleeding rates compare well to the published reports (5-7,31), the bleeding risk per treatment day of 1.2% during fondaparinux treatment in this study is likely overestimated (**Table 7**): 2 of 4 fondaparinux-treated patients had a severely impaired kidney function (20.8 and 27.4 ml/min), and 1 patient had moderately impaired kidney function (40 ml/min) (1 patient was not reported), but they were treated with an inappropriately high (for the degree of renal impairment) therapeutic dose of fondaparinux (1 × 7.5 mg per day), making bioaccumulation likely. Furthermore, 1 minor, clinically nonrelevant bleeding from a rectal angiodysplasia occurred in a in a 92-year-old female patient 17 days after single exposure with 1 × 5 mg of subcutaneously administered fondaparinux. No hemoglobin decrease was observed, and no medical interventions were necessary.

Another aspect of this study, for which hardly any data exist, is that patients with "true" HIT have an

TABLE 7 Complications of First-Line Alternative Anticoagulation per Treatment Day*

	Argatroban	Danaparoid	Fondaparinux
Treatment duration, days	7.5 (1.0-191.0)	8.0 (1.0-61.0)	4.0 (1.0-118.0)
Bleedings			
Bleeding complications	6.5	6.6	4.8†
Bleeding risk per treatment day	0.87	0.83	1.2
Thromboembolic events, arterial and venous			
Thromboembolic complications	8.7	8.2	0
Thrombosis risk per treatment day	1.16	1.03	<1.0

Values are median (range) or %. *Lepirudin was not analyzed due to the small first-line treatment group of only 4 patients. †Contains 1 bleeding event in a 92-year-old female patient with a minor nonclinically relevant bleeding from a rectal angiodysplasia with no drop in hemoglobin levels that occurred 17 days after single exposure with 1 × 5 mg of subcutaneously administered fondaparinux. No medical intervention was necessary.

increased risk for thrombosis, whereas those with a false diagnosis of HIT have a higher risk of bleeding (Online Tables 1 to 3). Alternative anticoagulation reduces the number of thromboembolic events. However, bleeding events in "true" HIT patients most likely reflect adverse effects of the anticoagulant rather than a consequence of thrombocytopenia per se (Online Table 2). Online Table 5 shows that prophylactic doses of danaparoid might not be sufficient in all cases to prevent thromboembolic complications adequately. Furthermore, bleeding complications occur more frequently with therapeutic doses of danaparoid and fondaparinux than prophylactic doses (Online Table 6). In case of fondaparinux, at least 3 bleeding complications might have occurred in the context of bioaccumulation and impaired kidney function (Online Table 6).

In conclusion, fondaparinux-treated patients with suspected HIT seem to have a low risk for thromboembolic events. This risk reduction considerably outweighs the probably overestimated bleeding risk of fondaparinux.

THE NUMBER OF FONDAPARINUX-TREATED PATIENTS WITH "TRUE" HIT. In order to explain the low numbers of HIT-specific complications in fondaparinux-treated patients with suspected acute HIT, these patients need to be assessed to determine whether they just had a lower probability for HIT, for example, a 4Ts score of 4 to 5 points, negative HIT diagnostics, and therefore, a lower risk for complications, especially thromboembolic events. Thus, for conclusions regarding use of fondaparinux in suspected acute HIT, the main question is of how reliably the study patients had "true" HIT.

Although no HIT-specific complications occurred among the fondaparinux-treated patients, their median 4Ts score was with 6 points in the high-risk category for underlying HIT of the 4Ts score. Regarding laboratory diagnostics, the anti-PF4/H-EIA (IgG/IgA/IgM or IgG) has a high sensitivity (≥99%) for detecting anti-PF4/heparin antibodies (5,24), its specificity is disproportionally lower; only approximately one-half of patients with a positive IgG/IgA/IgM or IgG EIA have platelet-activating antibodies that are detectable in the HIPA and thus are likely to have "true" HIT (24).

A clinically feasible approach, described by Greinacher et al. (24), combines the 4Ts score with laboratory HIT diagnostics. Due to the high sensitivity of PF4/H-EIA, HIT can be safely ruled out in patients with a negative test result and a low clinical pre-test probability (<4 points) (22,24). In patients with clinically suspected HIT, the final diagnosis of HIT requires either a strongly positive PF4/-H-EIA result and/or a positive functional platelet assay (22). Conversely, the diagnosis should be rejected when both the immunogenic and functional test results are negative, which applies to 87 (44.6%) of the study patients (**Table 8**, row A).

Patients with at least an intermediate risk of HIT (≥4 points) and a positive PF4/H-EIA result should be treated for HIT, but they should only be diagnosed with HIT when a functional HIT assay (i.e., SRA or HIPA) is concordantly positive (22,24). This applies to 51 (26.2%) of the study patients (1 patient had a 4Ts score of 3 points; however, he was included due to a high probability of underlying isolated immediate-type HIT, OD 1.2, HIPA positive). Of these 51 patients with presumably "true" HIT, 31 (60.8%) were treated with fondaparinux (first-line therapy: n = 27; second-line therapy: n = 4) (**Table 8**, row D, and Online Table 8). The OD was measured in 23 of these 31 patients, and the median OD was 1.5 (range 0.7 to 3.2).

The small number of patients (10 [5.1%]) with a negative PF4/H-EIA result and the presence of platelet-activating antibodies in the HIPA is in accordance with previous reports (24) and may reflect the occasional pathogenic association between HIT and IL-8 or NAP-2 (instead of PF4) (21), or alternatively, false-positive HIPA results due to non-HIT activating factors). Of the patients with possible PF4-independent HIT, 2 patients were treated second-line with fondaparinux (**Table 8**, row C, and Online Table 8).

In 47 (24.1%) patients, 25 with an intermediate (4 to 5 points) and 22 with a high (6 to 8 points) clinical probability of HIT, tested positive in a PF4/H-EIA assay alone. This constellation of features has the highest risk of overdiagnosing HIT (23). Raising the OD threshold for PF4/H-EIA would increase the probability of detecting platelet-activating antibodies in a functional assay (23,25). More specifically, increasing the threshold to 1.20 OD in combination with an intermediate or high 4Ts score would identify all of the same HIT-positive patients as the SRA alone (25). The ODs of 26 of these 47 patients were specified, with a median of 1.5 OD (range 0.7 to 3.3); thus, it is conceivable that at least several of them had HIT, but platelet-activating antibodies were possibly not detected due to the lower sensitivity of the functional HIPA. This explanation is particularly likely in the 7 patients with inconclusive HIPA results and a remarkably high median OD of 2.6 (range 1.4 to 3.0). Ten of the aforementioned 47 patients were treated with fondaparinux (first-line therapy: n = 6; second-line therapy: n = 4) (**Table 8**, row B, and Online

TABLE 8 Results of Laboratory HIT Diagnostics Stratified According to 4Ts Scores and First-Line Alternative Anticoagulants

	HIT Diagnostics, n		4Ts Scores (Points)						
	PF4/H-EIA	HIPA	3	4	5	6	7	8	UK
A	Negative	Negative	0	15	20	49	1	0	2
B	Positive	Negative	0	15	10	17	4	1	0
C	Negative	Positive	0	4	4	0	0	2	0
D	Positive	Positive	1	12	16	8	8	4	2
A	Negative	Negative	0	15	20	49	1	0	2
	Anticoagulant, n								
	A		0	6	6	7	0	0	0
	L		0	0	1	0	0	0	0
	D		0	7	6	2	1	0	0
	F		0	2	7	40	0	0	2
B	Positive	Negative	0	15	10	17	4	1	0
	Anticoagulant, n								
	A		0	5	4	5	1	1	0
	L		0	0	1	1	0	0	0
	D		0	8	4	8	3	0	0
	F		0	2	1	3	0	0	0
C	Negative	Positive	0	4	4	0	0	2	0
	Anticoagulant, n								
	A		0	0	2	0	0	1	0
	L		0	0	0	0	0	0	0
	D		0	4	2	0	0	1	0
	F		0	0	0	0	0	0	0
D	Positive	Positive	1	12	16	8	8	4	2
	Anticoagulant, n								
	A		0	1	2	2	1	2	0
	L		0	0	0	1	0	0	0
	D		0	4	3	3	4	1	0
	F		1	7	11	2	3	1	2

Missing or undeterminable results were counted as negative. The functional HIPA assay was performed using washed platelets. **Light blue shading**: B: ODs were determined in 26 of 47 patients. The median OD was 1.5 (range: 0.7 to 3.3), indicating clinically significant platelet-activating HIT antibodies, and thus, "true" HIT in at least 13 patients. Of these patients with "true" HIT, 2 patients were treated with fondaparinux (second-line therapy [Online Table 8]). For further details, see text. **Dark blue shading**: Patients with "true" HIT; of these 61 patients, 33 were treated with fondaparinux. C: Of 10 patients, 2 patients were treated with second-line fondaparinux (Online Table 8). D: Of 51 patients, 31 received fondaparinux: first-line therapy: n = 27; second-line therapy: n = 4 (Online Table 8). In total, 35 patients with "true" HIT were treated with fondaparinux first- or second-line therapy. (Row B: n = 2; Row C: n = 2; Row D: n = 31). (Patients with second-line therapy are displayed in Online Table 8 only).

OD = optical density; PF4 = platelet factor 4; UK = unknown 4Ts score but ≥4; other abbreviations as in **Tables 1 and 5**.

Table 8). The OD was reported for 4 of these 10 fondaparinux-treated patients, 2 of whom (with second-line therapy) were most likely to have HIT (OD 1.2, 4Ts score 6 points; OD of 1.8, 4Ts score 7 points, respectively). The ODs for the other 2 patients with monotherapy fondaparinux were 0.9 and 1.1, respectively.

In summary, on the basis of a prudent estimation, we identified 35 study patients with probable "true" HIT who were safely and effectively treated with fondaparinux (**Table 8**). This result is in line with the opinions of the leading experts in the field, who consider fondaparinux to most likely be a safe treatment option (11,31,32,33), and it complies with the American College of Chest Physicians recommendation that more clinical evidence be gathered before adjusting the current, prudent recommendations (5).

As outlined in the preceding text, many of the enrolled patients did not have HIT; however, this conclusion is based on a post hoc analysis that included laboratory test results. The value of our approach is that it was based on HIT management under real-life conditions, which require alternative anticoagulation to be begun upon the clinical estimation of HIT probability (on the basis of the 4Ts score) before laboratory test results are available. Given that one cannot be certain in real time whether a patient has HIT or not (pending laboratory results), it is appropriate to perform analyses, and to report the results, based upon categorizing those patients ultimately judged to have likely had "true" HIT, as well as those remaining patients in whom the diagnosis of HIT was unlikely.

CAN THE CONCEPT OF USING FONDAPARINUX IN HIT BE SUBSTANTIATED BY FURTHER CLINICAL AND EXPERIMENTAL DATA FROM THE LITERATURE? Clinically, the successful use of fondaparinux in patients with antecedent or acute HIT has been reported in limited case series over the years (6,7,34–37). These data are summarized in Online Table 9. By contrast, few patients have been documented with potential fondaparinux-associated HIT (8–12), although this issue has not been resolved (13–15), particularly in light of cases of "spontaneous" HIT syndrome (38), possibly caused by a misdirected primary immune response due to pre-immunization to PF4/bacteria complexes (39,40). Because the serological features of spontaneous HIT syndrome and fondaparinux-associated HIT are similar, that is, the patient's serum induces strong platelet activation in the absence of heparin, with increases in platelet activation in the presence of heparin (but not fondaparinux), with inhibition of platelet activation by high concentrations of heparin, at least some of the aforementioned patients with fondaparinux-associated thrombocytopenia, all of whom were in a proinflammatory state (major orthopedic or abdominal surgery or another critical medical condition), may have been cases of post-operative/inflammatory spontaneous HIT with coincidental fondaparinux use (provided there was definitely no perioperative heparin exposure).

Considering the molecular characteristics of fondaparinux, its association with HIT must be questioned because: 1) antigen formation by the PF4/heparin complex requires a polysaccharide chain of at least 8 to 10 saccharides (41); 2) fondaparinux is bound to antithrombin almost exclusively (>94%) (42); and 3) the short pentasaccharide chain is less likely to interact nonspecifically with PF4 (43). Furthermore, fondaparinux does not form ultralarge complexes (like heparin molecules), which provide the spatial matrix for an effective HIT-antibody-platelet interaction (44).

On the other hand, a certain immunogenicity of fondaparinux has been demonstrated by the generation of anti-PF4/heparin antibodies at similar frequencies during fondaparinux and enoxaparin treatment (17). Nevertheless, despite its immunogenicity, fondaparinux shows little or no cross-reactivity with either anti-PF4/heparin antibodies (45–47) or anti-PF4/fondaparinux antibodies (17) in the presence of PF4 in vitro, and little or no ability to activate platelets in the presence of HIT sera (45,47). However, the possibility of a low frequency (1% or less) of clinically relevant cross-reactivity of fondaparinux with HIT-antibodies does exist (18,19).

STUDY LIMITATIONS. The completeness of the medical records are limitations of any retrospective study. Due to the observational nature of the study, it cannot be guaranteed that the groups not receiving fondaparinux are proper control groups. Post hoc stratification according to therapy regimen may result in subgroups that are sometimes too small or insufficiently homogeneous to allow reasonable conclusions. Furthermore, not all the ODs from the PF4/H-EIAs were reported, which would have added more validity to the laboratory results, especially in patients with intermediate pre-test probabilities and missing functional platelet test results.

CONCLUSIONS

Our study provides additional support that fondaparinux seems to be an effective and safe alternative treatment option for clinically suspected acute HIT (4Ts score ≥4 points) and, most likely, for confirmed acute HIT (although fondaparinux is currently not approved for this purpose); no HIT-specific complications occurred in the patients who were treated with fondaparinux, even among those with a high clinical probability of HIT. Because appropriately powered, randomized, controlled trials with fondaparinux will not soon be available (5), and on the basis of these and other published, well-documented HIT cases, a moderate change in the status of fondaparinux in the guideline recommendations (5), from "off-label use only" to "possible use in patients with intermediate (or even high) risk of HIT," should be discussed. Because fondaparinux does not have an indication to treat acute HIT, there is a need for additional studies in this patient population due to the limitations of available treatments; lepirudin was recalled from the market in April 2012 (48), danaparoid access has been limited (due to manufacturing problems) (31), argatroban is contraindicated in severely impaired hepatic function and may be ineffective in patients with HIT-associated consumptive coagulopathy due to activated partial thromboplastin time confounding (5,49,50), the approved alternative anticoagulants have a high bleeding risk (31), and approximately 50% of patients with suspected acute HIT are currently treated off-label with fondaparinux (51).

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Several anticoagulants are approved for treatment of patients with life-threatening, prothrombotic, HIT, specifically the direct thrombin inhibitors argatroban and lepirudin and the factor Xa inhibitor danaparoid. On the basis of its favorable structural properties and ex vivo data, the pentasaccharide fondaparinux has been used off-label in patients with suspected acute HIT. This approach seems to be effective to prevent venous and arterial thromboembolic complications, and safe with regard to bleeding complications when compared with the approved anticoagulants.

TRANSLATIONAL OUTLOOK: Because of the limitations of approved treatment options for management of patients with suspected acute HIT, randomized trials are needed to directly compare the efficacy and safety of fondaparinux with currently approved alternatives, as well as other potential strategies, including oral anticoagulants that specifically target factor Xa and thrombin.

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KEY WORDS argatroban, danaparoid, fondaparinux, heparin, heparin-induced thrombocytopenia, lepirudin

APPENDIX For supplemental tables, please see the online version of this article.