Heparin-induced thrombocytopenia (HIT): Clinical and economic outcomes

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Summary

Heparin-induced thrombocytopenia (HIT) is an immune-mediated adverse drug reaction that occurs following exposure to unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH). HIT with thrombosis (HITT) can cause devastating venous thromboembolism or arterial clots, prolonged hospitalization, and increased costs. To explore the economic and clinical implications of HIT and HITT, we initiated a single-center patient registry. In this report, we describe patient characteristics, comorbidities, management strategies, clinical outcomes, and costs. We enrolled 349 hospitalized patients with an enzyme immunoassay-confirmed diagnosis of HIT over a 40-month period. Patients were assessed for the primary outcome of 30-day mortality, as well as baseline characteristics, development of thrombosis, and the economic impact of HIT. The primary outcome measure was 30-day mortality and occurred in 58 (16.6%) patients, 40 (15.3%) in the HIT group versus 18 (20.7%) in the HITT group (p=0.25). The frequency of HIT was greater in patients exposed to UFH than in patients exposed to LMWH (0.8% vs. 0.2%, respectively, p<0.001). Both HIT and HITT patients who were exposed to UFH had higher hospital costs than those exposed to LMWH ($113,100 vs. $56,352, respectively, p<0.001). HIT remains an important clinical problem with a high mortality rate and significant cost, regardless of development of thrombosis. Prospective controlled trials need to be conducted to determine the optimal strategy to reduce the frequency of HIT.

Keywords

Heparin, heparin-induced thrombocytopenia, thrombosis

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Introduction

Heparin-induced thrombocytopenia (HIT) is an immune-mediated adverse drug reaction that occurs following exposure to unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) (1). Commercial grade heparins are capable of stimulating an immune response in up to 5% of exposed individuals (2). Binding of HIT-inducing antibodies to a complex of heparin and platelet factor 4 (PF4) produces platelet activation and aggregation, leading to thrombus formation in either the venous or arterial system (3, 4). The spectrum of adverse events associated with generation of HIT-inducing antibodies ranges from no symptoms or signs to life-threatening heparin-induced thrombocytopenia with thrombosis (HITT) manifested by deep venous thrombosis (DVT), pulmonary embolism (PE), or arterial clots in the renal, cerebral, splenchnic, or coronary circulation (2, 5).

Whether UFH causes HIT more often than LMWH is controversial (6–8). Despite advances in HIT detection and management, HIT continues to be a serious clinical event with poor outcomes (9–11). Few data have provided the cost consequences and economic burden for those patients developing HIT and HITT (12).

To explore the pharmacoeconomic and clinical implications of HIT and HITT, we initiated a single-center patient registry at Brigham and Women's Hospital. In this report, we describe patient characteristics, comorbidities, management strategies, clinical outcomes, and costs.

Methods and materials

We enrolled hospitalized patients with a serologically confirmed diagnosis of HIT between July 2003 and December 2006. Patients were included if there was clinical suspicion (a platelet drop to <150X10^9/l or a 50% reduction of platelet count during hospitalization from baseline related to heparin) of HIT and a positive heparin-PF4 antibody enzyme-immunoassay (EIA) fol-

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Table 1: Baseline characteristics.

Characteristic	Isolated HIT (n=262)	HITT (n=87)	P-value
Age (mean years)	64.1 ± 14.9	63.4 ± 14.6	0.71
Sex (male)- no. %	139 (53.1)	47 (54)	0.87
Avg. length of stay (median)	25 ± 24.6	27.3 ± 19.5	0.38
Kidney disease	60 (22.9)	13 (14.9)	0.13
Liver disease	35 (13.4)	9 (10.3)	0.58
Cancer	50 (19.1)	29 (33.3)	0.01
Hypertension	148 (56.5)	47 (54.0)	0.69
Myocardial infarction	30 (11.5)	2 (2.3)	0.005
Coronary artery disease	127 (48.5)	31 (25.3)	0.05
Diabetes Mellitus	85 (32.4)	22 (25.3)	0.21
Pulmonary disease	77 (29.4)	26 (29.9)	0.93
Surgery during admission	157(59.9)	61 (70.1)	0.09
Type of surgery			
Cardiac surgery	108 (41.3)	32 (36.8)	0.46
Orthopedic surgery	4 (1.6)	4 (4.6)	0.1
All other surgeries	45 (17.2)	25 (29.8)	0.02
Thrombosis present prior to heparin	30 (11.5)	7 (8.1)	0.37
Mean baseline platelets ($X10^9$/l)	188 ± 101	214 ± 127	0.09
Mean platelet nadir ($X10^9$/l)	67.5 ± 34.5	77.7 ± 56.4	0.11
Time to platelet nadir (days)	11.2 ± 25.6	10.3 ± 11.2	0.69

Data are means + SD or Number (%), unless noted otherwise.

Table 2: Characteristics of heparin exposure.

Characteristic	Isolated HIT (n=262)	HITT (n=87)	P-value
Therapeutic dosing			
Treatment	93 (35.5)	27 (31)	0.45
Prophylaxis	111 (42.4)	28 (32.2)	0.09
Both	58 (22.1)	33 (37.9)	0.004
Indications for anticoagulation			
Prophylaxis	106 (40.5)	25 (28.7)	0.05
Atrial fibrillation	12 (4.6)	1 (1.1)	0.20
Cardiovascular surgery	15 (5.7)	5 (5.7)	0.79
Acute coronary syndrome	6 (2.3)	0	0.34
Mechanical heart valve	9 (3.4)	0	0.12
VTE treatment	18 (6.9)	7 (8.0)	0.14
Device or line placement	9 (3.4)	2 (2.3)	0.74
Cardiomyopathy or pulmonary hypertension	1 (0.4)	2 (2.3)	0.15
Dialysis	3 (1.1)	0	0.58
Stroke	1 (0.4)	2 (2.3)	0.15
Multiple indications	91 (34.7)	43 (49.4)	0.01
Type of heparin			
UFH	210 (80.1)	77 (88.5)	0.07
LMWH	24 (9.2)	1 (1.1)	0.01
Both	28 (10.7)	9 (10.4)	0.93
Administration method			
Subcutaneous	100 (38.2)	22 (25)	0.04
Intravenous	108 (41.2)	42 (48.3)	0.25
Both	48 (18.4)	23 (26.2)	0.11
Not specified (outside transfer)	9 (3.5)	5 (5.7)	0.35
Flush	4 (1.6)	0	-
Mean heparin exposure (days)	8.2 ± 9.1	10.7 ± 8.9	0.03
Percent receiving BID	42	25	0.01
Percent receiving TID	49	14	0.58
Mean start dose heparin IV (units/hour)	1,735 ± 2,548	1,507 ± 2,024	0.41
Mean start dose enoxaparin (mg)	44 ± 17.9	48 ± 21.2	0.19

Data are means + SD or Number (%), unless noted otherwise. VTE, venous thromboembolism; UFH, unfractionated heparin; LMWH, low-molecular-weight heparin; BID, twice daily; TID, three times daily; IV, intravenously.

lowing UFH or LMWH initiation (2, 13). Patients were stratified into two groups: HIT and HITT. All HIT patients who developed thrombosis following UFH or LMWH exposure were considered to have HITT. All other patients were classified as having HIT. Only the first admission was counted if a patient had subsequent hospitalizations during the study period.

We captured all hospitalization costs for each patient by using the hospital database and the proprietary software package, ECLIPSYS (Transitions Systems, Inc., Boston, MA, USA). Costs were further categorized as follows: operating room, clinical laboratory, radiology (magnetic resonance imaging, computer axial tomography, and ultrasound imaging), blood products, cardiac catheterization laboratory, anesthesia, pharmacy, and other (nursing staff, support staff, medical and surgical staff, dialysis, emergency, neurology/psychiatry, nutrition, respiratory, obstetrics/gynecology, oncology, orthopedics, physical therapy, supplies, and transplant). Costs were evaluated for HIT compared with HITT patients and for UFH compared with LMWH patients.

The primary clinical outcome was 30-day mortality, beginning the day of HIT diagnosis (anti-heparin-PF4 antibody positive). All symptomatic thromboses were confirmed with an appropriate imaging test (14–17). Bleeding was classified as major if it was overt and associated with a decrease in haemoglobin concentration of at least 2 g/dl, requiring a transfusion of two or more units of packed red blood cells, or was intracranial, retroperitoneal, or into a major prosthetic joint. Bleeding events that did not meet these criteria were classified as minor.

Statistical analysis

We used Chi-square tests or Fisher's exact tests to compare categorical variables and Student's t-tests to compare differences in means. All p-values were two-tailed and statistically significant at an alpha of ≤0.05.

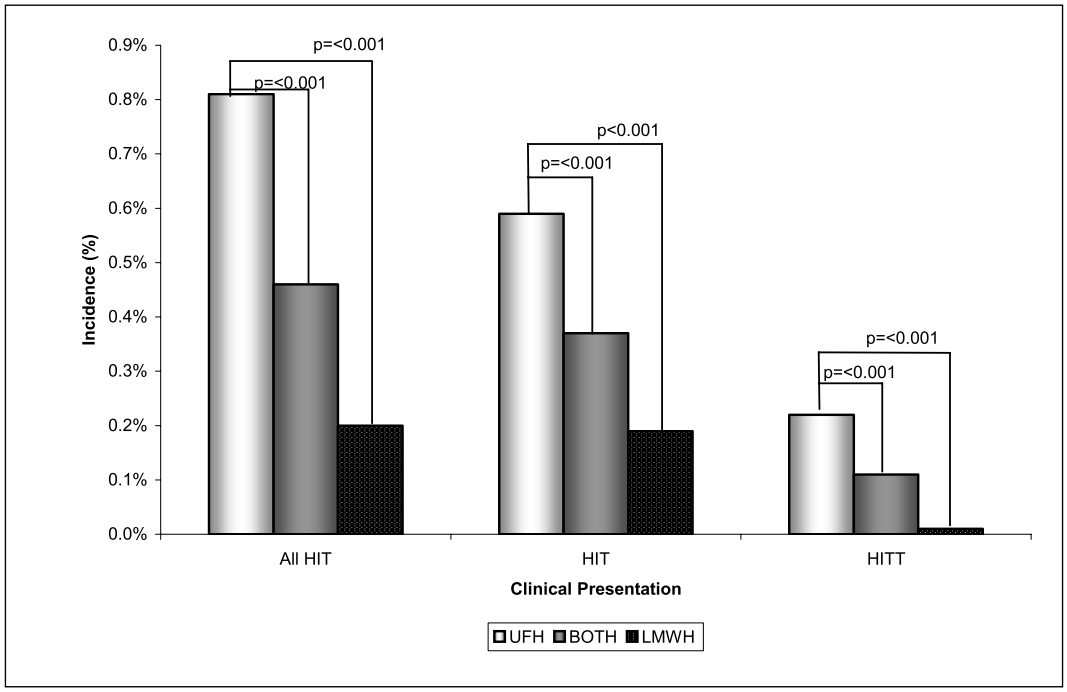

Figure 1: Frequency of all HIT, isolated HIT, and HITT according to causative agents. During the study period, 35,415 patients received unfractionated heparin (UFH), 12,611 received low-molecular-weight heparin (LMWH), and 8,088 received both. Of these patients, HIT developed in 287 (0.8%), 25 (0.2%), and 37 (0.5%), patients, respectively. P-value refers to comparisons with unfractionated heparin.

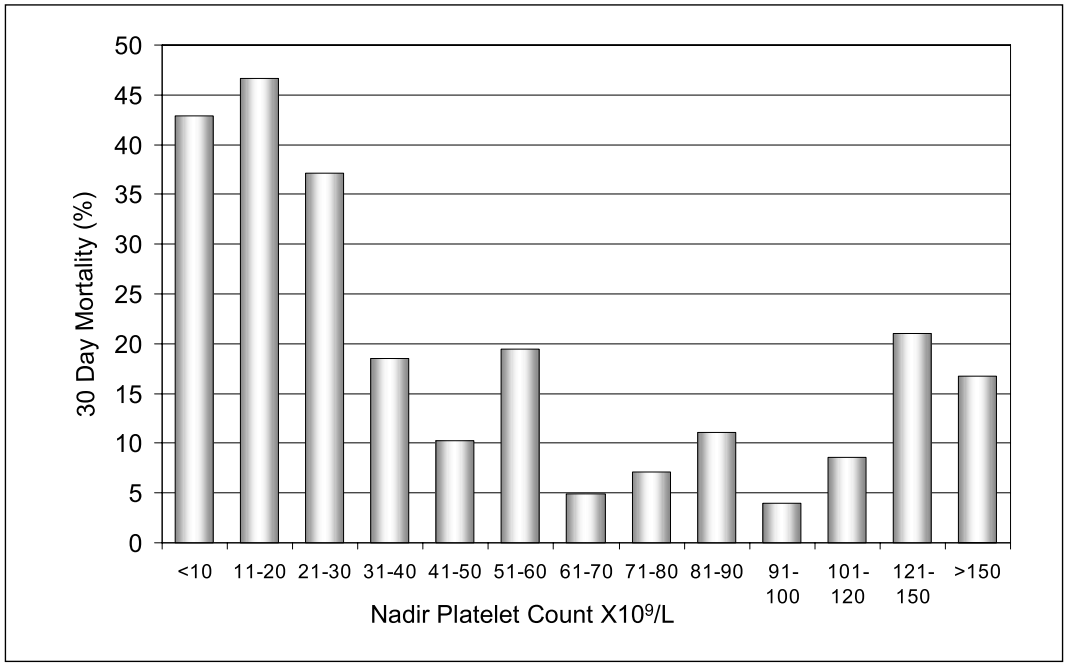

Figure 2: Platelet nadirs of patients who died within 30 days.

Results

Patient characteristics

Overall, 349 patients developed HIT confirmed by clinical and serologic diagnoses during the study period. Baseline characteristics of 262 (75.1%) HIT patients and 87 (24.9%) HITT patients are shown in Table 1. The two groups were similar except that HIT patients more often had myocardial infarction, whereas HITT patients more often had cancer. Baseline platelet counts, platelet nadir counts, and the time to platelet nadir were similar in both groups.

UFH was the presumed causative agent in 287 (82.2%), LMWH in 25 (7.2%), and both UFH and LMWH in 37 (10.6%). Over the study period, 56,114 patients were exposed to UFH or LMWH, 35,415 to UFH, 12,611 to LMWH, and 8,088 to both agents. HIT was more frequent in patients exposed to UFH (0.8%) than in those patients exposed to LMWH (0.2%, p<0.001) (Fig. 1).

Indications for anticoagulation were similar in both groups (Table 2), except that patients who eventually developed HIT less often received anticoagulation for both prophylaxis and treatment of thrombosis, 58/262 (22.1%), compared with patients who eventually developed HITT, 33/87 (37.9%) (p=0.004). Of

the 87 patients who developed HITT, 77 (87.5%), 1 (1.1%), and 9 (10.4%) patients had been exposed to UFH, LMWH, and both, respectively. Patients who received UFH developed HITT [77/287 (26.8%)] more often than those who received LMWH [1/25 (4%)] (p=0.01).

Most patients [337 (96.6%)] developed thrombocytopenia to less than $150X10^9$/l, including 256 (97.7%) with HIT and 81 (93.1%) with HITT. When stratified according to nadir platelet count, patients with marked thrombocytopenia, less than $40X10^9$/l, had a higher likelihood of 30-day mortality (33.3% vs. 12.8%, p<0.001) (Fig. 2).

After establishing the diagnosis of HIT or HITT, the most common parenteral anticoagulant prescribed was argatroban, especially in patients with HITT, followed by fondaparinux, bivalirudin, and lepirudin (Table 3). HIT patients were treated with a direct thrombin inhibitor or fondaparinux (58.0%) less frequently than HITT patients (86.2%) (p=0.002).

Table 3: Direct thrombin inhibitor and fondaparinux use.

Treatment	Isolated HIT (n=262)	HITT (n=87)	P-value
Argatroban	64 (24.4)	37 (42.5)	0.001
Fondaparinux	29 (11.1)	6 (6.9)	0.26
Bivalirudin	16 (6.1)	4 (4.6)	0.60
Lepirudin	3 (1.1)	1 (1.2)	0.79
Multiple agents	40 (15.3)	27 (31.0)	0.001
None	110 (42.0)	12 (13.8)	0.71

Data number (%), unless noted otherwise.

Death or non-fatal complications

The primary outcome measure of 30-day mortality occurred in 58 of the 349 patients (16.6%) (Table 4). The death rate was similar in HIT and HITT patients. There were 40 (15.3%) deaths in the HIT group versus 18 (20.7%) deaths in the HITT group (p=0.25). In-hospital mortality was similar, with 55 deaths in the HIT group (20.1%) and 19 in the HITT group (21.8%) (p=0.88). The most common cause of death in both groups was multisystem organ failure.

The thrombotic complications that occurred were in the venous circulation in 70 patients (80.5%). There were 26 isolated DVT, 31 PE alone or PE with DVT, and 13 episodes of venous gangrene. Thrombotic complications in the arterial circulation occurred in 17 patients (19.5%): 12 stroke, three aortic thrombosis, and two peripheral arterial occlusions.

There were no significant differences in major bleeding, minor bleeding, transfusions, or changes in haematocrit or haemoglobin values between the HIT and HITT groups.

Table 4: Death or non-fatal complications.

Outcomes	Isolated HIT (n=262)	HITT (n=87)	P-value
30-day mortality	40 (15.3)	18 (20.7)	0.25
In-hospital mortality	55 (21)	19 (21.8)	0.88
Bleeding events			
Major	16 (6.1)	7 (8.0)	0.62
Minor	13 (5.0)	8 (9.2)	0.15
Red blood cell transfusions	7.9 ± 8.7	9.9 ± 13.9	0.21
Mean baseline haematocrit	33.6 ± 5.3	35.7 ± 6.0	0.005
Mean haematocrit nadir	22.1 ± 4.5	23.6 ± 3.4	0.002
Venous thrombosis	--	70 (80.5)	--
PE alone or PE with DVT	--	31 (35.6)	--
Isolated DVT	--	26 (29.9)	--
Gangrene	--	13 (14.9)	--
Arterial thrombosis	--	17 (19.5)	--
Stroke	--	12 (13.8)	--
Aortic	--	3 (3.5)	--
Peripheral	--	2 (2.3)	--
Cause of death (Inpatient)			
Multi-system organ failure	53 (20.2)	14 (16.1)	0.01
Cerebral aneurysm rupture	0	1 (1.1)	0.26
Sepsis	2 (0.8)	0	0.72
Stroke (ICH)	0	4 (21.1)	0.002

Data are means + SD or Number (%), unless noted otherwise. PE, pulmonary embolism; DVT, deep venous thrombosis; ICH, intracranial haemorrhage.

Pharmacoeconomic outcomes

Total hospitalization costs were similar for HIT ($122,191 ± $87,440) and HITT ($112,281 ± $89,830) (p=0.84). The costs were also similar when pre-diagnosis and post-diagnosis expenses were compared (Table 5). Operating room costs were higher for HIT than HITT. Patients who were exposed to UFH had higher hospital costs than those exposed to LMWH ($113,100 vs. $56,325, respectively, p<0.001) (Table 6). All costs were greater in patients exposed to UFH, with the exception of pre- and post-HIT cardiac catheterization costs. There was no difference in the length of stay between these groups. More patients who received UFH underwent cardiac surgery (48%) compared to the LMWH patients (4%), p<0.001.

Discussion

This registry provides a contemporary profile of patients diagnosed with HIT and HITT. The most common cause of death was multisystem organ failure. While many of the patients who died had thrombosis and/or microemboli, it is difficult to isolate these thromboembolic events as the sole cause of mortality.

Most prior studies indicate that administration of UFH carries a higher risk than LMWH for developing HIT (6, 7). Our findings are consistent with the published literature. VTE prophylaxis was the primary reason for administration of heparin. Our data demonstrate that even when patients received lower, prophylactic doses of heparin, HIT was a very real concern. This risk, however, does not outweigh the overwhelming benefit of using VTE prophylaxis in patients at risk.

Table 5: Cost comparisons: HIT versus HITT.

Expense category pre-diagnosis	HIT (n= 262) pre-HIT expense ($)	HITT (n=87) pre-HIT expense ($)	P-value
All hospital costs	$57,325 ± 47,406	$50,978 ± 43,260	0.25
Pharmacy	$3,321 ± 4,388	$3,654 ± 4,148	0.52
Operating room	$20,178 ± 25,110	$11,234 ± 14,561	<0.001
Cardiac cath lab	$2,264 ± 4,814	$2,863 ± 7,114	0.46
Radiology	$1,953 ± 2,555	$3,716 ± 8,197	0.05
Clinical laboratories	$1,994 ± 1,839	$2,053 ± 1,987	0.81
Blood services	$1,928 ± 2,848	$1,622 ± 2,580	0.35
Anesthesia	$2,172 ± 987	$1,498 ± 1,189	<0.001
All other	$23,515 ± 24,968	$24,338 ± 23,490	0.78
Total anticoagulation	$306 ± 878	$472 ± 1,191	0.24
Post-diagnosis	**Post-HIT expense**	**Post-HIT expense**	
All hospital costs	$64,866 ± 84,903	$ 61,303 ± 73,563	0.71
Pharmacy	$8,072 ± 13,979	$10,834 ± 13,299	0.13
Operating room	$10,630 ± 28,835	$3,729 ± 11,824	0.002
Cardiac cath lab	$2,689 ± 7,077	$1,130 ± 3,990	0.011
Radiology	$2,341 ± 2,732	$3,200 ± 4,754	0.11
Clinical laboratories	$2,055 ± 3,121	$2,287 ± 2,633	0.49
Blood services	$1,651 ± 4,323	$1,785 ± 3,547	0.77
Anesthesia	$1,345 ± 2,073	$469 ± 1,044	<0.001
All other	$36,082 ± 55,171	$37,870 ± 48,330	0.77
Total anticoagulation	$4,451 ± 8,749	$5,547 ± 8,273	0.31
Length of stay (days)	25 ± 25	27 ± 19	0.44
Total hospital costs	$122,191 ± 87,440	$112,281 ± 89,830	0.37

Data are means ± SD. *Cardiac cath lab=cardiac catheterization laboratory.

Table 6: Cost comparisons: UFH versus LMWH.

Expense category pre-diagnosis	UFH (n= 287) pre-HIT expense ($)	LMWH (n=25) pre-HIT expense ($)	P-value
All hospital costs	$55,064 ± 46,351	$22,987 ± 17,133	<0.001
Pharmacy	$3,295 ± 4,357	$1,927 ± 2,507	0.02
Operating room	$17,867 ± 21,923	$1,617 ± 0	<0.001
Cardiac cath lab	$2,437 ± 5,745	$9,690 ± 2,148	0.01
Radiology	$2,452 ± 5,057	$1693 ± 2,213	0.16
Clinical laboratories	$2,003 ± 1,908	$1325 ± 994	0.005
Blood services	$1,958 ± 2,985	$745 ± 906	<0.001
Anesthesia	$2,124 ± 945	$315 ± 0	<0.001
All other	$22,928 ± 24,282	$14394 ± 11,795	0.004
Total anticoagulation	$354 ± 1,001	$193 ± 269	0.05
Post-diagnosis	**Post-HIT expense**	**Post-HIT expense**	
All hospital costs	$58,036 ± 64,690	$33,338 ± 23,770	<0.001
Pharmacy	$9,163 ± 14,713	$5,103 ± 6,527	0.01
Operating room	$11,813 ± 28,452	$4,537 ± 4,713	0.07
Cardiac cath lab	$2,463 ± 6,876	$3,058 ± 6,537	0.67
Radiology	$2,819 ± 3,643	$1,516 ± 1,919	0.005
Clinical laboratories	$2,208 ± 3,157	$1,134 ± 953	0.001
Blood services	$1,870 ± 4,507	$573 ± 947	0.001
Anesthesia	$1,411 ± 1,958	$764 ± 922	0.005
All other	$37,760 ± 56,176	$16,653 ± 14,860	<0.001
Total anticoagulation	$5,591 ± 9,731	$3,144 ± 4,762	0.03
Length of stay (days)	25.5 ± 24.2	21 ± 12	0.1
Total hospital costs	$113,100 ± 84,380	56,325 ± 52,370	<0.001

Data are means ± SD. *Cardiac cath lab=cardiac catheterization laboratory. UFH, unfractionated heparin; LMWH, low-molecular-weight heparin.

Recent data demonstrate an inverse relationship between thrombocytopenia, less than $150X10^9$/l, and mortality (18). By definition, all patients enrolled in our registry had thrombocytopenia. When stratified according to nadir platelet count, patients with more severe thrombocytopenia had a higher rate of mortality.

Patient characteristics were similar between the isolated HIT and HITT groups, although more HIT patients suffered from myocardial infarction and more HITT patients had cancer. Patients with myocardial infarction were more likely to have undergone cardiac catheterization. In general, patients exposed to heparin during cardiac catheterization often develop PF4 antibodies in the absence of thrombotic events (19). Patients with cancer have demonstrated a higher likelihood of developing HITT (20).

In our registry, neither diagnosis nor therapy was controlled. However, the strength of this report is the representation of actual practice from a large number of HIT patients based upon clinical and serologic diagnoses. We did not capture patients who may have developed late onset HIT after discharge. At the other extreme, we did not detect patients who may have developed early, rapid-onset HIT due to re-exposure to heparin, with rapid and sudden fatal clotting complications prior to serologic confirmation of HIT. Instead, we included only those patients with clinical suspicion and serologic evidence of developing HIT during admission, as well as having an identifiable heparin exposure.

It is likely that in some cases, the positive PF4 EIA was an epiphenomenon in which the assay was positive despite a low pretest probability of HIT (21). Utilization of a functional assay or a formalized clinical scoring system may improve the accuracy of HIT diagnosis (22, 23). We did not use a formal clinical scoring system to assess patients despite the risk of a false positive PF4-dependent EIA. The ordering of the in-house EIA was dependent upon the practitioner's clinical suspicion of HIT based on thrombocytopenia following heparin administration (24). The use of a functional assay in addition to the EIA in testing for suspected HIT has been shown to exclude the diagnosis of HIT in 30–50% of patients who were positive with the EIA alone. However, use of a functional assay is not common practice in the United States.

HIT patients generate a heavy burden in terms of resource consumption and hospital expense. We found no differences in the total hospital costs associated with caring for patients with

HIT or HITT. In both instances, average total hospital costs per patient exceeded $100,000. In the period following diagnosis (anti-heparin-PF4 antibody positive), pharmacy costs comprised the highest component of total hospital costs. We did not isolate costs such as adverse events that may have been associated with the treatment of HIT (25).

The costs in patients suspected to have HIT are very high and driven in part, by the increased cost of alternative anticoagulation. If 30% of these patients were assumed to have a "false positive" EIA, the estimated cost savings in this series of 349 patients would have been $724,692, simply by avoiding the use of direct thrombin inhibitors or fondaparinux. These excess drug therapy costs are far greater than the cost of using a functional assay to confirm the diagnosis of HIT in all patients.

In summary, HIT remains an important clinical problem with a high mortality rate, regardless of development of HITT. Prevention of HIT should be our goal. Prospective controlled trials need to be conducted to determine the optimal strategy to reduce the frequency of HIT.

What is known about this topic?

– Heaprin-induced thrombocytopenia (HIT) is associated with thrombosis, increased mortality, and heavy economic burden.
– Unfractionated heparin probably causes HIT more often than low-molecular-weight heparin (LMWH).
– The relationship between platelet nadir and mortality in patients with HIT is uncertain.

What does this paper add?

– In our registry, thrombosis developed in one of every four patients with HIT. Thirty-day mortality occurred in 17% of patients (15% of isolated HIT patients and 21% HIT with thrombosis patients). The average total hospital cost per patient exceeded $100,000 per admission.
– The administration of UFH carried a four times higher risk than LMWH for developing HIT.
– Patients with more severe thrombocytopenia (platelet count <30 $X10^9$) had a higher rate of mortality.

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