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CLINICAL TRIALS AND OBSERVATIONS

Direct oral anticoagulants for treatment of HIT: update of Hamilton experience and literature review

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Key Points

- New data plus a literature review documented new thrombosis in only 1 (2.2%) of 46 patients with acute HIT who were treated with rivaroxaban.
- The literature review found similarly favorable results, albeit with fewer patients, when apixaban and dabigatran were used to treat acute HIT.

Direct oral anticoagulants (DOACs) are attractive options for treatment of heparin-induced thrombocytopenia (HIT). We report our continuing experience in Hamilton, ON, Canada, since January 1, 2015 (when we completed our prospective study of rivaroxaban for HIT), using rivaroxaban for serologically confirmed HIT (4Ts score ≥4 points; positive platelet factor 4 [PF4]/heparin immunoassay, positive serotonin-release assay). We also performed a literature review of HIT treatment using DOACs (rivaroxaban, apixaban, dabigatran, edoxaban). We focused on patients who received DOAC therapy for acute HIT as either primary therapy (group A) or secondary therapy (group B; initial treatment using a non-DOAC/non-heparin anticoagulant with transition to a DOAC during HIT-associated thrombocytopenia). Our primary end point was occurrence of objectively documented thrombosis during DOAC therapy for acute HIT. We found that recovery without new, progressive, or recurrent thrombosis occurred in all 10 Hamilton patients with acute HIT treated with rivaroxaban. Data from the literature review plus these new data identified a thrombosis rate of 1 of 46 patients (2.2%; 95% CI, 0.4%-11.3%) in patients treated with rivaroxaban during acute HIT (group A, n = 25; group B, n = 21); major hemorrhage was seen in 0 of 46 patients. Similar outcomes in smaller numbers of patients were observed with apixaban (n = 12) and dabigatran (n = 11). DOACs offer simplified management of selected patients, as illustrated by a case of persisting (autoimmune) HIT (>2-month platelet recovery with inversely parallel waning of serum-induced heparin-independent serotonin release) with successful outpatient rivaroxaban management of HIT-associated thrombosis. Evidence supporting efficacy and safety of DOACs for acute HIT is increasing, with the most experience reported for rivaroxaban. (*Blood*. 2017;130(9):1104-1113)

Introduction

Heparin-induced thrombocytopenia (HIT) is an acquired prothrombotic disorder that usually requires treatment with a rapid-acting, non-heparin anticoagulant.[1-3] To date, treatment options during acute HIT have focused on parenteral anticoagulants, either on-label, such as argatroban or (in non-US jurisdictions) danaparoid, or off-label, such as fondaparinux or bivalirudin.[1-6] When longer-term anticoagulation is required, usually because of the presence of HIT-associated thrombosis, transition is often made from parenteral anticoagulation to a vitamin K antagonist (VKA) such as warfarin after platelet count recovery. (Earlier transition to VKA therapy is avoided because of increased risk of warfarin-induced microthrombosis during acute HIT.[3,7])

Direct oral anticoagulants (DOACs) such as the direct factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) or the direct thrombin inhibitor dabigatran are attractive treatment options for HIT[8-11] for several reasons. First, there is no potentially deleterious immunologic interaction between these agents and HIT antibodies.[12-14] Second, unlike VKAs, DOACs have a rapid onset of action and do not cause reductions in protein C natural anticoagulant activity, suggesting that they may be useful during the acute phase of HIT.[15] Third, DOACs should also be effective during longer-term anticoagulation after platelet count recovery, thus avoiding the risk and expense of transition from parenteral to oral VKA anticoagulation. Transition to VKA therapy increases cost[16] because of the need to await platelet count recovery,[3] and thus a longer hospitalization to administer an intravenous anticoagulant such as argatroban.

We recently reported a prospective observational study[17] that described the use of rivaroxaban for treatment of serologically confirmed HIT. Although the results were encouraging, the trial was closed prematurely because of slow patient recruitment. On the basis of our positive trial experience, some clinicians in our medical community have continued to use rivaroxaban for treating patients with acute HIT. This gave us the opportunity to report on the subsequent posttrial experience with this agent in additional patients.

HIT treatment can be divided into sequential but distinct phases,[18] including acute HIT (HIT with thrombocytopenia) and subacute HIT (HIT soon after platelet count recovery), because the high initial prothrombotic risk (initial thrombosis rate, up to 5% per day) progressively lessens during platelet count recovery.[19,20] Accordingly,

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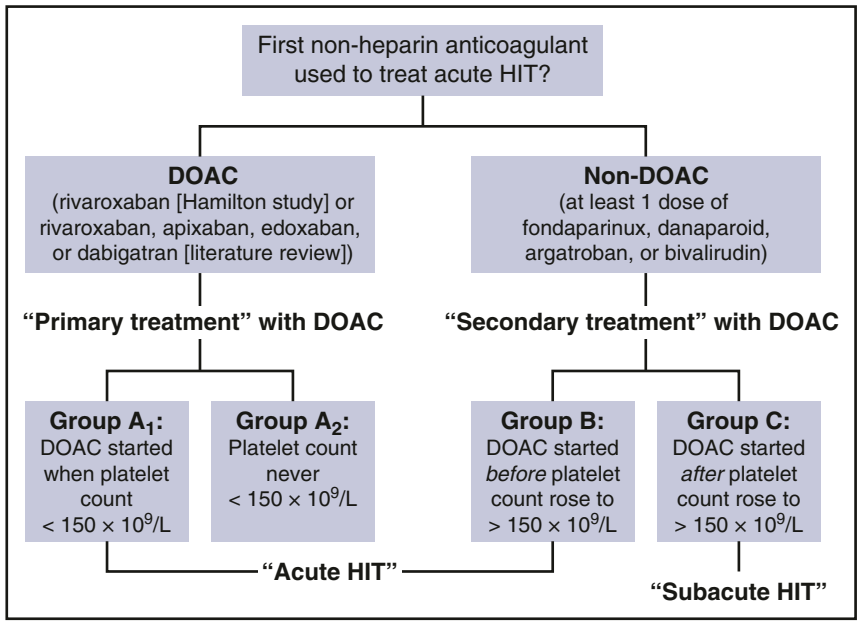

Figure 1. Classification into HIT treatment phase groups A (subgroups A_1 and A_2), B, and C.

we evaluated HIT treatment outcomes with DOAC therapy on the basis of whether the DOAC was the initial non-heparin anticoagulant selected to treat HIT (ie, primary therapy of acute HIT) or whether a switch was made from initial treatment with a standard HIT drug to DOAC therapy while the patient was still thrombocytopenic (ie, secondary therapy of acute HIT), or whether transition to a DOAC occurred only after platelet count recovery (ie, secondary therapy of subacute HIT). In theory, the risk of poor outcomes and adverse events of DOAC therapy for treating HIT, whether thrombotic (new, progressive, recurrent) or hemorrhagic, would be expected to be highest during acute HIT. Therefore, we were mainly interested in patients who received a DOAC for primary or secondary treatment of HIT during acute thrombocytopenia, although we also analyzed outcomes in patients who received a DOAC for subacute HIT.

The risk of thrombosis is highest among patients who have a true diagnosis of HIT vs non-HIT thrombocytopenia.[21] Thus we used a clinical-pathological approach (defined below) for local patients to confirm their diagnosis of HIT on the basis of laboratory detection of anti-PF4/heparin antibodies with platelet-activating properties. Although such strict laboratory criteria could not always be used for patients in our literature review, we sought to ensure that analyzed patients could be classified as having probable HIT.

The purpose of our study was first to determine the frequency of thrombotic events and major bleeding events for patients with a probable diagnosis of HIT who were treated with rivaroxaban in Hamilton, and second to review the literature on DOAC therapy for patients with a probable diagnosis of HIT, focusing on patients who received DOAC therapy during acute HIT. In addition, we analyzed these data separately for the different DOACs (rivaroxaban, apixaban, edoxaban, dabigatran).

Methods

Identification of patients with HIT treated with rivaroxaban in Hamilton

We used records from the McMaster Platelet Immunology Laboratory to identify patients at 4 Hamilton acute care hospitals who tested positive for HIT antibodies after January 1, 2015, on the basis of (1) positive immunoglobulin G–specific anti-PF4/heparin enzyme immunoassay[22] and (2) positive serotonin-release assay (SRA), with at least 50% serotonin release (means at 0.1 and 0.3 U/mL heparin).[23] Medical and laboratory records of these patients were reviewed to determine whether they had a clinical picture consistent with HIT (ie, 4Ts score of at least 4 points) and with no diagnosis more compelling than HIT. This clinical-pathological framework for diagnosis of HIT follows the recommendations of a working group of the International Society on Thrombosis and Haemostasis.[24] The choice of agent used to treat HIT in Hamilton was at the discretion of the individual physician.

Classification into HIT treatment phase groups A (subgroups A_1 and A_2), B, and C

We used the following classification of patient treatment groups for the Hamilton patients who received rivaroxaban to treat HIT and for the patients in our literature review (Figure 1). Patients were classified as treatment group A if a DOAC was used as primary therapy for HIT (ie, the DOAC was the first non-heparin anticoagulant used for treatment of acute HIT). Patients were further subclassified into subgroup A_1 if the DOAC was started while the patient was still thrombocytopenic (platelet count $<150 \times 10^9$/L) or subgroup A_2 if the DOAC was started as the primary anticoagulant but the platelet count never fell below 150×10^9/L. Note that patients in subgroup A_2 include 3 Hamilton patients in whom HIT was suspected because of adrenal hemorrhagic necrosis, which is an indicator of potential HIT-associated adrenal vein thrombosis,[1] despite the absence of thrombocytopenia as conventionally defined by a threshold platelet count of 150×10^9/L. Such patients presumably still have a degree of hypercoagulability, so it seemed reasonable to classify these patients as a subgroup of group A.

Patients were classified as group B if during treatment of acute HIT at least 1 dose with 1 or more non-heparin anticoagulants other than a DOAC was given (eg, fondaparinux, danaparoid, argatroban, bivalirudin) but in whom transition to secondary treatment with a DOAC occurred before the platelet count increased to above 150×10^9/L. We also classified as group B 1 patient (literature review) whose platelet count (154×10^9/L) was only marginally above 150×10^9/L and in whom the preceding non-heparin anticoagulant (argatroban) was given for only 2 days. We used the descriptive term "acute HIT" to describe patients within groups A_1, A_2, or B.

Patients were classified as group C if they received treatment with 1 or more non-heparin anticoagulants other than a DOAC and in whom transition to secondary treatment with a DOAC occurred only after the platelet count had recovered to $\geq 150 \times 10^9$/L; all of these patients had received initial non-DOAC/non-heparin anticoagulation for at least 3 days. The descriptive term "subacute HIT" was used to describe patients in group C.

Table 1. Characteristics and outcomes of 16 Hamilton patients with HIT treated with rivaroxaban

Patient age (years)	Sex	4Ts score (points)	EIA-IgG (OD units)	Serotonin-release assay peak % release	Patient clinical setting	HIT-associated thrombosis	Platelet count at rivaroxaban start	Anticoagulant before rivaroxaban	Rivaroxaban dosing (at least for the first 30 days)	Days to platelet recovery	Study events*
Group A_1											
66	F	6	1.67	90	CA-DVT	No	107	None	20 mg once per day ≥30 days	8	None
79	F	5	2.15	97	CA-PE	No	78	None	15 mg twice per day ×3 weeks; then 20 mg ≥30 days	3	None
60	F	5	3.07	98†	Multiple myeloma flush‡	No	25	None	15 mg twice per day ×6 days; then 20 mg once per day ≥30 days	17	None
64	F	8	2.35	100†	Multiple myeloma flush‡	Upper limb DVT	35	None	15 mg twice per day ×3 weeks; then 20 mg once per day ≥30 days	12	None
94	F	7	2.48	97	Hip fracture thromboprophylaxis§	Lower limb DVT	56	None	15 mg twice per day ×3 weeks; then 20 mg once per day ≥30 days	4	None
62	M	6	1.66	92	CA-DVT	No	49	None	20 mg once per day ≥30 days	3	None
72	M	7	2.08	100†	General surgery thromboprophylaxis	PE	86	None	15 mg twice per day ×3 weeks; then 20 mg once per day ≥30 days	4	None
Group A_2											
83	F	6	2.17	95	Hip fracture thromboprophylaxis§	Bilateral adrenal hemorrhage	415	None	10 mg once per day ≥30 days	NA	None
Group B											
54	F	6	2.10	100†	CA-DVT/PE	No	64	Fondaparinux ×1 day	15 mg twice per day ×3 weeks; then 20 mg once per day ×3 days, then 10 mg once per day ≥30 days (chemotherapy-induced thrombocytopenia)	7	None
69	F	8	2.48	100†	Post–coronary artery bypass grafting‖	Yes	73	Fondaparinux ×4 days	15 mg twice per day ×12 weeks; then 20 mg once per day ≥30 days (see Figure 2)	60	None

All 16 patients tested positive by immunoglobulin G (IgG)–specific EIA (median, 2.26 optical density [OD] units; range, 1.11-3.07 OD units) and by polyspecific EIA-IgGAM (median, 3.05 OD units; range, 1.55-4.11 OD units) (individual data for the EIA-IgGAM not shown). Of the 43 SRA-positive patients with probable HIT identified in the 3 Hamilton hospitals during the time frame of this study, 16 received rivaroxaban, and 10 could have received rivaroxaban (but were treated with an alternative anticoagulant, most often fondaparinux). The remaining 17 patients were ineligible to receive rivaroxaban (renal insufficiency, n = 7; intubated/critically ill, n = 5; withdrawal of care or death before SRA result became available, n = 4; treatment with phenytoin, n = 1). All patients in groups A and B were started on at least 20 mg/d (ie, 10 mg or 15 mg twice per day or 20 mg once per day), although the A_2 patient was started on 10 mg/day (reflecting adrenal hemorrhage). Three of the six group C patients received 10 mg/d, with the remaining patients receiving larger doses.

CA-DVT, cancer-associated deep vein thrombosis; CA-PE, cancer-associated pulmonary embolism; DVT, deep vein thrombosis; EIA-GAM, polyspecific EIA that detects anti-PF4/polyanion antibodies of IgG, IgA, and/or IgM isotypes (PF4 Enhanced; Immucor GTI Diagnostics, Waukesha, WI); F, female; M, male; NA, not applicable; OD, optical density; PE, pulmonary embolism.

*Study events include 30-day thrombosis event rate, thrombosis while receiving rivaroxaban, and major bleeding while receiving rivaroxaban (all 16 patients had follow-up until at least 30 days after starting rivaroxaban).

†Indicates possible presence of heparin-independent (autoimmune) HIT antibodies, as shown by serotonin-release >50% even in the absence of heparin (ie, at 0 U/mL unfractionated heparin [buffer control]).

‡Multiple myeloma patients who were exposed to heparin only through heparin flushes for apheresis catheter management during stem cell harvesting for planned autologous stem cell transplantation.

§Includes preoperative unfractionated heparin followed by postoperative low-molecular-weight heparin.

‖Performed using cardiopulmonary bypass.

Table 1. (continued)

Patient age (years)	Sex	4Ts score (points)	EIA-IgG (OD units)	Serotonin-release assay peak % release	Patient clinical setting	HIT-associated thrombosis	Platelet count at rivaroxaban start	Anticoagulant before rivaroxaban	Rivaroxaban dosing (at least for the first 30 days)	Days to platelet recovery	Study events*
Group C											
55	F	5	2.49	95	Post–abdominal aortic aneurysm thromboprophylaxis	No	163	Fondaparinux ×5 days	10 mg once per day ×17 days	NA	None
78	M	6	2.89	97†	General surgery thromboprophylaxis	DVT	203	Argatroban ×3 days; Fondaparinux ×51 days	20 mg once per day ≥30 days	NA	None
56	F	5	1.28	84	Medical prophylaxis	No	332	Fondaparinux ×11 days	10 mg once per day ≥30 days	NA	None
92	F	6	2.40	96	Hip fracture thromboprophylaxis§	No	159	Fondaparinux ×7 days	10 mg once per day ≥30 days	NA	None
72	M	5	1.11	91	Post–coronary artery bypass grafting‖	No	192	Fondaparinux ×5 days	20 mg once per day ≥30 days	NA	None
74	M	6	2.82	97	Post–aortic valve replacement‖	No	361	Fondaparinux ×10 days	15 mg twice per day ×3 weeks; then 20 mg ≥30 days	NA	None

All 16 patients tested positive by immunoglobulin G (IgG)–specific EIA (median, 2.26 optical density [OD] units; range, 1.11-3.07 OD units) and by polyspecific EIA-IgGAM (median, 3.05 OD units; range, 1.55-4.11 OD units) (individual data for the EIA-IgGAM not shown). Of the 43 SRA-positive patients with probable HIT identified in the 3 Hamilton hospitals during the time frame of this study, 16 received rivaroxaban, and 10 could have received rivaroxaban (but were treated with an alternative anticoagulant, most often fondaparinux). The remaining 17 patients were ineligible to receive rivaroxaban (renal insufficiency, n = 7; intubated/critically ill, n = 5; withdrawal of care or death before SRA result became available, n = 4; treatment with phenytoin, n = 1). All patients in groups A and B were started on at least 20 mg/d (ie, 10 mg or 15 mg twice per day or 20 mg once per day), although the A_2 patient was started on 10 mg/day (reflecting adrenal hemorrhage). Three of the six group C patients received 10 mg/d, with the remaining patients receiving larger doses.

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‡Multiple myeloma patients who were exposed to heparin only through heparin flushes for apheresis catheter management during stem cell harvesting for planned autologous stem cell transplantation.

§Includes preoperative unfractionated heparin followed by postoperative low-molecular-weight heparin.

‖Performed using cardiopulmonary bypass.

For Hamilton patients within groups B and C, we recorded the dosing and duration of the initial non-heparin anticoagulant(s) prior to starting rivaroxaban as well as the platelet count at transition. We also recorded dosing of rivaroxaban.

Approval for this study was provided by the Hamilton Integrated Research Ethics Board in accordance with the Declaration of Helsinki.

Study outcomes

Similar to our previous study,[17] the primary outcome measure was the 30-day incidence of new symptomatic, objectively confirmed venous and arterial thromboembolism in the cohort of patients with confirmed HIT within group A_1, A_2, or B. (In our previous prospective cohort study, there were no patients included with confirmed HIT who would have been classified as group C). Secondary objectives included the incidence of symptomatic thromboembolism while being treated with rivaroxaban and the following outcomes while being treated with rivaroxaban: incidence of venous and arterial thromboembolism, incidence of major bleeding, and time to platelet recovery. Major bleeding was defined per International Society on Thrombosis and Haemostasis criteria.[25] Time to platelet count recovery was defined as days to achieve platelet count $\geq 150 \times 10^9$/L determined directly (from daily in-patient measurements) or indirectly (through extrapolation when the platelet count normalized during outpatient follow-up).

Literature review and evaluation

We performed a systematic review of the literature for published reports on the use of DOACs for the treatment of 1 or more patients with HIT. We searched the MEDLINE electronic database (English and non-English language) from January 2007 to March 2017 using the terms "heparin-induced thrombocytopenia," "rivaroxaban," "apixaban," "dabigatran," "edoxaban," and "direct oral anticoagulants." We also manually reviewed the reference lists of all review articles that discussed DOAC therapy of HIT. We contacted corresponding authors to clarify details regarding diagnosis or treatment if those were not reported. Wherever possible, we tried to analyze data at the patient level. When patients were reported in aggregate form, we included them only if the study methods indicated that all or most of the included patients were probable HIT. We excluded patients who did not seem to have HIT on the basis of the information provided, or when insufficient data were available. In almost all separately assessed patients, a diagnosis of probable HIT could be made on the basis of the 4Ts score (4 points or greater) together with corroborating laboratory detection of HIT antibodies, but we also accepted patients whose clinicians practiced in a setting in which laboratory testing for HIT antibodies was not available, but sufficient clinical details were presented to make the diagnosis of HIT probable (ie, 4Ts score of 6 points or greater, and an alternate non-HIT diagnosis was unlikely). We also excluded patients who were SRA positive but enzyme immunosorbent assay (EIA) negative, given that such patients most likely represent false-positive SRA results.[26] All patients, including the Hamilton patients and those reported in the literature review, were reviewed by all 3 authors, and any discrepancies were resolved by consensus.

Analysis plan and statistics

We determined the 30-day thrombotic event rate (or until last follow-up indicated, if less than 30 days), the thrombotic event rate while receiving DOAC therapy, and the major bleeding rate (while receiving DOAC therapy) for patients who received a DOAC for primary treatment of acute HIT (ie, groups A_1 and A_2) or for secondary treatment of acute HIT (group B). Our main analysis was for patients who received a DOAC for acute HIT (ie, analysis of combined groups A_1, A_2, and B), but we also reviewed the experience for patients with subacute HIT (group C).

Results

Characteristics and treatment outcomes of the Hamilton HIT-positive patients

Sixteen patients were identified in Hamilton who were treated with rivaroxaban for HIT (of a total of 43 SRA-positive patients with probable HIT) since January 15, 2015 (Table 1). All patients treated with rivaroxaban had a 4Ts score of 4 points or greater (median, 6 points), a positive immunoglobulin G–specific EIA (median, 2.26 optical density [OD] units; range, 1.11-3.07 OD units), and a strongly positive SRA (>80% serotonin release). Six of the patients (37.5%) had HIT-associated thrombosis; if thrombosis before HIT occurrence was also included, then 10 (62.5%) of the 16 patients had thrombosis. Eight of the patients (50.0%) received rivaroxaban as primary anticoagulant therapy for HIT, 7 of whom were thrombocytopenic at the start of rivaroxaban (median platelet count, 56×10^9/L; range, 25 to 107×10^9/L) and thus were classified as group A_1; an eighth patient who received rivaroxaban as primary therapy never had thrombocytopenia as conventionally defined and had HIT recognized during investigations of bilateral adrenal hemorrhages (group A_2).

Two additional patients were classified as group B, because they began treatment with rivaroxaban while they were thrombocytopenic but after initially receiving a brief treatment course of fondaparinux. One patient received a single 7.5-mg injection of fondaparinux, with rivaroxaban started the next day when the platelet count was 64×10^9/L. Another post–cardiac surgery patient who was diagnosed as an outpatient with delayed-onset HIT[27] complicated by pulmonary embolism (based on the timing and clinical course of thrombocytopenia, pleuritic chest pain with high-probability ventilation-perfusion lung scanning, and the laboratory detection of autoimmune-like HIT antibodies featuring strong serum-induced platelet activation even in the absence of heparin) was re-admitted and given four 10-mg injections of fondaparinux (patient weight >100 kg); because the patient desired out-of-hospital treatment with an oral anticoagulant, she was discharged to home and was given rivaroxaban (platelet count at discharge, 74×10^9/L). Her clinical course (summarized in Figure 2) showed gradual platelet count recovery that inversely paralleled the decline in serum-induced platelet activation (percent serotonin release at 0 U/mL heparin [buffer control]). She remained thrombosis and hemorrhage free while receiving rivaroxaban (last follow-up, 136 days after starting rivaroxaban).

The remaining 6 patients began rivaroxaban only as secondary therapy and after recovery of the platelet count to at least 150×10^9/L (ie, they were classified as group C). Each of these 6 patients received at least 1 month of rivaroxaban therapy.

Remarkably, none of the 16 patients developed a thrombotic event at the 30-day follow-up or while receiving rivaroxaban (median duration of rivaroxaban treatment, 3 months; range, 17 days to >1 year). None of the 16 patients required limb amputation, none developed major hemorrhage while receiving rivaroxaban, and none died (up to the 3-month follow-up).

Literature review

Identifying and classifying HIT patients treated with a DOAC. Excluding the 16 patients reported in this study, our literature review identified 73 patients from 25 articles reported as having received a DOAC for treatment of acute or subacute HIT.[17,28-51] However, 9 patients[30,48-51] were excluded because they did not seem to have a probable diagnosis of HIT; 5 patients tested negative for anti-PF4/heparin antibodies[30,40]; 1 patient had subclinical anti-PF4/heparin antibody seroconversion (as acknowledged by the authors)[48]; 1 patient had onset of thrombocytopenia too early to be a result of HIT (and testing for HIT antibodies was not performed)[49]; and 2 other patients had insufficient information available to conclude that HIT was the probable diagnosis.[50,51] The remaining 64 patients were included in our analysis.

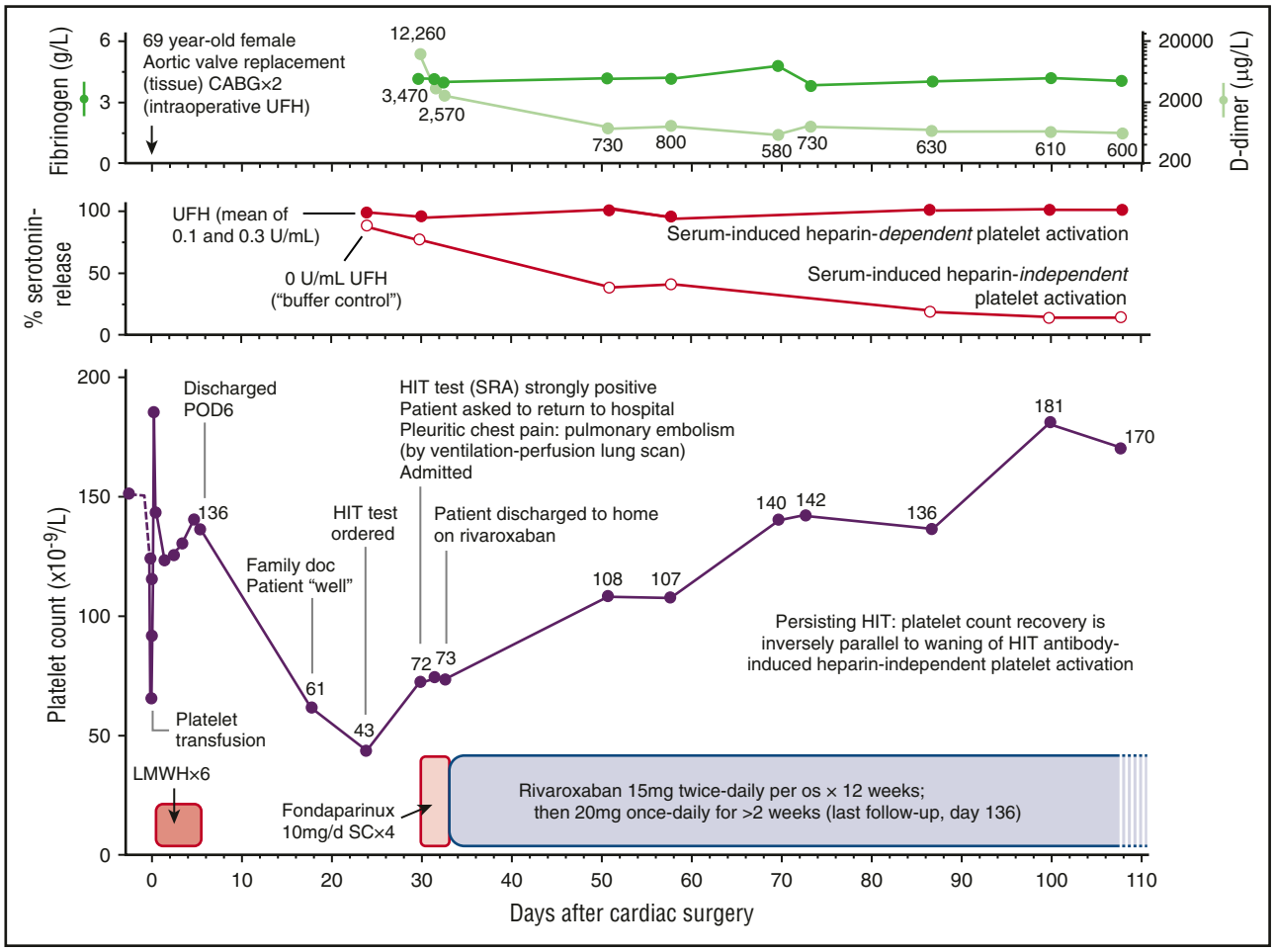

Figure 2. Patient with autoimmune HIT (delayed-onset and persisting HIT) who was switched from fondaparinux to rivaroxaban during acute thrombocytopenia (group B). The gradual recovery in platelet count inversely paralleled the gradual decline in serum-induced percent serotonin release at 0 U/mL heparin (buffer control; open circles), a phenomenon that has previously been reported in patients with autoimmune HIT.[28] CABG, coronary artery bypass grafting; LMWH, low-molecular-weight heparin (dalteparin); POD, postoperative day; SC, subcutaneous; UFH, unfractionated heparin.

For all but 1 article (which described 20 patients with antibody-positive HIT),[30] the patients were presented individually, allowing evaluation of whether HIT was likely present or not. However, in the report describing 20 patients (each of whom had either a positive EIA or a positive SRA) for whom the data were presented in aggregate fashion, all 20 patients received secondary treatment with a DOAC but after receiving a mean of only 32 hours of argatroban; moreover, the mean platelet count at initiation of DOAC therapy was approximately 90 × 10^9/L (Mohsen Sharifi, personal communication) and thus we classified the 20 patients as group B.

Of the 80 patients identified as having received a DOAC for treatment of probable HIT (including the 16 Hamilton patients newly reported here), we were primarily interested in the 69 patients who were classified as either group A_1 (n = 25), group A_2 (n = 5), or group B (n = 39), of which 46 patients (66.6%) were treated with rivaroxaban, 12 (17.4%) with apixaban, none with edoxaban, and 11 (15.9%) with dabigatran.

Patients treated with rivaroxaban. Table 2 summarizes the experience with rivaroxaban for treatment of acute HIT, including the Hamilton experience, for patients who received this DOAC as primary therapy (groups A_1 and A_2) or as secondary therapy in which transition occurred while the patient still had HIT-associated thrombocytopenia (group B). The data are organized per article. We identified 46 patients with probable HIT who were treated with rivaroxaban: 25 as primary therapy (A_1, n = 21; A_2, n = 4) and 21 as secondary therapy started during thrombocytopenia (B, n = 21). Only 1 (2.2%) of the 46 patients developed a possible progression of thrombosis (central venous catheter-associated DVT that resolved completely after removal of the catheter and during continued therapy with rivaroxaban). None (0%) of the 46 patients experienced a major bleed while receiving rivaroxaban.

For the 21 patients in group B who received rivaroxaban after transition from another non-heparin anticoagulant, the median duration of preceding non-heparin anticoagulant was only 2 days (range, 1-16 days), with 18 of 21 patients receiving 3 days or fewer of preceding non-heparin anticoagulation; for the 3 patients who received longer preceding non-heparin anticoagulation (for 4 days [Table 1], 10 days,[28] and 16 days[34]), the platelet counts were all $<75 \times 10^9$/L at DOAC start, and in 2 of the patients (Figure 2),[28] the presence of strong autoimmune-like HIT antibodies was documented, which produced strong platelet activation even in the absence of heparin (persisting HIT).

Patients treated with apixaban or dabigatran. Table 3 lists probable HIT patients treated with apixaban or dabigatran as primary treatment or as secondary treatment during thrombocytopenia (none of the patients were treated with edoxaban). A total of 23 patients were treated with either apixaban (n = 12) or dabigatran (n = 11).

Table 2. Literature review of rivaroxaban for probable HIT (including new patients reported in this article): primary or secondary treatment during acute HIT (groups A_1, A_2, and B)

Study author	Reference	No. of patients	Group			Median platelet count at rivaroxaban start	HIT-associated thrombosis*		Outcome			
			A_1	A_2	B				Thrombosis		Bleed	
							No.	%	No.	%	No.	%
Rivaroxaban-Hamilton experience												
Linkins et al	17	12	3	2	7	56	6		1		0†	
This study		10	7	1	2	64	5		0		0	
Rivaroxaban-other (non-Hamilton) centers												
Kopolovic and Warkentin	28	1	0	0	1	30	0		0		0	
Ng et al, Ong et al‡	29, 36	9	9	0	0	64	9		0		0	
Sharifi et al§	30	9‡	0	0	9	90‡	4		0		0	
Hantson et al	31	1	0	0	1	30	1		0		0	
Abouchakra et al	32	1	1	0	0	25	1		0		0	
Sartori et al	33	1	0	1	0	150	1		0		0	
Casan et al	34	1	0	0	1	48	1		0		0	
Samoš et al	35	1	1	0	0	65	1		0		0	
Summary		46	21	4	21	73	29/46‖	63.0	1/46	2.2	0/46	0

Information on clinical setting was available for 37 patients (ie, all but 9 patients from 1 of the studies[30]): post–cardiac surgery/post–vascular surgery/post–percutaneous coronary intervention (n = 10); treatment of venous thromboembolism (n = 9); post–orthopedic surgery (n = 8); hemodialysis (n = 4); heparin flushes for catheters (n = 3); medical thromboprophylaxis (n = 2); and general surgery thromboprophylaxis (n = 1). One patient[17] had limb amputation (frequency, 1 [2.2%] of 46); this patient reportedly had limb ischemia secondary to inoperable arterial thrombosis before starting rivaroxaban.

*Thrombus that occurred in association with HIT, not thrombosis present before HIT.

†Bleed that occurred 9 days after stopping rivaroxaban is not included here.

‡The articles by Ng et al and Ong et al are combined because the 3 patients first reported by Ng et al are also included among the 9 patients reported by Ong et al; the median platelet count data were provided by Ng and Ong (Heng Joo Ng and Shin-Yeu Ong, Singapore General Hospital, Singapore, Singapore, e-mail, 4 January 2017).

§Aggregate data only, rather than data for individual patients (per Sharifi et al); the estimated mean platelet count at the start of DOAC was $\sim 90 \times 10^9$/L; in addition, 2 of the 11 patients who received rivaroxaban tested negative for HIT antibodies, and thus are excluded in this table.

‖Most of the HIT-associated thrombotic events were venous; however, 3 patients had 1 or more arterial thrombi (bilateral lower limb,[17] radial artery,[31] or carotid artery/saphenous vein graft to coronary artery[32]) of whom 2 patients were shown to have clinical improvement along with partial resolution of arterial thrombi (the third patient did not have repeat imaging performed).

Only 1 patient had a possible thrombotic event while receiving a DOAC (multiple strokes, which might have been present before starting dabigatran).[45] None of the patients experienced major bleeding.

Patients with probable HIT transitioned to a DOAC after platelet count recovery. Including the 6 Hamilton patients in group C (Table 1), we identified a total of 11 patients who received a DOAC after platelet count recovery from HIT (rivaroxaban, n = 7; apixaban, n = 3; edoxaban, n = 0; dabigatran, n = 1).[40,47] None of the patients developed a thrombotic problem. One patient had a major bleed secondary to known varices.

Discussion

We found that the continuing use of rivaroxaban in Hamilton further supports the efficacy of this DOAC for treating acute HIT. We identified 10 patients with strong clinical and laboratory evidence for HIT who received rivaroxaban for treatment of acute HIT. None of these 10 patients developed recurrent thrombosis, limb amputation, major bleeding, or died (up to the 3-month follow-up). In our previous study, 1 of 12 patients who received rivaroxaban for HIT had a questionable thrombotic event. Of note, this patient had central venous catheter-associated right upper-limb DVT that may have extended while receiving rivaroxaban; however, after subsequent removal of the central venous catheter and during continuing treatment with rivaroxaban, the patient's HIT resolved completely, and follow-up ultrasound showed complete resolution of DVT. Thus, all 22 patients in Hamilton with acute HIT who were treated with rivaroxaban (ie, 12 in our prospective study; 10 in our retrospective follow-up study reported here) had successful outcomes. Although 1 (4.5%) of the 22 Hamilton patients underwent limb amputation, this patient was judged to have had irreversible limb ischemia before rivaroxaban was initiated. Furthermore, this frequency of HIT-associated limb amputation (~5%) is similar to that reported in the literature for patients treated with fondaparinux (~6%),[2] danaparoid (~5%),[52] and argatroban (~8%).[53]

Our favorable experience with rivaroxaban is supported by our review of the literature. Including the new patients in Hamilton (this study), as well as our previous published experience with the DOACs,[17] there have now been 46 patients with probable HIT who received rivaroxaban during acute thrombocytopenia as either primary or secondary treatment (Table 2). The only reported thrombotic event was the aforementioned Hamilton patient with questionable DVT progression (who ultimately had complete resolution of thrombosis on continued rivaroxaban treatment). Thus, the frequency of new, progressive, or recurrent thrombosis is only 2.2% (95% CI, 0.4%-11.3%; 1 of 46 patients). The major bleeding rate was 0%. Although there are fewer data for apixaban and dabigatran, the experience with these DOACs is also favorable (Table 3).

Moreover, the favorable experience was seen in different clinical settings of HIT: of the 49 patients for whom the clinical setting was reported (see legends for Tables 2 and 3), 11 (22.4%) were post–cardiovascular surgery or post–percutaneous coronary intervention, 11 (22.4%) were post–orthopedic surgery, 14 (28.6%) were being treated for venous thromboembolism, 5 (10.2%) had complicated use of heparin given for hemodialysis, and 8 (16.3%) were receiving heparin thromboprophylaxis, including heparin flushes for catheter maintenance. Although most patient groups likely represented a selected subgroup of patients deemed suitable for DOAC therapy, for the study from Singapore of 9 patients,[29,36] treatment with rivaroxaban represented their main therapeutic option, because standard HIT agents (fondaparinux, argatroban) were not available in that jurisdiction.

Table 3. Literature review of apixaban or dabigatran for probable acute HIT (including new patients reported in this article): primary or secondary treatment (groups A_1, A_2, and B)

			Group				HIT-associated thrombosis*		Outcome: Thrombosis		Outcome: Bleed	
Study author	Reference	No. of patients	A_1	A_2	B	Median platelet count at DOAC start	No.	%	No.	%	No.	%
Apixaban												
Sharifi et al†	30	5	0	0	5	90‡	1		0		0	
Larsen et al	37	1	1	0	0	112	0		0		0	
Delgado-García et al§	38, 39	1	1	0	0	25	1		0		0	
Kunk et al	40	5	0	0	5	111	3		0		0	
Total		12	2	0	10	90‡	5/12‖	41.7	0/12	0	0/12	0
Dabigatran												
Sharifi et al†	30	6	0	0	6	90‡	2		0		0	
Anniccherico et al	41, 42	1	0	0	1	120	1		0		0	
Mirdamadi§	43	1	1	0	0	32	1		0		0	
Tardy-Poncet et al	44	1	0	0	1	56	0		0		0	
Noel et al	45	1	0	1	0	216	1		1¶		0	
Bircan and Alanoglu§	46	1	1	0	0	52	1		0		0	
Total		11	2	1	8	58	6/11‖	54.5	1/11	9.1	0/11	0

Information on clinical setting was available for 12 patients (ie, all but 11 patients from 1 of the studies[30]): post–cardiac surgery/post–vascular surgery (n = 1), treatment of venous thromboembolism (n = 5), post–orthopedic surgery (n = 3), hemodialysis (n = 1), medical thromboprophylaxis (n = 1), and periprocedural thromboprophylaxis (n = 1). No patients had limb amputation.

*Thrombus that occurred in association with HIT, not thrombosis present before HIT.

†Aggregate data only, rather than data for individual patients presented in this article.

‡Platelet count at start of DOAC estimated to be 90 (Mohsen Sharifi, Arizona Cardiovascular Consultants & Vein Clinic and A.T. Still University, e-mail, 5 February 2017).

§No laboratory testing for HIT antibodies was available; however, the patient was included because sufficient clinical information was provided to make a diagnosis of HIT (with associated HIT-related thrombosis) highly probable.

‖Most of the HIT-associated thrombotic events were venous (predominantly DVT and PE); however, 1 patient had HIT-associated non-ST-elevation myocardial infarction.[45]

¶Patient with essential thrombocythemia developed HIT with platelet count fall from 750 to 216 $\times$ 10^9/L; dabigatran was given for atrial fibrillation, as the clinicians initially deemed HIT to be unlikely; however, signs of stroke became evident shortly thereafter with computed tomography imaging confirming multiple cerebral infarcts; when the serotonin-release assay returned positive for HIT antibodies, dabigatran was switched to lepirudin.

The consistency of efficacy of DOAC therapy for acute HIT, despite the relatively small published numbers, is strikingly reminiscent of what was observed with fondaparinux several years ago. For example, in 2011, one of us (T.E.W.) presented a tabular summary of the experience with fondaparinux in patients with clinical and laboratory evidence of HIT (all of the patients were at least EIA positive); there were 52 patients reported (from 4 studies), of whom 34 (65%) had HIT-associated thrombosis.[2] Remarkably, none of the 52 patients had evidence of new, progressive, or recurrent thrombosis, data similar to what we observed with rivaroxaban (0 of 52 vs 1 of 46). In 2008, the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines suggested that fondaparinux was a reasonable treatment option for HIT, albeit as a weak (ie, grade 2C) recommendation based on retrospective observational data.[54] Today, fondaparinux has emerged as the most widely used non-heparin anticoagulant for treatment of HIT in several jurisdictions.[4,5] And although a more recent retrospective study of fondaparinux therapy for HIT reported a somewhat higher frequency of thrombotic events (7 [16%] of 44), those authors found that this frequency was not higher than that observed in propensity score–matched HIT patients treated in their institution with either danaparoid or argatroban (5 [25%] of 20). They thus concluded that fondaparinux had effectiveness and safety similar to that of the other 2 standard treatments for HIT.[5] Given the fixed-dose oral administration of DOACs and the simplicity of transition from in-patient to longer-term out-patient anticoagulation with these agents, it seems likely that DOAC therapy, like fondaparinux, could become a common off-label treatment for HIT.

Ironically, despite the status of argatroban as an approved anticoagulant treatment for HIT, data supporting its efficacy in patients with probable HIT on the basis of laboratory confirmation of HIT antibodies is lacking. The argatroban approval trials[55,56] performed in the 1990s enrolled patients on the basis of clinical suspicion of HIT alone (without requirement for a positive test for HIT antibodies), and although the frequency of antibody-positive status was reported to be only 57% in 1 of the studies,[55] the thrombotic event rate has not (to the best of our knowledge) been reported for the subgroup of patients likely to have had HIT on the basis of serologic detection of HIT antibodies. The aforementioned study by Kang et al[5] reported a thrombotic rate of 25% for patients treated with either danaparoid or argatroban but did not specify which patients with laboratory-confirmed HIT were treated with argatroban. The thrombosis rate was reported to be 10 (21%) of 47 for patients treated with argatroban in a larger group classified as having suspected HIT. However, similar data are not available for patients with rigorously confirmed HIT. Thus, despite the small numbers of patients with DOAC-treated HIT described in the literature, we believe that the published experience with these drugs may already exceed that published for argatroban. Moreover, there are several reports describing failure of argatroban therapy in patients with severe HIT complicated by coagulopathy in whom inappropriate dose interruption or reductions occurred because of partial thromboplastin time (PTT) confounding.[57,58] This problem of PTT confounding is not seen with DOACs, because DOAC dosing is not adjusted according to PTT, international normalized ratio, or other global coagulation assays.

Strengths of our study include the rigorous definition of HIT for the Hamilton patients (including the detection of platelet-activating antibodies by SRA), as well as a review of the literature conducted at the individual patient level. In addition, we focused our analysis on patients with acute HIT on the basis of starting DOAC therapy when the patient was thrombocytopenic. A major limitation of our study is the possibility that patients treated with DOAC represent a selected subgroup of HIT patients with an unusually favorable prognosis. We acknowledge that patients in the intensive care unit or those who have renal insufficiency are unlikely to receive DOAC therapy. Furthermore,

there may be reporting bias for the literature review (especially case reports). Nonetheless, the favorable experience with DOACs suggests that these agents are able to control the hypercoagulability of HIT and could be considered as an off-label option for treating this condition.

In conclusion, DOACs seem to be safe and effective for treatment of acute HIT, with the most experience reported for rivaroxaban. We recommend that clinicians consider reporting their experience with DOAC therapy for acute HIT, including detailed clinical and laboratory evidence supporting the diagnosis, to add to the emerging evidence.

Note added in proof

A new single-center retrospective study reporting on 12 patients with probable HIT who were treated with a DOAC (apixaban, n = 9; rivaroxaban, n = 3) during or soon after recovery from acute thrombocytopenia (5 as primary therapy, 7 as secondary therapy after initial argatroban) was recently published (Davis KA, Davis DO. *Eur J Haematol*. doi:10.1111/ejh.12921 [published ahead of print 3 July 2017]). All 12 patients had successful outcomes, including normal platelet counts at discharge and no thrombotic or bleeding complications; postdischarge follow-up information was not available.

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Authorship

Contribution: T.E.W. wrote the first draft of the manuscript; M.P. and L.-A.L. subsequently provided input; T.E.W., L.-A.L., and M.P. were responsible for reviewing patient files; and all authors reviewed and approved the final version of the manuscript.

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