Received: 9 May 2022 | Accepted: 18 July 2022

DOI: 10.1111/jth.15826

ORIGINAL ARTICLE

Temporal presentations of heparin-induced thrombocytopenia following cardiac surgery: A single-center, retrospective cohort study

Theodore E. Warkentin[1,2,3,4] | Jo-Ann I. Sheppard[1] | Richard P. Whitlock[5]

[1]Department of Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario, Canada

[2]Department of Medicine, McMaster University, Hamilton, Ontario, Canada

[3]Transfusion Medicine, Hamilton Regional Laboratory Medicine Program, Hamilton, Ontario, Canada

[4]Service of Benign Hematology, Hamilton Health Sciences, Hamilton, Ontario, Canada

[5]Department of Surgery, Division of Cardiac Surgery, McMaster University, Hamilton, Ontario, Canada

Correspondence
Theodore E. Warkentin, Hamilton Regional Laboratory Medicine Program, Room 1-270B, Hamilton General Hospital (Hamilton Health Sciences), 237 Barton St. East, Hamilton, ON L8L 2X2, Canada.
Email: twarken@mcmaster.ca

Abstract

Background: Heparin-induced thrombocytopenia (HIT) is an important adverse drug reaction that can occur postcardiac surgery. Preoperative exposure to unfractionated heparin (UFH) is common, raising the issue of how frequently cardiac surgery-associated HIT occurs after immunizing preoperative exposure to heparin.

Objective: To determine the frequency and clinical picture of HIT occurring within 4 days of cardiac surgery (early presentation) versus later presentations (typical, delayed).

Methods: We identified patients with laboratory-confirmed HIT following cardiac surgery over 30 years in a single cardiac surgery center. Three different clinical presentations of HIT were identified: typical (HIT-related platelet count fall beginning between postoperative days [PODs] 5–10), delayed (patients with falls after POD10 or who presented following hospital discharge), and early (established before POD5, including during cardiac surgery [acute intraoperative HIT]).

Results: Of 129 patients identified with HIT complicating cardiac surgery, 100 had typical and 16 had delayed presentation of HIT; only 13 patients (10.1%) presented with early HIT, all of whom had received exposure to UFH during the 10 days before cardiac surgery. No patient was identified in whom remote preoperative UFH exposure was implicated in explaining early HIT. Notably, five patients appeared to have had acute intraoperative HIT, without immediate adverse consequences.

Conclusions: Approximately 90% of patients with HIT after cardiac surgery appear to develop this complication due to immunization triggered by cardiac surgery; however, in approximately 10% of patients, early presentation during the first four PODs (or intraoperatively) can be explained by recent immunizing exposure to heparin.

KEYWORDS
cardiopulmonary bypass, heparin, platelet count, thrombocytopenia, thrombosis

Manuscript handled by: Matthew Rondina

Final decision: Matthew Rondina and 18-Jul-2022

1 | INTRODUCTION

Heparin-induced thrombocytopenia (HIT) is an immune reaction caused by platelet-activating antibodies that target the cationic protein, PF4, when its structure has been modified by heparin or other polyanions.[1–3] As a general rule, there is a minimum interval of 5 days between the administration of an immunizing heparin exposure and the beginning of the HIT-related platelet count fall, which reflects the minimum time needed to form clinically significant levels of heparin-dependent platelet-activating antibodies.[4–7] Moreover, HIT represents a "point immunization" event because most HIT-related platelet count falls occur in a narrow window between days 5 and 10 postexposure (day 0 = day of immunizing heparin exposure), even in patients in whom heparin administration is continued beyond postoperative day (POD) 10.[8] This characteristic profile of HIT, known as typical (or typical-onset) HIT, has been incorporated into scoring systems for HIT.[9,10]

Pioneering studies of HIT following cardiac surgery by Pouplard and colleagues[11–14] and other investigators[15–17] are consistent with intraoperative exposure to heparin during cardiac surgery representing the typical day 0 immunizing event, as shown by the characteristic HIT-related platelet count fall that begins during the POD5–10 window. Moreover, the oftentimes large (40%–60%)[18] early postoperative platelet count fall (resulting from fluid administration with hemodilution, and platelet losses to the cardiopulmonary bypass [CPB] device and wound hemostasis), with platelet count nadirs occurring on PODs 1–3, followed by subsequent platelet count recovery, means that when HIT occurs postcardiac surgery, it usually exhibits a biphasic platelet count decline.[6–8,12–15] Indeed, Pouplard and coworkers found that this biphasic platelet count decline profile predicted for HIT with high specificity in postcardiac surgery patients.[12]

Another feature of cardiac surgery, in comparison with many other patient populations that develop HIT, is a high frequency of exposure to heparin before cardiac surgery, either many months or years before (remote exposure), or in the recent preoperative period, or both.[6] This raises the possibility that in some patients the onset of HIT could be related to preoperative heparin exposure, rather than intraoperative or postoperative heparin administration.

In our current study, we wished to determine the various temporal presentations of HIT following cardiac surgery. In particular, we aimed to ascertain the proportion of patients who developed the typical picture of HIT (i.e., platelet count fall beginning during the POD5–10 window), as well as patients who developed HIT before and after this typical time period. Moreover, among patients who exhibited an early presentation of HIT (i.e., POD4 or sooner), we sought to identify the occurrence and timing of preoperative heparin exposure, and if present, to determine whether it was remote (more than 100 days ago), recent (10–100 days) or in the immediate preoperative period (within 10 days presurgery). Finally, because our study provided a relatively large number of patients with laboratory-documented HIT in one cardiac surgical center, it provided an opportunity to characterize the clinical picture of HIT in the postcardiac surgery patient population.

Essentials

- Timing of HIT postcardiac surgery could be influenced by preoperative heparin exposure.
- We found that 13/129 (10.1%) of HIT cases occurred within the first 4 days postcardiac surgery.
- All 13 patients with early-onset HIT had received heparin during the 10-day period pre-surgery.
- Very recent preoperative heparin exposure can explain early-onset HIT postcardiac surgery.

2 | PATIENTS AND METHODS

We performed a retrospective observational cohort study of patients identified as having postcardiac surgery HIT, from July 1, 1990, until December 31, 2021, based on: (1) positive testing by the serotonin-release assay (SRA; a test for platelet-activating antibodies)[19,20]; (2) positive testing by at least one PF4-dependent enzyme-immunoassay (EIA; test for anti-PF4/heparin antibodies); and (3) preceding cardiac surgery involving CPB performed at the Hamilton General Hospital (regional cardiac surgery center) (Study Flow Diagram, Figure 1). We used an in-house immunoglobulin G (IgG)-specific EIA[21] and a polyspecific commercial anti-PF4/polyvinyl sulfonate EIA (PF4 Enhanced, Immucor, Dartmouth, Nova Scotia).[22,23] Moreover, all patients were judged by the primary clinical investigator (T.E.W.) to have a clinical picture at least plausibly explained by HIT (generally, a platelet count fall bearing a temporal relationship to heparin administration, and without a more plausible clinical explanation [i.e., a 4Ts score of at least 4 points]).[9] We made a single exception to include a patient who tested repeatedly SRA-negative but who was previously judged to have had probable HIT[24] based on high clinical probability for HIT (per 4Ts), three strong positive PF4-dependent EIAs (the previously mentioned two EIAs), plus a commercial IgG-specific EIA (PF4 IgG assay, Immucor),[23] as well as positive results in two rapid immunoassays (latex immunoturbidimetric assay,[25] chemiluminescence immunoassay[26]). This exception was made to maintain consistency between this report and others from our center listing cases with a probable diagnosis of HIT postcardiac surgery.

The study was approved by the Hamilton Integrated Research Ethics Board (Project #11374).

2.1 | Data collection and descriptive analyses

Data were systematically collected, including platelet counts (presurgery baseline, early postoperative nadir [lowest on POD1-3], pre-HIT platelet count peak, HIT-related platelet count nadir), heparin exposures (including preoperative heparin exposures), objectively documented thrombotic events, survival to discharge (or transfer to another institution), limb amputation (or limb amputation

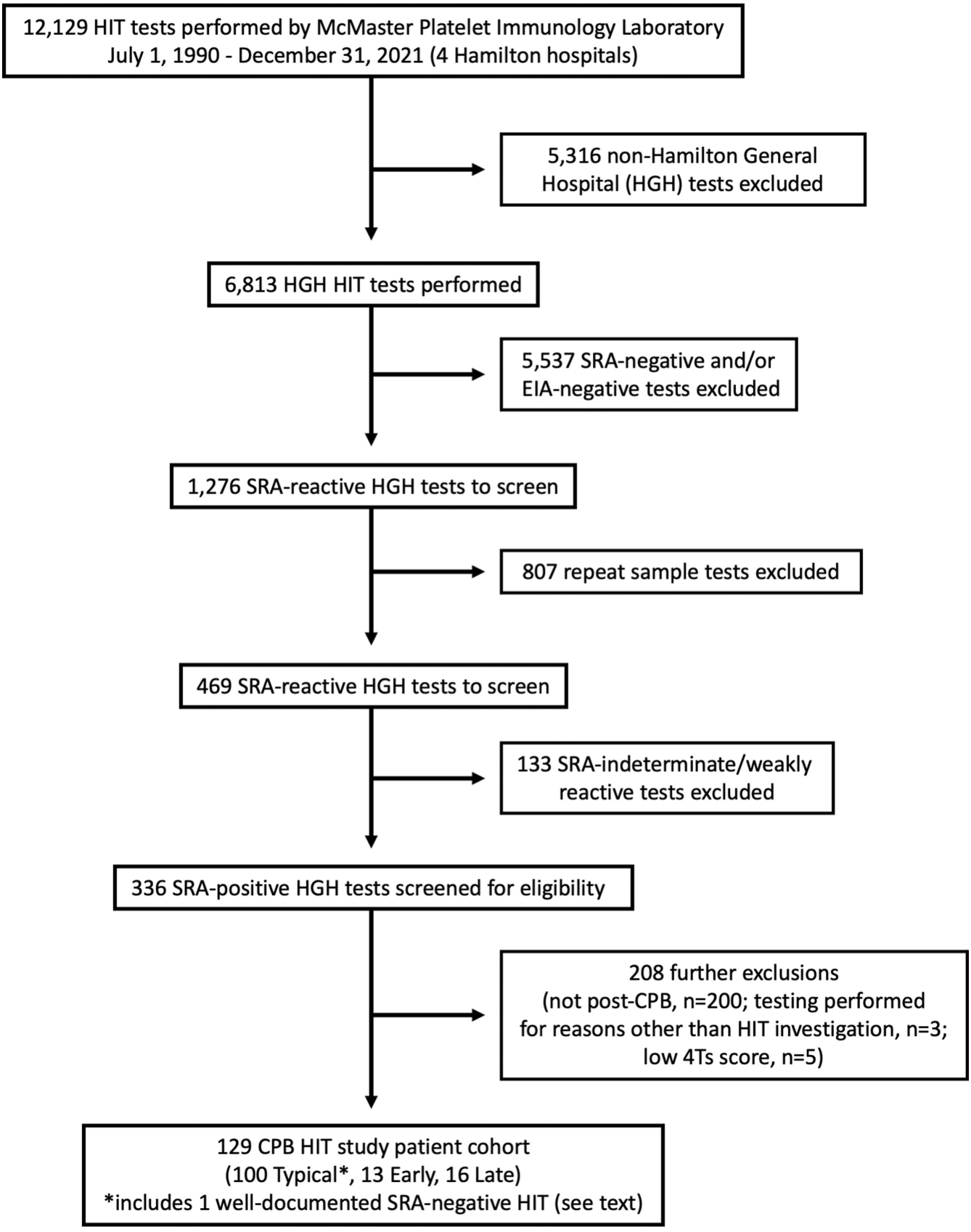

FIGURE 1 Study flow diagram. From an initial log of 12 129 blood samples investigated for HIT from four Hamilton hospitals, 129 postcardiac surgery patients from a single center were identified with likely HIT. Abbreviations: CPB, cardiopulmonary bypass (heart surgery); HIT, heparin-induced thrombocytopenia; SRA, serotonin-release assay.

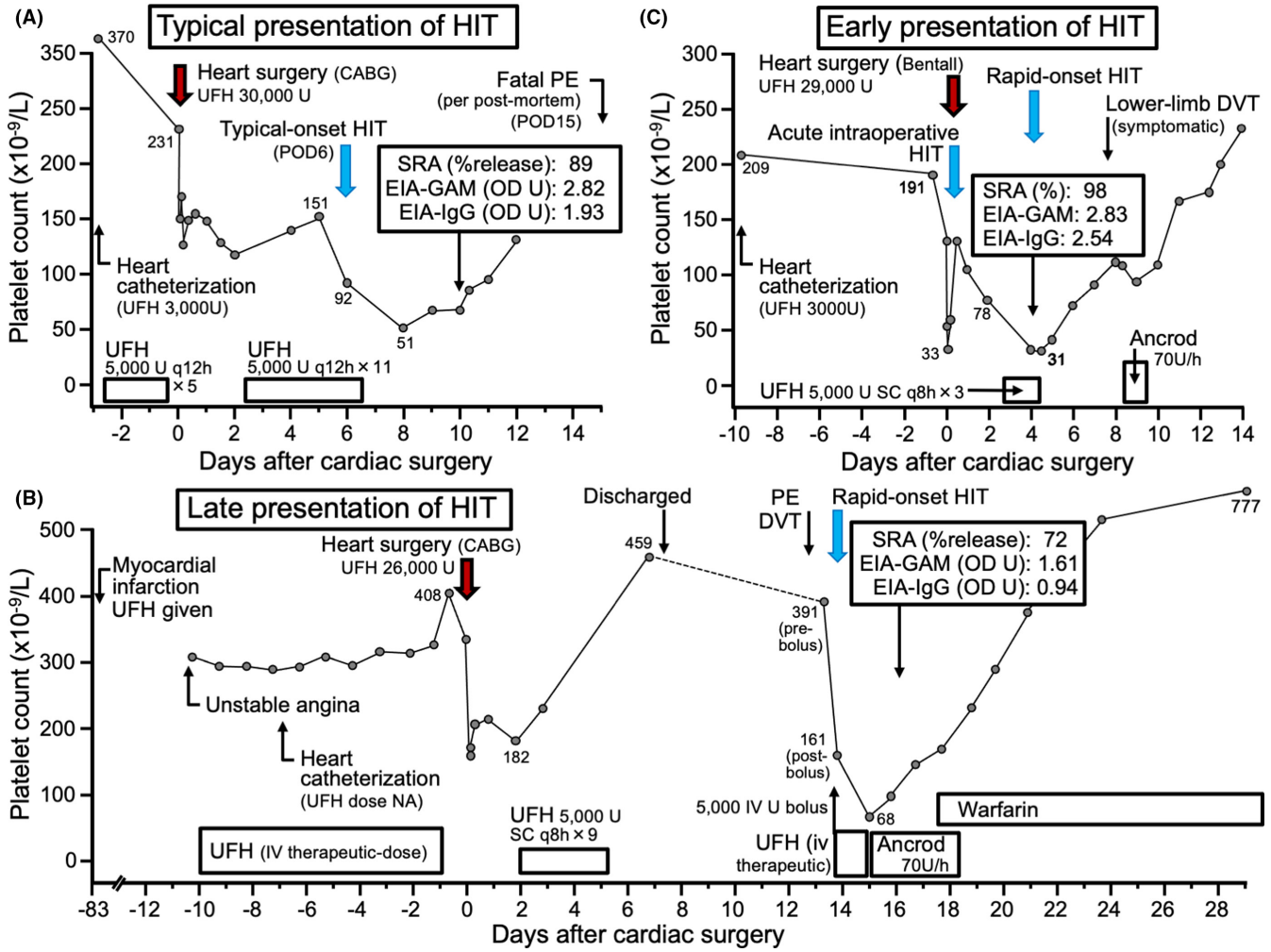

FIGURE 2 Three different temporal presentations of HIT postcardiac surgery. (A) Typical-onset HIT postcardiac surgery: This 68-year-old female developed HIT beginning on POD6 following coronary artery bypass (CABG) surgery while receiving routine UFH thromboprophylaxis. No anticoagulant treatment for HIT was given, as this case dates from 1992 (before recognition that "isolated HIT" should receive anticoagulant therapy in most situations). The patient died of pulmonary embolism (PE) on POD15 (proven at postmortem examination). (B) Late presentation of HIT postcardiac surgery: This 63-year-old male was discharged to home following uneventful CABG. He developed symptoms of PE and DVT on POD14 (platelet count 391×10^9/L). Rapid-onset HIT was diagnosed after the platelet count abruptly fell to 68×10^9/L after administration of therapeutic-dose UFH. (C) Early presentation of HIT postcardiac surgery: This 65-year-old female underwent heart catheterization 10 days before heart surgery (Bentall procedure for sinus of Valsalva aneurysm); there was no other known prior heparin exposure. HIT was diagnosed on POD4 based on a rapid decline in platelet count (from 78 to 31×10^9/L) upon starting UFH thromboprophylaxis postsurgery. It was inferred that the patient had likely developed acute intraoperative HIT, based upon the following four considerations: (1) heparin exposure 10 days before cardiac surgery (i.e., sufficient time to form high levels of platelet-activating HIT antibodies [i.e., the presumed immunizing heparin exposure]); (2) marked intraoperative platelet count nadir (33×10^9/L) following intraoperative exposure to 29 000 U of UFH; (3) rapid fall in platelet count during the early postoperative period; and (4) strong positive test for HIT antibodies on blood sample obtained on POD4 (i.e., too soon to be explained by heart surgery as representing the immunizing heparin exposure). Abbreviations: CABG, coronary artery bypass surgery; DVT, deep venous thrombosis; EIA-GAM, enzyme-immunoassay (detecting IgG, IgA, and/or IgM antibodies); HIT, heparin-induced thrombocytopenia; IV, intravenous; NA, not available; OD, optical density; PE, pulmonary embolism; POD, postoperative day; SC, subcutaneous; SRA, serotonin-release assay; U, units; UFH, unfractionated heparin.

inevitability among patients who died with severe limb necrosis), and death. Thrombotic events were classified as arterial, venous, or microvascular (venous limb gangrene; warfarin-associated skin necrosis complicating HIT). Miscellaneous HIT-associated events included postbolus anaphylactoid reactions[27] and necrotizing and nonnecrotizing skin lesions at heparin injection sites.[28]

Patients underwent daily platelet count monitoring until discharge from hospital; this made it relatively straightforward to determine the POD onset of the HIT-related platelet count fall. Heparin thromboprophylaxis was routinely administered to our postcardiac surgery patient population, although the specific regimen changed over time, as follows: unfractionated heparin (UFH) every 8 h by subcutaneous (SC) injection (1990–1995); UFH every 12 h by SC injection (1996–2010); and then the low molecular weight heparin (LMWH), dalteparin, 5000 U every 12 h by SC injection (first postoperative dalteparin dose, 2500 U; subsequent doses, 5000 U) (2011–present).

We classified the temporal presentation of HIT as follows. Typical HIT was defined as onset of the HIT-related platelet count fall between PODs 5 and 10 (inclusive)[4]; in all cases, this represented a second platelet count fall, thus exhibiting the characteristic biphasic platelet count profile described in the literature.[6–8,12–15] Late (or delayed) presentation of HIT was defined as patients who presented with HIT following hospital discharge, or patients whose HIT occurred during the same hospitalization for heart surgery but only after POD10. Among patients with late presentation of HIT, some manifested abrupt platelet count declines upon restarting heparin—classified as "rapid-onset HIT"[4]—whereas others that presented following discharge with thrombocytopenia and thrombosis and whose SRA yielded strong heparin-independent serotonin-release, were classified as "autoimmune HIT" (aHIT).[29,30] Early presentation of HIT (or early-onset HIT) was defined as those patients in whom onset of HIT during the early postoperative period (up to POD4) could be clearly identified.

For all study patients, we identified presurgery heparin exposures, with particular focus on patients with early-onset HIT, given that preoperative heparin exposure could be crucial in explaining the atypical clinical presentation. Results of HIT antibody testing, including from preoperative samples (when available), were also used to help establish early-onset HIT.

2.2 | Consideration regarding duplicate reporting

The authors have had a longstanding interest in HIT and consequently some of the individual postcardiac surgery HIT patients have been previously reported,[31–48] or included as data points in (noncardiac surgery focused) retrospective[44,49,50] or prospective[51] HIT studies. The relevant data from these patient cases needed to be included in this report so that the full spectrum of postcardiac surgery HIT at our cardiac surgery center, over the approximate 3-decade time span, could be determined. However, to avoid duplicate reporting of individual cases, we ensured that none of the seven representative cases described in detail in this current study have previously been reported. Further, when patient-specific data are shown, any cases previously reported are clearly indicated as such (with the published reference given) in the corresponding tables.

2.3 | Data analysis and statistics

Descriptive data included means (± standard deviation) and medians (with interquartile range [IQR]). Unpaired Student *t* tests were applied to compare variables with normal distributions. Analysis of variance was used to compare data from multiple groups.

For determining the ratio of venous:arterial (V:A) thrombosis, we considered each patient to contribute a maximum of 1 venous or arterial thrombotic event, irrespective of how many venous or arterial thrombi they developed; for the minority of patients who developed both venous and arterial thrombotic events associated with HIT, we ascribed a value of 0.5 each to venous and to arterial thrombosis. To illustrate, if among eight patients with HIT, five patients had venous thrombosis, one patient had arterial thrombosis, and two patients had both venous and arterial thrombosis, the V:A ratio would have been calculated as $5+(0.5\times2):1+(0.5\times2)=6:2=3$.

3 | RESULTS

3.1 | First three cases: Three different temporal presentations of postcardiac surgery HIT

The first three postcardiac surgery patients identified during the study time frame were diagnosed in 1992 (Figure 2); each patient case represented one of the three different clinical presentations of HIT. Figure 2A illustrates the profile of typical HIT, with the patient's platelet count fall beginning on POD6 (see blue arrow) while receiving UFH thromboprophylaxis. This patient died of pulmonary embolism (PE) on POD15 following hospital discharge. Of note, this patient represents a historically significant case because this fatal HIT outcome triggered a study[52] investigating the natural history of isolated HIT (i.e., HIT recognized because of an unexpected platelet count fall rather than because of thrombosis that draws attention to thrombocytopenia). The results of this study,[52] which identified a high frequency of thrombosis in patients with isolated HIT (~50%)—including a ~5% frequency of sudden death—helped inform later HIT treatment guidelines recommending therapeutic-dose anticoagulation for treatment of isolated HIT.[53]

Figure 2B illustrates a late (delayed) presentation following hospital discharge, with HIT recognized after UFH was given on POD14 for PE, which triggered rapid-onset HIT (see blue arrow); this patient was also shown to have lower-limb deep vein thrombosis (DVT).

Figure 2C illustrates an early presentation of HIT, which was confirmed by strong-positive SRA with POD4 blood sample. Case analysis—including the observation that the sole prior heparin exposure had occurred 10 days before surgery at heart catheterization (i.e., sufficient time for HIT antibodies to be generated by the time of surgery)—plus the marked intraoperative thrombocytopenia (33×10^9/L) and early severe postoperative thrombocytopenia (31×10^9/L)—permitted us to infer that acute intraoperative HIT had likely occurred. Moreover, this case of early HIT prompted the primary author (T.E.W.) subsequently to obtain wherever possible earlier blood samples in subsequent cases of early presentation of HIT to help establish a diagnosis of acute intraoperative HIT. This approach is discussed further in Section 3.6. Both patients shown in Figure 2B,C were treated with the defibrinogenating agent, ancrod[54] (no longer used to treat HIT).

3.2 | Clinical picture of postcardiac surgery HIT: Overall patient population

We identified 129 patients diagnosed with postcardiac surgery HIT. Typical HIT represented the most common clinical presentation ($n = 100$ cases). Early and late presentations of HIT were seen in 13

TABLE 1 Clinical and laboratory characteristics of 129 patients with HIT postcardiac surgery

	All patients ($N = 129$)	Typical ($n = 100$)	Early ($n = 13$)	Late ($n = 16$)
Male:female	72:57	52:48	8:5	12:4
Age (mean, SD)	69.5 (8.7)	70.6 (8.7)	64.8 (8.3)	67.1 (6.8)
Coronary artery bypass grafting (CABG)	68	56	6	6
CABG and valve and/or aortic arch surgery	34	24	2	8
Valve and/or aortic arch surgery (no CABG)	26	20	4	2
Other (myxoma resection)	1	0	1	0
Any preoperative exposure to heparin	118 (91%)	91 (91%)[a]	13 (100%)	14 (88%)[b]
Serotonin-release (maximum) with heparin, median (IQR)	95.0 (89.0, 100.0)	94.0 (88.0, 99.3)	99.0 (98.0, 100.0)	97.5 (85.3, 100.0)
EIA-IgGAM OD values, median (IQR)	2.66 (2.12, 2.84)	2.68 (2.19, 2.85)	2.78 (2.46, 2.84)	2.35 (1.73, 2.75)
EIA-IgG OD values, median (IQR)	2.25 (1.73, 2.60)	2.26 (1.77, 2.61)	2.38 (1.80, 2.64)	2.23 (1.32, 2.52)
Percent platelet count fall (median)	64.4	64.1	60.3	69.2
Platelet count nadir, median (IQR)	68 (40–88)	68 (45–88)	44 (28–68)	72 (40–100)
Any HIT-related clinical event[c] (%)	82 (64)	60 (60)	8 (62)	14 (88)
Any thrombosis	77	58	8	11
Venous thrombosis (number with PE)	57 (22)	46[d] (16)	4 (0)	7 (6)
Arterial thrombosis	16	8[e]	4	4
Both venous and arterial thrombosis	4	4[f]	0	0
None of the three previous categories	52	42	5	5
Microvascular	7	6[g]	1	0
Miscellaneous	8	3[h]	0	5[i]
Amputation	6	4[j]	1[k]	1[l]
Death	17	13[m]	3[n]	1[o]

Note: The footnotes provide additional clinical information, as well as providing citations for previously published cases.[31–43]

Abbreviations: DIC, disseminated intravascular coagulation; DVT, deep-vein thrombosis; EIA, enzyme immunoassay; HIT, heparin-induced thrombocytopenia; IQR, interquartile range; LMWH, low molecular weight heparin; OD, optical density; PE, pulmonary embolism; POD, postoperative day; SPG, symmetrical peripheral gangrene; UFH, unfractionated heparin.

[a]Nine patients had no previous history of heparin exposure before emergency cardiac surgery (acute aortic dissection, $n = 4$; acute myocardial infarction with shock, $n = 2$; and three with acute complications during heart catheterization [e.g., coronary artery dissection, $n = 3$]).

[b]Two patients had no previous history of heparin exposure (acute aortic dissection, $n = 1$; acute cardiogenic shock, $n = 1$).

[c]Includes at least one: confirmed thrombosis (venous, arterial, or both; note—all patients with microvascular thrombosis had at least one macrovascular venous or arterial thrombosis), anaphylactoid reaction after intravenous heparin bolus or subcutaneous LMWH injection; filter clotting (hemodialysis); or nonnecrotizing skin lesions at heparin injection sites (no necrotizing skin lesions were noted in this study).

[d]Venous thrombotic events were predominantly DVT (10 patients with unilateral lower limb DVT alone; one patient previously reported in detail[31]), eight patients with unilateral lower limb DVT plus PE, six patients with bilateral lower-limb DVT (one of whom also with PE, and two of whom also had unilateral upper limb DVT), six patients with unilateral upper limb DVT (one patient previously reported[32]), three patients with bilateral upper limb DVT, one patient with unilateral lower limb DVT and unilateral upper limb DVT, one patient with bilateral upper limb DVT and unilateral lower limb DVT and PE, and six patients with PE who did not have documented DVT; patients with other types of thrombi included two patients with atrial thrombosis, one patient with adrenal hemorrhagic infarction presumed to have adrenal vein thrombosis (patient included in three previous reports[33–35]), and two patients with bowel ischemia secondary to mesenteric vein thrombosis.

[e]Arterial thrombotic events include five patients with thrombotic stroke, two patients with limb artery thrombosis (one patient reported previously[36]), and one patient with fulminant clinical course with multiarterial thrombosis.

[f]Four patients had both venous and arterial thrombosis, including two patients with unilateral lower limb DVT and thrombotic stroke, one patient with unilateral lower and upper limb DVTs plus thrombotic stroke, and one patient with upper limb DVT and thrombotic stroke.

[g]Includes the following events: (1) concomitant warfarin-induced skin necrosis (in the setting of HIT-associated DVT; $n = 1$); (2) warfarin-induced multiple upper and lower limb digit ischemic necrosis in the setting of HIT-associated DVT ($n = 1$; previously reported[37]); (3) venous limb gangrene in associated with HIT-associated DVT ($n = 2$; both patients previously reported[38,39]); (4) diffuse multiextremity microvascular thrombosis without limb gangrene in patients with at least one macrothrombosis; $n = 2$; one patient with a platelet count nadir of 2×10^9/L was previously reported[40]; all six of the aforementioned patients are included in one of the preceding categories, "Venous thrombosis," "Arterial thrombosis," or "Both venous and arterial thrombosis." This category excludes one patient with postcardiac surgery shock-associated (non-HIT) DIC complicated by SPG for which UFH was given where no definite thrombotic events occurred during subsequent development of HIT (the SPG was established prior to development of HIT).

[h]Includes: (1) one patient who developed acute anaphylactoid reaction after IV bolus heparin (POD9) who did not have documented thrombosis (described in a previous report[41]); (2) one patient who had nonnecrotizing skin lesions at UFH injection sites (who also had PE; described in a previous report[42]); and (3) one patient who developed repeated filter thrombosis during continuous renal replacement therapy (not included as either venous or arterial thrombosis).

[i]Includes three patients with post-IV UFH bolus anaphylactoid reaction (1 with VTE), 1 patient with post-SC LMWH anaphylactoid reaction (with VTE, previously reported[43]), and one patient with nonnecrotizing skin lesions at heparin injection sites (no venous or arterial thrombosis).

[j]Includes: limb loss secondary to limb artery thrombosis ($n = 1$), multidigit necrosis secondary to warfarin-induced microthrombosis complicating HIT ($n = 1$),[37] symmetrical peripheral gangrene in patient who had combination of sepsis and HIT ($n = 1$); and multilimb venous limb gangrene associated with severe HIT-associated DIC ($n = 1$).

[k]Multilimb venous limb gangrene associated with severe HIT-associated DIC ($n = 1$).

[l]Above-elbow amputation following limb artery thrombosis; HIT diagnosed after rapid-onset HIT occurred on POD13 when heparin was given to treat acute limb ischemia.[39]

[m]HIT caused or contributed significantly to death in seven of the 13 patients, including: fatal PE ($n = 1$); bowel infarction ($n = 1$); thrombotic stroke ($n = 3$), fulminant clinical course with multiple life-threatening thrombotic events ($n = 2$).

[n]HIT caused or contributed significantly to death in all three patients, including: thrombotic stroke, multilimb venous limb gangrene, and fulminant clinical course with multiple life-threatening thrombotic events ($n = 1$).

[o]HIT contributed to death through thrombotic stroke ($n = 1$).

and 16 patients, respectively. Table 1 summarizes data for the overall 129 patient population, as well as breaking down the data for the three different temporal presentations.

The majority of patients (82/129; 63.6%) developed one or more HIT-related clinically evident complications, most frequently, thrombosis ($n = 77$ [59.7%] patients had one or more thrombotic events). The overall ratio of V:A thrombosis was 59:18 (i.e., approximately 3:1). Twenty patients (15.5%) developed arterial thrombosis; the most common arterial thrombotic event was stroke, which occurred in 14 patients. Consistent with overall venous thrombosis predominance, we observed that there were more patients who developed PE versus patients who developed any arterial thrombotic event (22 patients vs. 20 patients, respectively).

For eight patients, miscellaneous complications of HIT were observed, most notably acute anaphylactoid reactions (post-UFH bolus, $n = 4$; post-SC LMWH injection, $n = 1$), but also nonnecrotizing skin lesions at heparin injection sites ($n = 2$) and recurrent filter thrombosis during hemodialysis ($n = 1$).

The median HIT-related platelet count nadir for the 129 patients was 68×10^9/L; the median platelet count fall was 64.4% (defined as percent platelet count fall from the postoperative peak platelet count). The lower median platelet count nadir (44×10^9/L; IQR, 28–68; range, 16–84) for patients with early presentation of HIT reflects HIT coinciding with (expected) early postcardiac surgery thrombocytopenia.

3.3 | Clinical picture of typical HIT

We identified 100 patients, representing 77.5% of the overall patient population, with a typical presentation of HIT. Figure 3 summarizes these 100 patients.

Figure 3A shows the platelet count distributions for the 100 patients with typical presentation of HIT, for four time points: preoperative baseline, early postoperative platelet count nadir (lowest platelet count on PODs 1–3, inclusive), postoperative peak platelet count (i.e., the highest platelet count that immediately preceded the HIT-related platelet count fall), and the platelet count nadir attributable to HIT. The data show a substantial early platelet count fall (~54%, from preoperative median of 232 to 107×10^9/L). Subsequently, there was a substantial increase in platelet count, to a median of 185×10^9/L. Thereafter, a substantial fall in platelet count occurred in association with HIT to median nadir value of 68×10^9/L. The figure clearly shows the biphasic platelet count pattern characteristic of typical HIT.

Figure 3B shows the distribution of the HIT-associated relative platelet count fall, expressed as per cent platelet count decline from the postoperative peak platelet count. Most patients (76/100 [76%]) developed at least a 50% or greater decline in the platelet count, with all but one of the remaining 24 patients exhibiting a 30.0% to 49.9% decrease in the platelet count. The majority of patients developed HIT-associated thrombosis, most often venous thrombosis (predominantly, PE and/or DVT), with a V:A thrombosis ratio of 48:10.

HIT-related platelet count falls typically evolved relatively quickly: among the 76 patients with typical HIT who exhibited a >50% decline in the platelet count, once the initial platelet count fall had begun, it took only an additional 2 days (median; IQR, 1–2.25) to reach the 50% decline threshold.

Figure 3C shows the distribution of day of onset of HIT: the median day of onset was POD7. Interestingly, there was a trend to a higher frequency of thrombosis with a later day of onset of HIT: the frequency of thrombosis was 31.6% for patients with onset of HIT on POD5, versus a frequency of 58.9% for patients with onset of HIT on either POD6 or POD7, and a frequency of 76% for patients with onset of HIT on POD8 or later. The median platelet count decrease was similar between the 58 patients with HIT-associated thrombosis versus the 42 patients without HIT-associated thrombosis (67.8% vs. 59.8%; $p = .11$).

We evaluated whether there were any differences between preoperative platelet count, early postoperative platelet count nadir (PODs 1–3), postoperative peak platelet count (pre-HIT), and HIT-associated platelet count nadir, between the 58 patients with HIT-associated thrombosis versus the 42 patients without HIT-associated thrombosis. No significant differences were observed between the two groups in any of these parameters (data not shown).

Figure 3D shows the distribution of the HIT-related platelet count nadir values for the 100 patients with typical HIT. Thrombotic

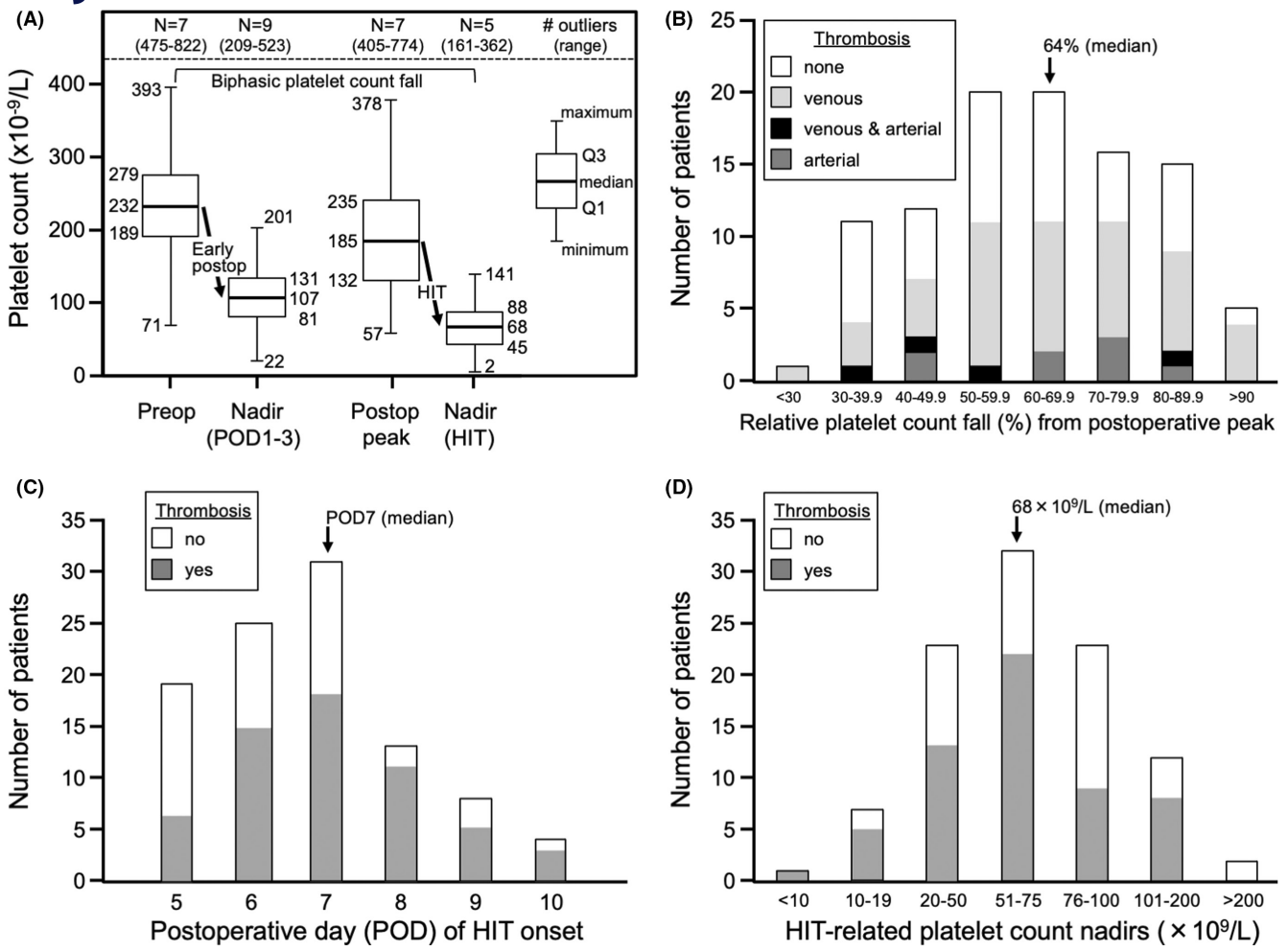

FIGURE 3 Clinical and laboratory picture of typical HIT postcardiac surgery. (A) Platelet count distributions at four time points: Preoperative (preop), nadir (POD1-3), postoperative peak (i.e., pre-HIT), nadir (HIT). The data are shown as median, IQR (Q1-Q3), minimum (lowest platelet count value observed within the lower boundary of 1.5 times the IQR below the Q1 data point), and maximum (which refers to the highest platelet count value within the boundary of 1.5 times the IQR above the Q3 data point); note that there were several outlier platelet count values above the maximum value (outlier data points are indicated in the graph). The data show the characteristic biphasic platelet count decline: the initial early postoperative (postop) platelet count fall, followed by the HIT-related platelet count fall, shown by the respective arrows. (B) Distribution of relative platelet count declines. The numbers of patients exhibiting various degrees of relative platelet count decline (expressed as percent platelet count fall from the postoperative peak platelet count) is shown. The shading indicates the numbers of patients with venous, arterial, or both venous/arterial thromboses. (C) Distribution of POD of HIT onset. The median day of onset of HIT was POD7. The gray shading indicates the numbers of patients who developed HIT-related thrombosis. (D) Distribution of HIT-related platelet count nadirs. The gray shading indicates the numbers of patients who developed HIT-related thrombosis. The median platelet count nadir of HIT was 68×10^9/L. Abbreviations: HIT, heparin-induced thrombocytopenia.

events were evenly distributed across the range of platelet count nadirs. However, neither of the two patients with a platelet count nadir of $>200 \times 10^9$/L developed thrombosis. Interestingly, one patient had a Jak2-positive myeloproliferative disorder (MPD); HIT was recognized when the postoperative platelet count fell, beginning on POD6, from 774 to 362×10^9/L (53.2% fall).

3.4 | Previous heparin exposure does not affect timing of onset of typical HIT

Among the 100 patients with typical HIT, we investigated whether there was any association between the timing of onset of HIT with preoperative heparin exposure. For the nine patients without known prior exposure to heparin (i.e., emergency cardiac surgical procedures), the median (IQR) POD of onset of HIT was day 7 (6–8); for the 18 patients with remote preoperative heparin exposure more than 100 days ago (but not more recent), the corresponding values were 7 (6, 7); for the 30 patients with previous heparin exposure more than 10 days before surgery (including patients who also had remote heparin exposure >100 days before)—but not within the preceding 10 days—the corresponding data were 6 (6, 7); finally, for the 43 patients who received heparin in the 10 days before surgery (regardless of whether they had received heparin before that), the median onset of HIT was 7 (6–8). No significant differences were seen among these 4 groups (f-ratio, 0.85; $p = .47$).

Only one of the 129 study patients had a previous remote history of HIT; this patient developed typical-onset HIT while receiving fondaparinux thromboprophylaxis postcardiac surgery, which was given because of previous HIT complicating cardiac surgery performed 11 years earlier at another surgical center (previously reported in a study[31] describing repeat heparin exposure in patients with a previous history of HIT). Of note, both episodes of postcardiac surgery HIT began on POD7, illustrating well that history of heparin exposure (and—in this case—a previous episode of HIT itself) does not influence timing of subsequent HIT.

3.5 | Clinical picture of late (delayed) presentation of HIT

We identified 16 patients, representing 12.4% of the overall HIT population, who had late presentations of HIT (after POD10). These 16 patients comprised three subgroups: patients who presented following discharge with thrombosis and thrombocytopenia ($n = 3$); patients who presented postdischarge with a normal platelet count but who developed an abrupt platelet count fall when heparin was restarted (rapid-onset HIT; $n = 8$); and patients who developed HIT during their initial hospitalization, but only after POD10, usually as a result of resumption of heparin administration later during hospitalization (often by intravenous heparin bolus), with the clinical picture of rapid-onset HIT ($n = 5$). These 16 patients are summarized in Table 2.

For the first three patients listed in Table 2, the clinical picture was consistent with "delayed-onset HIT" (i.e., presenting several days after last exposure to heparin), an entity classified as an aHIT disorder.[29,30,34] Consistent with this clinical picture was the observation that all three patients' serum caused >80% serotonin release even in the absence of heparin.

As noted, for the remaining 13 patients, all had the clinical picture of rapid-onset HIT beginning after POD10 (i.e., an abrupt drop

TABLE 2 Sixteen patients with delayed presentation of HIT

Age/sex	POD presentation	Events	Ref
Readmitted after hospital discharge with thrombocytopenia and thrombosis (autoimmune HIT[a])			
61F	POD10	PE, DVT (lower limb) on POD10; platelet count = 11; last heparin exposure (postoperative UFH thromboprophylaxis), 4 days previous	
61F	POD13	Saddle PE, DVT (lower and upper limb) on POD13; platelet count = 30; last heparin exposure (LMWH thromboprophylaxis), 6 days previous	
69F	POD30	PE on POD30; platelet count = 72; last heparin exposure (LMWH thromboprophylaxis), 25 days previous	[44]
Readmitted after hospital discharge: platelet count >100 but rapid-onset HIT on heparin restart			
63M	POD13	PE, DVT (lower limb); ASR-post UFH bolus (plt 391→68)	Figure 2B
64M	POD19	DVT (lower limb), PE; plt 302→144 on restarting UFH	
66F	POD31	Readmission for sternal wound infection; ASR after accidental 50 000 U UFH bolus[b] (plt 270→32)	[45]
68M	POD12	Readmission (abdominal pain); plt 172→95 on UFH restart	
66M	POD65	DVT (lower limb); ASR post-LMWH injection (plt 179→76)	[43]
62M	POD16	DVT (lower limb), PE; plt 237→82 on SC therapeutic-dose LMWH (dalteparin)	
68M	POD11	Readmission (mediastinitis); plt 113→42 on SC LMWH (dalteparin) 5000 U q12h restart; no apparent HIT-related complications[c]	
80M	POD13	Readmission (thrombotic stroke); plt 165→36 with IV UFH	
Index hospitalization: rapid HIT (after POD10) following UFH resumption or dose escalation			
65M	POD11	ASR post-UFH bolus; plt 311→193	[46]
65M	POD12	Stroke (POD7); plt 154→47 with IV UFH	
57M	POD11	Stroke (POD11); plt 318→113 with IV UFH to treat stroke	
78M	POD16	Nonnecrotizing skin lesions at UFH injection sites; plt 381→235 with LMWH (dalteparin) for atrial fibrillation	
80M	POD13	Radial artery thrombosis; plt 193→78 when IV UFH given to treat thrombosis; below-elbow amputation	

Abbreviations: ASR, acute systemic (anaphylactoid) reaction; DVT, deep vein thrombosis; F, female; HIT, heparin-induced thrombocytopenia; LMWH, low molecular weight heparin; M, male; PE, pulmonary embolism; plt, platelet count; POD, postoperative day; UFH, unfractionated heparin.

[a]The three patients who were readmitted with thrombocytopenia and thrombosis were diagnosed with autoimmune HIT (delayed-onset HIT) based on thrombocytopenia and thrombosis more than 5 days after last exposure to heparin plus strong heparin-independent platelet activation (>80% serotonin-release at 0 U/ml heparin).

[b]Patient received 50 000 U of UFH rather than the intended 50 U UFH line "flush."

[c]The patient's mild thrombocytopenia (plt = 113) on readmission was attributed to "mediastinitis"; however, the SRA showed substantial heparin-independent serotonin-release (77%), consistent with a potential diagnosis of aHIT (with rapid-onset HIT on restarting heparin).

in platelet count upon restarting or increasing the dose of heparin), usually because of occurrence of thrombosis ($n = 8$). As expected, all 13 patients with rapid-onset HIT had a history of recent heparin exposure (within the preceding 10- to 100-day period); by way of comparison, for the 100 patients with typical-onset HIT postcardiac surgery, only 30 (30.0%) patients had a similar recent preoperative heparin exposure (13/13 vs. 30/100; $p < .001$).

3.6 | Clinical picture of early presentation of HIT, including acute intraoperative HIT

We identified 13 patients in whom HIT was recognized within the first four PODs (Table 3). Interestingly, for five of these patients (the first five patients listed in Table 3), it appeared that the patients had also developed acute intraoperative HIT. For three of these patients, presence of platelet-activating antibodies at the time of surgery was proven; for the other two patients, heart surgery was performed 9 and 10 days after recent preceding heparin exposure (i.e., sufficient time to form platelet-activating antibodies), and together with the development of abrupt platelet count decrease on heparin restart in the early postoperative period, it could be logically inferred that HIT antibodies were likely present at the time of cardiac surgery.

For the five patients who appeared to have had acute intraoperative HIT, only one patient had any unexpected intraoperative or immediate postoperative abnormality, and that was occurrence of "platelet clumping in the bypass" (per the operative note). None of the five patients developed an intraoperative clinically evident thrombotic or other untoward event. The recognition of acute intraoperative HIT occurred only when subsequent postcardiac surgery platelet count declines led to the diagnosis of early presentation of HIT, and where subsequent case analysis and (in three cases) availability of earlier blood samples resulted in establishing that acute intraoperative HIT had likely occurred.

Figures 2C and 4A,B show the clinical and platelet count profiles for three of the patients with acute intraoperative HIT (detailed accounts of the remaining two patients have been reported previously[47,48]). For the patient shown in Figure 4A, a blood sample available from the day before heart surgery showed presence of heparin-dependent platelet-activating antibodies. Further, the platelet count decline from 192 to 161×10^9/L immediately before cardiac surgery, which began on day 7 following initiation of therapeutic-dose LMWH, suggests that the patient may have been in the early stages of HIT when cardiac surgery was performed.

For the patient shown in Figure 4B, the 45.9% platelet count fall from 307 to 166×10^9/L beginning approximately 1 week into a course of UFH followed by LMWH (dalteparin), in addition to the strong positive test for platelet-activating antibodies (100% serotonin release) from a blood sample available from the day of surgery, suggests that the patient may have had unrecognized HIT for several

TABLE 3 Patients with early postoperative HIT (including acute intraoperative HIT)

Age/sex	POD onset of HIT (days [d] after heparin)	Events, including platelet count nadir (if not already shown in figure)	Ref
Acute intraoperative HIT ($n = 5$)			
65F	0 (10 d after heart catheterization)	No intraoperative complications; DVT (lower limb) on POD7	Figure 2C
46M	0 (7 d after LMWH)	No intra-/postoperative thrombotic complications	Figure 4A
68M	0 (UFH and LMWH in preceding 3 weeks)	No intra-/postoperative thrombotic complications; patient appears to have had unrecognized HIT at time of cardiac surgery	Figure 4B
67F	0 (6 d after UFH)	No intraoperative complications; later, developed overt DIC with small upper limb (right internal jugular) DVT identified on POD8; plt nadir = 28	[47]
77M	0 (9 d after UFH)	No intra-/postoperative thrombotic complications; "platelet clumping on the oxygenator"; plt nadir = 28 (POD7)	[48]
Early postoperative HIT (before POD4)			
68M	2 (8 d after UFH)	No thrombotic events; plt nadir = 68	
71M	2 (6 d after UFH)	Bowel infarction (mesenteric vein); bilateral lower limb DVT	Figure 5A
62M	2 (7 d after UFH)	Postoperative thrombotic stroke (POD2); plt nadir = 72	
61F	4 (8 d after UFH)	Postoperative thrombotic stroke; plt nadir = 80	
66F	3 (6 d after UFH)	Multiple DVTs (upper-limb and bilateral lower limb); venous limb gangrene; plt nadir = 16	[38]
76M	3 (6 d after UFH)	Left ventricle apex thrombosis; plt nadir = 65	
58M	4 (7 d after UFH)	Multiple arterial thrombosis/fulminant course (death)	Figure 5B
57F	3 (7 d after UFH)	No thrombotic events; plt nadir = 84	

Abbreviations: DIC, disseminated intravascular coagulation; DVT, deep venous thrombosis; F, female; HIT, heparin-induced thrombocytopenia; LMWH, low molecular weight heparin; M, male; plt, platelet count; POD, postoperative day; UFH, unfractionated heparin.

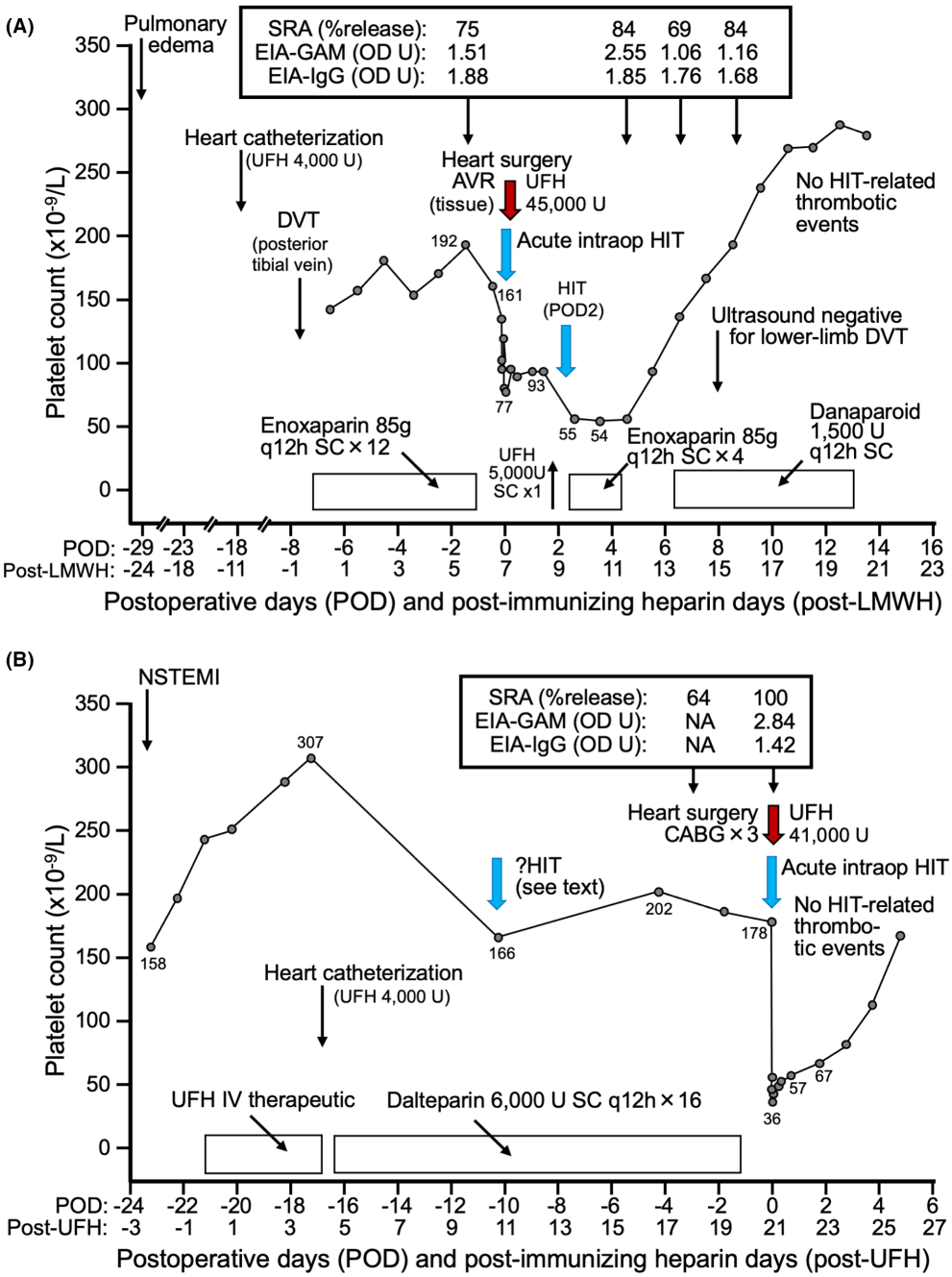

FIGURE 4 Two patients with acute intraoperative HIT. (A) This 46-year-old male with acute intraoperative HIT may have been in the early stage of HIT at the time of heart surgery based upon the platelet count fall from 192 to 161×10^9/L immediately before heart surgery, which occurred on day 7 following initiation of therapeutic-dose LMWH (enoxaparin); HIT was not clinically suspected at this time. HIT was diagnosed when an unexpected platelet count decline to 55×10^9/L occurred on POD2, with repeat value of 54×10^9/L (nadir; POD3), after starting postoperative UFH (one dose) followed by LMWH, corroborated by positive testing for HIT antibodies. A preoperative sample was identified, which confirmed presence of HIT antibodies prior to cardiac surgery. No HIT-related thrombotic or other untoward events were identified. (B) This 68-year-old male may have had unrecognized HIT at the time of cardiac surgery, based on an otherwise unexplained decline in the platelet count from 307 to 166×10^9/L that occurred approximately 7–10 days after starting intravenous therapeutic UFH. HIT was clinically suspected immediately following heart surgery based on a marked postoperative platelet count decline to 36×10^9/L (nadir), corroborated by positive testing for HIT antibodies. A preoperative sample was identified, which confirmed presence of HIT antibodies before cardiac surgery. No HIT-related thrombotic or other untoward events were identified. Abbreviations: AVR, aortic valve replacement; CABG, coronary artery bypass surgery; DVT, deep vein thrombosis; EIA, enzyme-immunoassay; GAM, immunoglobulin G/IgA/IgM; HIT, heparin-induced thrombocytopenia; INR, international normalized ratio; intraop, intraoperative; IV, intravenous; LMWH, low molecular weight heparin; NSTEMI, non-ST elevation myocardial infarction; OD, optical density; POD, postoperative day; q12h, every 12 h; SC, subcutaneous; SRA, serotonin-release assay; U, units; UFH, unfractionated heparin.

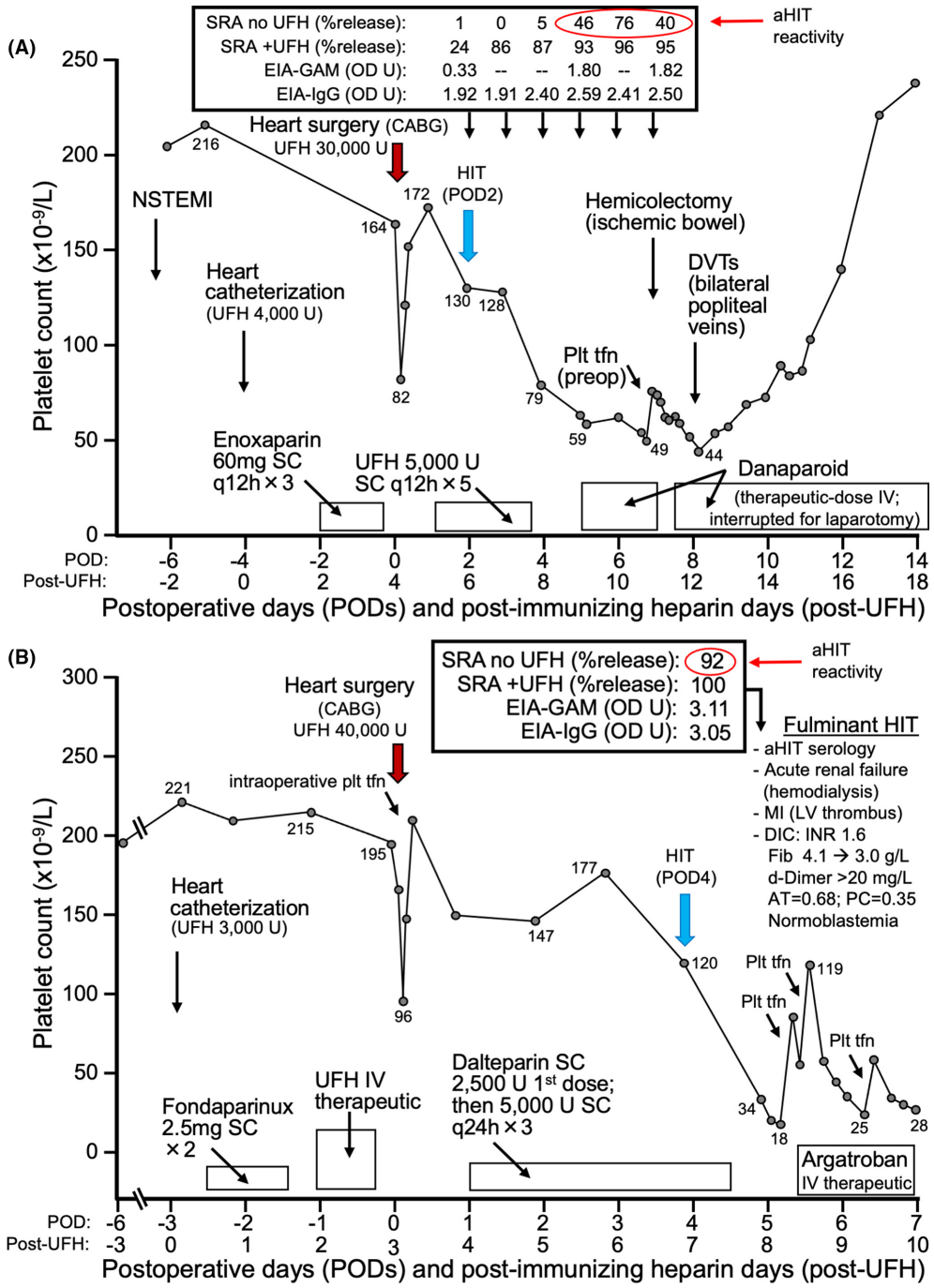

FIGURE 5 Two patients with early postcardiac surgery HIT. (A) This 71-year-old male patient developed HIT on POD2 complicated by progressive thrombocytopenia despite stopping postoperative UFH thromboprophylaxis, and which was complicated by ischemic bowel requiring hemicolectomy, and bilateral popliteal vein deep venous thrombosis (DVT). The SRA showed 76% serotonin release (maximum) at 0 U/ml and >90% serotonin-release at 0.1–0.3 U/ml heparin, a serological profile consistent with autoimmune HIT (aHIT). The patient was exposed to UFH at heart catheterization 4 days before surgery; accordingly, the onset of HIT appeared to begin 6 days after immunizing heparin exposure. (B) This 58-year-old male patient developed HIT on POD4 complicated by progressive thrombocytopenia, overt DIC, and multisite arterial thrombosis with multiorgan failure including acute renal failure requiring hemodialysis, with a fatal outcome. The SRA showed 92% serotonin-release at 0 U/ml and 100% serotonin-release at 0.1–0.3 U/ml heparin, a serological profile consistent with aHIT. The patient was exposed to UFH at heart catheterization 3 days before surgery; accordingly, the onset of HIT appeared to begin 7 days after immunizing heparin exposure. Abbreviations: aHIT, autoimmune HIT; AT, antithrombin activity; CABG, coronary artery bypass surgery; DIC, disseminated intravascular coagulation; DVTs, deep vein thromboses; EIA, enzyme-immunoassay; Fib, fibrinogen; GAM, IgG/IgA/IgM; INR, international normalized ratio; IV, intravenous; MI (LV thrombus), myocardial infarction (complicated by left ventricular thrombus); NSTEMI, non-ST elevation myocardial infarction; OD, optical density; PC, protein C activity; Plt tfn (preop), platelet transfusion (given preoperatively); POD, postoperative day; q12h, every 12 h; q24h, every 24 h; SC, subcutaneous; SRA, serotonin-release assay; U, units; UFH, unfractionated heparin.

days immediately before cardiac surgery. Neither patient developed intraoperative or postoperative thrombotic or other untoward events.

We also identified an additional eight patients in whom it could be discerned that HIT began on PODs 1 through 4 (inclusive). For all eight patients, recent preoperative exposure to UFH was documented, and indeed, it was evident that the timing of onset of the early postoperative HIT matched the onset of platelet count fall that would have been expected if the preoperative heparin exposure had been the immunizing heparin exposure (i.e., platelet count fall beginning during the subsequent day 5–10 window [median day 7]).

For six of these eight patients, postoperative thrombotic complications occurred, including early postoperative thrombotic strokes in two patients. Two illustrative cases of early presentation of HIT are shown in Figure 5. Figure 5A shows a case of progressive early postoperative thrombocytopenia complicated by bowel infarction secondary to mesenteric venous thrombosis. Although HIT was shown by serial platelet count changes and HIT antibody testing to have likely begun on POD2, this represented a day 6 onset in relation to preoperative UFH exposure (4000 U at heart catheterization). Figure 5B shows a case of fulminant postoperative HIT with multisystem organ failure, including acute renal failure, related to multisite arterial thrombosis and disseminated intravascular coagulation (DIC). Although HIT began on POD4, this represented a day 7 onset in relation to preoperative UFH exposure (3000 U at heart catheterization). Both patients had the serological profile of aHIT, with strong heparin-independent serotonin-release (76% and 92%, respectively, for the two patients depicted in Figure 5A,B).

3.7 | Miscellaneous observations

Some notable additional observations from our study include the finding that three (2.3%) of the 129 study patients had Jak2-positive MPD; this finding is consistent with MPD being a risk factor for HIT.[55–57] Only one of the 129 patients had adrenal hemorrhagic necrosis; this is consistent with most patients who develop this complication of HIT (or spontaneous HIT) being postorthopedic surgery patients.[58,59]

4 | DISCUSSION

Heparin exposure during cardiac surgery is known to be highly immunizing.[11,12,33,60] Given that it generally takes 5 or more days before onset of thrombocytopenia following an immunizing heparin exposure,[4–6,9,10] it was not surprising that most patients (~90%) identified in our study with HIT following cardiac surgery (with documented intraoperative heparin exposure) did not develop their HIT-related platelet count fall (and/or associated thrombotic events) until 5 or more days following cardiac surgery. However, 13 of 129 patients, or approximately 10% of our subjects, developed HIT within the first 4 PODs. Analysis of these 13 patients revealed two interesting findings. First, all 13 patients had received recent exposure to UFH, namely within 10 days before cardiac surgery, and the onset of thrombocytopenia appeared to correspond closely to this preoperative exposure to heparin. Second, for five of our patients with early presentation of HIT, it appeared that the patients had developed acute intraoperative HIT, based on a marked intraoperative fall in their platelet count and, more importantly, exposure to UFH within an appropriate preoperative period to explain HIT provoking levels of platelet-activating anti-PF4 antibodies at the time of surgery; moreover, for three of these patients, available blood samples established preoperative presence of platelet-activating anti-PF4/heparin antibodies; in the two patients for whom no preoperative blood sample was available, preceding exposure to UFH had occurred 9 and 10 days preoperatively, making it very likely that HIT antibodies were present at time of cardiac surgery (thus explaining marked intraoperative thrombocytopenia in one patient, and potentially the finding of platelet clumping in the CPB circuit in the other patient); as well as the abrupt platelet count fall when heparin was restarted in the early postoperative period (both patients).

Remarkably, none of the five patients with acute intraoperative HIT developed any immediate clinically evident adverse consequences. The diagnosis of HIT only became apparent when unexpected further platelet count declines were noted in the postoperative period. This lack of acute intraoperative complications is consistent with a previous commentary,[48] noting that there is a striking paucity of medical literature describing acute intraoperative HIT (to our knowledge, only one report described occurrence of acute intraoperative HIT[61]). Clearly, given the ubiquity of preoperative heparin to cardiac surgery patients, it would seem likely that many patients must undergo cardiac surgery with platelet-activating antibodies being present. Further studies are needed to better discern the frequency and clinical impact of acute intraoperative HIT.

Nevertheless, even if intraoperative or immediate postoperative complications related to acute intraoperative HIT are infrequent (a tentative conjecture based upon limited observations), it is clear that progression of HIT during the early postoperative period, as a result of immunizing effects of recently administered preoperative heparin, can be life-threatening. As shown in Figure 5A,B, severe thrombotic complications were seen in two such patients who had the clinical and serological profile of aHIT that began early in the postoperative period. Moreover, two other patients developed early postoperative strokes (Table 3). Per Table 1, there was a high frequency of HIT-associated thrombosis, as well as HIT-associated mortality, irrespective of which temporal presentation of HIT the patients were classified into (early, typical, late).

Most patients in our study developed a typical presentation of HIT (i.e., onset of the HIT-related platelet count fall during the usual POD5-10 window [inclusive]). Consistent with previous studies,[4,62] previous heparin exposure (including exposure in the remote past defined as >100 days presurgery) did not influence timing of onset of typical HIT. This is consistent there being a minimum period—generally 5 days—before the beginning of a platelet count fall related to an immunizing exposure to heparin (such as intraoperative administration of UFH

for cardiac surgery). This minimum 5-day period is seen irrespective of whether the patient had no previous heparin exposure (as seen in nine of our patients who underwent emergency cardiac surgery) or whether there had been previous heparin exposure in the remote or recent past. The only exception was for the 10% of patients who developed early postoperative HIT (within the first 4 PODs) in which case they invariably had received heparin in the very recent past (within 10 days presurgery): in such patients, the recent preoperative heparin exposure—rather than the intraoperative exposure to heparin during CPB—represented the presumptive immunizing heparin exposure.

Another interesting observation was the venous thrombotic predominance of HIT. Recently, Gruel and colleagues noted that postcardiac surgery patients had a relatively high frequency of arterial thrombosis (~13%);[3] indeed, we observed a remarkably similar frequency of arterial thrombosis (20/129, 15.5%). However, in contrast to the French study, where the frequency of venous thrombosis was 9.4%, we identified venous thrombosis complicating postcardiac surgery HIT in 57/129 (44.2%) patients; indeed, approximately one in six patients (22/129, or 17.1%) in our study developed symptomatic PE. The relatively high frequency of venous thrombosis in our patient population could reflect differences in in screening for venous thrombosis; in our center, routine screening by ultrasound for lower-limb DVT (and often for upper-limb DVT) was common, a practice that developed after a publication[52] indicating a high frequency of venous thrombosis in HIT patients.

Pouplard and colleagues also recommend using a 40% or greater fall in the platelet count—during the appropriate period—as indicating a high probability of postcardiac surgery HIT. Indeed, a 40% threshold (vs. a 50% platelet count decline threshold) identified 88 (vs. 76) patients with typical HIT (Figure 3B), supporting use of a 40% platelet count threshold, while (per the French authors) still maintaining good diagnostic specificity. A minimum 30% platelet count fall was seen in 99/100 patients with typical HIT, supporting a 30% decline threshold (which yields 1 point in the 4Ts scoring system[9]) as a potential threshold to consider HIT in the appropriate clinical context.

Per Pouplard and colleagues,[12] a biphasic postcardiac surgery platelet count decline that occurs on/after POD5 is unexpected, and points with high specificity toward a potential diagnosis of HIT. In contrast, early postoperative platelet count falls are universal, expected, and thus almost never indicate HIT (estimated frequency <1/1000). Although our study indicates that such an early postoperative presentation of HIT can occur (~10% of recognized HIT cases), appropriate suspicion for such an unlikely scenario would depend on whether there is a timing relationship with a recent preoperative heparin exposure (usually UFH), a greater-than-expected degree of platelet count decline (difficult to define objectively), and occurrence of untoward clinical events (e.g., thrombosis).

Our study has limitations. It represents the experience of a single cardiac surgery center, with its own approach to postoperative anticoagulation and relatively unique institutional approach to laboratory testing for HIT antibodies (SRA, EIA); moreover, all cases were reviewed by a single HIT expert, without independent adjudication. Our study is retrospective, and undoubtedly some postcardiac surgery patients who developed HIT may not have been recognized, or—in the case of late presentations of HIT—may have been diagnosed following presentation with complications of HIT to other hospitals in our region.

In summary, we report on a 3-decade experience of serologically confirmed HIT observed in one cardiac surgery center. We found that approximately 10% of patients developed HIT in the early postoperative period, a clinical presentation that can be explained by recent preoperative heparin exposure. Our study also illustrates the high frequency of thrombotic events associated with HIT, including venous thrombosis.

AUTHOR CONTRIBUTIONS

T.E.W.: planning the study, data review, analysis, and interpretation of the results, primary role in writing the paper, and approval of the final version of the manuscript; J.I.S.: data analysis, preparing figures, laboratory testing, critical review of the manuscript, and approval of the final version of the manuscript. R.P.W.: planning the study, critical review of the manuscript and approval of the final version of the manuscript.

ACKNOWLEDGMENTS

The authors thank Erin Marie Pankratz and Kyle Hukezalie for assistance with data collection and thank the McMaster Platelet Immunology Laboratory for HIT antibody testing.

CONFLICT OF INTEREST

T.E.W. has received lecture honoraria from Alexion and Instrumentation Laboratory, and royalties from Informa (Taylor & Francis); has provided consulting services to Aspen Canada, Aspen Global, CSL Behring, Ergomed, Paradigm Pharmaceuticals, and Octapharma; has received research funding from Instrumentation Laboratory; and has provided expert witness testimony relating to heparin-induced thrombocytopenia (HIT) and non-HIT thrombocytopenic and coagulopathic disorders. J.I.S.: None. R.P.W.: None.

ORCID

Theodore E. Warkentin https://orcid.org/0000-0002-8046-7588
Jo-Ann I. Sheppard https://orcid.org/0000-0002-4402-7809
Richard P. Whitlock https://orcid.org/0000-0002-6863-5884

REFERENCES

1. Greinacher A. Clinical practice. Heparin-induced thrombocytopenia. *N Engl J Med*. 2015;373(3):252-261.
2. Cuker A. Clinical and laboratory diagnosis of heparin-induced thrombocytopenia: an integrated approach. *Semin Thromb Hemost*. 2014;40(1):106-114.
3. Gruel Y, Vayne C, Rollin J, et al. Comparative analysis of a French prospective series of 144 patients with heparin-induced thrombocytopenia (FRIGTIH) and the literature. *Thromb Haemost*. 2020;120(7):1096-1107.
4. Warkentin TE, Kelton JG. Temporal aspects of heparin-induced thrombocytopenia. *N Engl J Med*. 2001;344(17):720-728.
5. Lubenow N, Kempf R, Eichner A, Eichler P, Carlsson LE, Greinacher A. Heparin-induced thrombocytopenia: temporal pattern of

thrombocytopenia in relation to initial use or reexposure to heparin. *Chest*. 2002;122(1):37-42.
6. Pishko AM, Cuker A. Heparin-induced thrombocytopenia in cardiac surgery patients. *Semin Thromb Hemost*. 2017;43(7):691-698.
7. Pishko AM, Cuker A. Heparin-induced thrombocytopenia and cardiovascular surgery. *Hematology Am Soc Hematol Educ Program*. 2021;2021(1):536-544.
8. Warkentin TE. Clinical picture of heparin-induced thrombocytopenia. In: Warkentin TE, Greinacher A, eds. *Heparin-Induced Thrombocytopenia*. 5th ed. CRC Press; 2013:24-76.
9. Lo GK, Juhl D, Warkentin TE, Sigouin CS, Eichler P, Greinacher A. Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. *J Thromb Haemost*. 2006;4(4):759-765.
10. Cuker A, Arepally G, Crowther MA, et al. The HIT expert probability (HEP) score: a novel pre-test probability model for heparin-induced thrombocytopenia based on broad expert opinion. *J Thromb Haemost*. 2010;8(12):2642-2650.
11. Pouplard C, May MA, Iochmann S, et al. Antibodies to platelet factor 4-heparin after cardiopulmonary bypass in patients anticoagulated with unfractionated heparin or a low-molecular-weight heparin: clinical implications for heparin-induced thrombocytopenia. *Circulation*. 1999;99(19):2530-2536.
12. Pouplard C, May MA, Regina S, Marchand M, Fusciardi J, Gruel Y. Changes in platelet count after cardiac surgery can effectively predict the development of pathogenic heparin-dependent antibodies. *Br J Haematol*. 2005;128(6):837-841.
13. Pouplard C, Regina S, My MA, Gruel Y. Heparin-induced thrombocytopenia: a frequent complication after cardiac surgery. *Arch Mal Coeur Vaiss*. 2007;100(6–7):563-568.
14. Gruel Y, Pouplard C. Post-operative platelet count profile: the most reliable tool for identifying patients with true heparin-induced thrombocytopenia after cardiac surgery. *J Thromb Haemost*. 2010;8(1):27-29.
15. Lillo Le-Louët A, Boutouyrie P, Alhenc-Gelas M, et al. Diagnostic score for heparin-induced thrombocytopenia after cardiopulmonary bypass. *J Thromb Haemost*. 2004;2(11):1882-1888.
16. Selleng S, Selleng K, Wollert HG, et al. Heparin-induced thrombocytopenia in patients requiring prolonged intensive care unit treatment after cardiopulmonary bypass. *J Thromb Haemost*. 2008;6(3):428-435.
17. Selleng S, Malowsky B, Strobel U, et al. Early-onset and persisting thrombocytopenia in post-cardiac surgery patients is rarely due to heparin-induced thrombocytopenia even when antibody tests are positive. *J Thromb Haemost*. 2010;8(1):30-36.
18. Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia and cardiac surgery. *Ann Thorac Surg*. 2003;76(6):2121-2131.
19. Warkentin TE, Hayward CPM, Smith CA, Kelly PM, Kelton JG. Determinants of donor platelet variability when testing for heparin-induced thrombocytopenia. *J Lab Clin Med*. 1992;120(3):371-379.
20. Warkentin TE, Arnold DM, Nazi I, Kelton JG. The platelet serotonin-release assay. *Am J Hematol*. 2015;90(6):564-572.
21. Horsewood P, Warkentin TE, Hayward CPM, Kelton JG. The epitope specificity of heparin-induced thrombocytopenia. *Br J Haematol*. 1996;95(1):161-167.
22. Visentin GP, Ford SE, Scott JP, Aster RH. Antibodies from patients with heparin-induced thrombocytopenia/thrombosis are specific for platelet factor 4 complexed with heparin or bound to endothelial cells. *J Clin Invest*. 1994;93(1):81-88.
23. Warkentin TE, Sheppard JI, Moore JC, Kelton JG. The use of well-characterized sera for the assessment of new diagnostic enzyme-immunoassays for the diagnosis of heparin-induced thrombocytopenia. *J Thromb Haemost*. 2010;8(1):216-218.
24. Warkentin TE, Sheppard JI, Smith JW, et al. Combination of two complementary automated rapid assays for diagnosis of heparin-induced thrombocytopenia (HIT). *J Thromb Haemost*. 2020;18(6):1435-1446.
25. Warkentin TE, Sheppard JI, Linkins LA, Arnold DM, Nazy I. Performance characteristics of an automated latex immunoturbidimetric assay [HemosIL® HIT-Ab$_{(PF4-H)}$] for the diagnosis of immune heparin-induced thrombocytopenia. *Thromb Res*. 2017;153:108-117.
26. Warkentin TE, Sheppard JI, Linkins LA, Arnold DM, Nazy I. High sensitivity and specificity of an automated IgG-specific chemiluminescence immunoassay for diagnosis of HIT. *Blood*. 2018;132(12):1345-1349.
27. Warkentin TE, Greinacher A. Heparin-induced anaphylactic and anaphylactoid reactions: two distinct but overlapping syndromes. *Expert Opin Drug Saf*. 2009;8(2):129-144.
28. Warkentin TE. Heparin-induced skin lesions. *Br J Haematol*. 1996;92(2):494-497.
29. Greinacher A, Selleng K, Warkentin TE. Autoimmune heparin-induced thrombocytopenia. *J Thromb Haemost*. 2017;15(11):2099-2114.
30. Warkentin TE. Platelet-activating anti-PF4 disorders: an overview. *Semin Hematol*. 2022;59(2):59-71.
31. Warkentin TE, Sheppard JI. Serological investigation of patients with a previous history of heparin-induced thrombocytopenia who are reexposed to heparin. *Blood*. 2014;123(16):2485-2493.
32. Warkentin TE, Moore JC, Vogel S, Sheppard JI, Warkentin NI, Eikelboom JW. The serological profile of early-onset and persisting post-cardiac surgery thrombocytopenia complicated by “true” heparin-induced thrombocytopenia. *Thromb Haemost*. 2012;107(5):998-1000.
33. Warkentin TE, Sheppard JI, Horsewood P, Simpson PJ, Moore JC, Kelton JG. Impact of the patient population on the risk for heparin-induced thrombocytopenia. *Blood*. 2000;96(5):1703-1708.
34. Warkentin TE, Kelton JG. Delayed-onset heparin-induced thrombocytopenia and thrombosis. *Ann Intern Med*. 2001;135(7):502-506.
35. Warkentin TE. Heparin-induced thrombocytopenia. *Curr Hematol Rep*. 2002;1(1):63-72.
36. Warkentin TE. Think of HIT. *Hematology Am Soc Hematol Educ Program*. 2006;408-414.
37. Warkentin TE, Whitlock RP, Teoh KHT. Warfarin-associated multiple digital necrosis complicating heparin-induced thrombocytopenia and Raynaud's phenomenon after aortic valve replacement for adenocarcinoma-associated thrombotic endocarditis. *Am J Hematol*. 2004;75(1):56-62.
38. Bakchoul T, Jouni R, Warkentin TE. Protamine (heparin)-induced thrombocytopenia: a review of the serological and clinical features associated with anti-protamine/heparin antibodies. *J Thromb Haemost*. 2016;14(9):1685-1695.
39. Warkentin TE. Heparin-induced thrombocytopenia in critically ill patients. *Semin Thromb Hemost*. 2015;41(1):49-60.
40. Warkentin TE. Agents for the treatment of heparin-induced thrombocytopenia. *Hematol Oncol Clin N Am*. 2010;24(4):755-775. ix.
41. Selleng K, Selleng S, Raschke R, et al. Immune heparin-induced thrombocytopenia can occur in patients receiving clopidogrel and aspirin. *Am J Hematol*. 2005;78(3):188-192.
42. Warkentin TE. New approaches to the diagnosis of heparin-induced thrombocytopenia. *Chest*. 2005;127(2 suppl):35S-45S.
43. Hillis C, Warkentin TE, Taha K, Eikelboom JW. Chills and limb pain following administration of low-molecular-weight heparin for treatment of acute venous thromboembolism. *Am J Hematol*. 2011;86(7):603-606.
44. Warkentin TE, Pai M, Linkins LA. Direct oral anticoagulants for treatment of HIT: update of Hamilton experience and literature review. *Blood*. 2017;130(9):1104-1113.
45. Warkentin TE. Heparin-induced thrombocytopenia and the anesthesiologist. *Can J Anesth*. 2002;49(6 suppl):S36-S49.
46. Warkentin TE, Hirte HW, Anderson DR, Wilson WEC, O'Connell GJ, Lo RC. Transient global amnesia associated with acute heparin-induced thrombocytopenia. *Am J Med*. 1994;97(5):489-491.

47. Warkentin TE, Sheppard JI. Clinical sample investigation (CSI) hematology: pinpointing the precise onset of heparin-induced thrombocytopenia (HIT). *J Thromb Haemost*. 2007;5(3):636-637.
48. Warkentin TE. Acute intraoperative HIT during heart surgery: why so rare? *Thromb Res*. 2016;146:110-112.
49. Warkentin TE, Pai M, Sheppard JI, Schulman S, Spyropoulos AC, Eikelboom JW. Fondaparinux treatment of acute heparin-induced thrombocytopenia confirmed by the serotonin-release assay: a 30-month, 16-patient case series. *J Thromb Haemost*. 2011;9(12):2389-2396.
50. Linkins LA, Warkentin TE, Pai M, et al. Rivaroxaban for treatment of suspected or confirmed heparin-induced thrombocytopenia study. *J Thromb Haemost*. 2016;14(6):1206-1210.
51. Linkins LA, Bates SM, Lee AYY, Heddle NM, Wang G, Warkentin TE. Combination of 4Ts score and PF4/H-PaGIA for diagnosis and management of heparin-induced thrombocytopenia: prospective cohort study. *Blood*. 2015;126(5):597-603.
52. Warkentin TE, Kelton JG. A 14-year study of heparin-induced thrombocytopenia. *Am J Med*. 1996;101(5):502-507.
53. Cuker A, Arepally GM, Chong BH, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia. *Blood Adv*. 2018;22(2):3360-3392.
54. Demers C, Ginsberg JS, Brill-Edwards P, et al. Rapid anticoagulation using ancrod for heparin-induced thrombocytopenia. *Blood*. 1991;78(9):2194-2197.
55. Spectre G, Kalish Y, Schliamser L, Varon D. Heparin-induced thrombocytopenia in myeloproliferative disorders: a rare or underdiagnosed complication? *Am J Hematol*. 2008;83(5):420-423.
56. Bovet J, De Maistre E, Bejot Y, Girodon F. Are myeloproliferative neoplasms a risk factor for heparin-induced thrombocytopenia? *Br J Haematol*. 2016;175(3):537-539.
57. Castelli R, Gallipoli P, Schiavon R, Teatini T, Deliliers GL, Bergamaschini L. High prevalence of heparin induced thrombocytopenia with thrombosis among patients with essential thrombocytemia [sic] carrying V617F mutation. *J Thromb Thrombolysis*. 2018;45(1):106-113.
58. Warkentin TE, Safyan EL, Linkins LA. Heparin-induced thrombocytopenia presenting as bilateral adrenal hemorrhages. *N Engl J Med*. 2015;372(5):492-494.
59. Warkentin TE, Greinacher A. Spontaneous HIT syndrome: knee replacement, infection, and parallels with vaccine-induced immune thrombotic thrombocytopenia. *Thromb Res*. 2021;204:40-51.
60. Bauer TL, Arepally G, Konkle BA, et al. Prevalence of heparin-associated antibodies without thrombosis in patients undergoing cardiopulmonary bypass surgery. *Circulation*. 1997;95(5):1242-1246.
61. Khoury M, Pitsis A, Poumpouridou-Kioura H, et al. Acute intraoperative heparin-induced thrombocytopenia (HIT) and thrombosis during coronary artery bypass grafting: two case reports providing evidence for the role of preoperative LMWH in triggering sensitization. *Thromb Res*. 2016;146:126-130.
62. Warkentin TE, Sheppard JI, Moore JC, Cook RJ, Kelton JG. Studies of the immune response in heparin-induced thrombocytopenia. *Blood*. 2009;113(20):4963-4969.

How to cite this article: Warkentin TE, Sheppard J-A, Whitlock RP. Temporal presentations of heparin-induced thrombocytopenia following cardiac surgery: A single-center, retrospective cohort study. *J Thromb Haemost*. 2022;20:2601-2616. doi: 10.1111/jth.15826