The incidence of heparin-induced thrombocytopenia in medical patients treated with low-molecular-weight heparin: a prospective cohort study

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In contrast with extensive documentation in patients treated with unfractionated heparin (UFH), the incidence of heparin-induced thrombocytopenia (HIT) in medical patients receiving low-molecular-weight heparin (LMWH) is less well defined. In a prospective cohort study, the platelet count was monitored in 1754 consecutive patients referred to 17 medical centers and treated with LMWH for prophylaxis or treatment of thromboembolic disorders. The diagnosis of HIT was accepted in case of a platelet drop of at least 50%, the absence of obvious explanations for thrombocytopenia, and the demonstration of heparin-dependent IgG antibodies. HIT developed in 14 patients (0.80%; 95% CI, 0.43%-1.34%), in all of them within the first 2 weeks, and was more frequent in patients who had (1.7%) than in those who had not (0.3%) been exposed to UFH or LMWH (OR = 4.9; 95% CI, 1.5-15.7). The prevalence of thromboembolic complications in HIT patients (4 of 14; 28.6%) was remarkably higher than that (41 of 1740; 2.4%) observed in the remaining patients (OR = 16.6; 95% CI, 5.0-55.0). Immune thrombocytopenia and related thromboembolism may complicate the clinical course of medical patients treated with LMWH with a frequency that is not different from that observed with the use of UFH. The previous administration of heparin increases the rate of HIT. (Blood. 2005;106: 3049-3054)

Introduction

Although the incidence of heparin-induced thrombocytopenia (HIT) and its clinical features have been thoroughly investigated in patients treated with unfractionated heparin (UFH),[1-4] much less attention has been paid to the risk of this threatening complication of heparin treatment in patients receiving low-molecular-weight heparin (LMWH). Indeed, the risk of this immune disorder from LMWH prophylaxis or treatment is generally reputed to be much lower than that observed with the use of UFH,[1-4] although cases of HIT are occasionally encountered in clinical practice. Accordingly, there is an increasing tendency to withhold platelet surveillance from medical patients treated with prophylactic or therapeutic doses of LMWH, especially outside hospital departments.[1]

To our knowledge, only limited information on the rate of HIT in patients receiving LMWH is available. In 2 prospective controlled studies, addressing the rate of HIT in patients randomized to UFH or LMWH for prevention[5] and treatment[6] of deep vein thrombosis (DVT), respectively, clinical or laboratory evidence of HIT was found in patients treated with LMWH to a significantly lower extent than in those who received UFH. Although this information is reassuring, there is the need for more extensive information coming from cohort studies to better quantify the true rate of immune thrombocytopenia and HIT-related complications in different settings of patients treated with LMWH.

To estimate the incidence and timing of HIT in medical patients requiring the administration of LMWH for various indications either in the hospital or at home, we performed a multicenter prospective cohort study in 1754 consecutive patients referred to 17 departments of internal medicine. All patients recruited for this investigation were followed for the occurrence of HIT and overt thromboembolic events.

Patients, materials, and methods

Study design

This was a prospective cohort multicenter study specifically designed to determine the incidence of HIT in both hospitalized and nonhospitalized medical patients receiving LMWH, as well as the occurrence of arterial or venous thrombotic events related to this complication. The study was conducted according to the ethical principles stated in the Declaration of Helsinki, and the protocol was approved by the Institutional Review Board of each participating center.

Inception cohort

Consecutive patients referred to 17 departments of internal medicine between March 2003 and September 2004 were eligible for the study provided that they had indications to receive subcutaneous LMWH for prophylaxis or treatment of arterial or venous thromboembolic diseases. Patients who were already receiving UFH or LMWH at referral were excluded as were those who had an abnormal baseline platelet count ($< 150 \times 10^9$/L or $> 450 \times 10^9$/L), had hematologic malignancies, were

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An Inside *Blood* analysis of this article appears in the front of this issue.

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receiving radiotherapy or chemotherapy, or had clinical or laboratory findings compatible with disseminated intravascular coagulation (DIC), sepsis, liver cirrhosis, hypersplenism, or severe renal insufficiency.

At referral, all patients included in the study received a thorough medical history and physical examination with particular attention to any previous (documented or likely) exposure to UFH or LMWH.

In patients requiring the prevention of thromboembolism, prophylactic doses of LMWH were programmed for variable periods of time, usually covering the entire period of risk. In patients with acute thromboembolic disorders, LMWH was administered in fixed therapeutic doses adjusted to body weight, with oral anticoagulation started in the first week of treatment, and heparin interrupted when the international normalized ratio (INR) reached a value more than or equal to 2.0 in 2 consecutive determinations. In a minority of patients a longer course of LMWH, not followed by oral anticoagulants, was programmed.

Doses and duration of prophylactic or therapeutic LMWH were left to the discretion of the attending physician.

Development of HIT

A platelet count was performed at baseline and thereafter at least every 2 or 3 days. The diagnosis of HIT was suspected in all cases of platelet drop of at least 50% of pretreatment value, provided that this was confirmed by a second determination. In all patients in whom a likely explanation for thrombocytopenia (hemodilution from fluids/blood, sepsis, DIC, other drug reactions, etc) could not be found, a blood sample was obtained for the subsequent determination of heparin-dependent antibodies. The diagnosis of HIT was accepted in case of demonstration of heparin-dependent antibodies. In case of the patient's unexpected death precluding the laboratory determination, the diagnosis of HIT was accepted if there was no other obvious clinical explanation for thrombocytopenia and the platelet drop had occurred at least 5 days after the start of heparin use.

The first day of heparin use was calculated as day zero, and the day when a drop in the platelet count of at least 50% was observed was assumed to be the day of HIT occurrence.

All included patients underwent their laboratory and clinical observations for the entire duration of drug administration (plus an additional 3-day period), for a maximum of 1 month. In a subgroup of consecutive patients enrolled at 3 participating centers, clinical information was obtained, along with a platelet count, 1 month after LMWH cessation to check the development of delayed HIT.

Laboratory determination of heparin-dependent IgG antibodies

Both an antigen and a functional assay were performed to detect heparin-dependent antibodies according to previously described methods.[7-9] Blood samples were collected from a brachial vein with a fine needle in sodium citrate 1:10 (antigen assay) and without anticoagulant (functional assay). Samples were then centrifuged at 10 000*g* for 3 minutes and stored at −70°C.

The samples were screened by an antigen assay that detects antibody mixture of IgG, IgA, and IgM antibodies against platelet factor 4 complexed with polyvinyl sulfonate (Genetic Testing Institute, Brookfield, WI).[7,8] Absorbance of the substrate of alkaline phosphatase was measured at 405 nm. This test was followed, in case of a positive result, by the search for HIT antibodies of the IgG class using a single anti-IgG alkaline phosphatase conjugate Fc specific (Sigma Chemical, St Louis, MO). The cut-off value of optical density (OD) for the antibody determination was assessed using plasma samples of 43 patients who did not develop thrombocytopenia within 48 hours of LMWH start; the value was found to be 0.4 for the antibodies mixture and 0.3 for IgG antibodies.

The functional test was done with a modification of the visual evaluation of heparin-induced platelet activation (HIPA) assay.[9] Fresh blood was obtained from 3 donors with clinical history of HIT and collected into acid-citrate-dextrose (1:5 vol/vol). Platelet-rich plasma (PRP) was separated by centrifugation at 150*g* for 12 minutes and apyrase 4 U/mL (Sigma Chemical) was added; after centrifugation at 600*g*, platelets were resuspended in calcium- and albumin-free Tyrode buffer, pH 6.2, containing apyrase 2 U/mL. After a further centrifugation at 600*g*, platelets were resuspended to a final concentration of 250×10^9/L in Tyrode buffer, pH 7.4, containing 1 mM $MgCl_2$ and 2 mM $CaCl_2$. The test mixture consisted of 20 μL heat-inactivated patient serum, 10 μL heparin 0.3 and 100 IU/mL (Epsoclar, Novate Milanese, Italy) or buffer, and 70 μL washed platelets. The test mixture was placed in the wells of a microtiter plate (Greiner, Nurtingen, Germany) containing 2 steel spheres, and agitated for 45 minutes at 25°C in a magnetic stirrer (900 rpm). After stirring, the transparency of the suspension using low but not high heparin concentration was considered as a positive result. Platelets stimulated by 5 μM ionophore A23187 (Sigma), and reference HIT serum giving a positive result with a lag time of about 20 minutes, served as positive controls.

The laboratory determination was performed at either of 2 participating centers (Padua and Palermo, Italy), which adopted an identical approach.

Thromboembolic complications

The clinical suspicion of venous or arterial thromboembolism was confirmed by the following objective tests: compression ultrasound or venography in case of suspected DVT, ventilation/perfusion lung scanning, spiral computed tomography (CT) or pulmonary angiography in case of suspected pulmonary embolism, electrocardiography with enzymatic support in case of suspected myocardial infarction, and cerebral CT scan or magnetic resonance imaging in case of suspected stroke. In case of death, the cause was either investigated by autopsy or adjudicated according to the opinion of a physician unaware of the study aims.

Analysis

We evaluated the proportion, and its 95% confidence interval (CI), of patients who developed HIT among all those who were treated with LMWH.

Odds ratios (ORs) and their 95% CIs were used to describe the association between HIT and potential predisposing factors, and between thromboembolic complications and HIT. An OR was considered to be statistically significant when the lower limit of the 95% CI was at least 1.0.

The χ^2 test was used to compare proportions; a P value below .05 indicated a statistically significant difference.

Results

Patients

Of 2403 eligible patients, 629 (26.2%) were excluded because of ongoing LMWH administration (n = 240), abnormal platelet count at baseline (n = 181), concomitant radiotherapy or chemotherapy (n = 84), hematologic malignancies (n = 48), liver cirrhosis (n = 31), severe renal insufficiency (n = 23), septicemia (n = 12), or DIC (n = 10). Of the remaining 1774 patients, 20 refused to participate. Therefore, 1754 patients were included in the study, of whom 816 (46.5%) had LMWH treatment entirely in the hospital and the remaining 938 (53.5%) primarily on an ambulatory basis.

The main demographic and clinical characteristics of study patients are shown in Table 1. Of the 1754 patients, 376 (21.4%) received prophylactic low-dose LMWH, 728 (41.5%) therapeutic doses adjusted to body weight, and the remaining 650 (37.1%) intermediate doses (either fixed or adjusted to body weight); 268 (15.3%) were affected by malignancy; 598 (34.1%) had previous administration of UFH or LMWH, including 60 who had received either drug in the previous 3 months; and finally, 32 (1.8%) were pregnant patients.

The median duration of LMWH administration was 8 days (range, 2-30 days); 713 patients (40.6%) received up to 7 days of treatment, an additional 712 patients (40.6%) up to 14 days, 142 (8.1%) up to 21 days, and the remaining 187 (10.7%) up to 30 days. Of the entire cohort, 320 patients (18.2%), consecutively enrolled

Table 1. Main demographic and clinical characteristics of study patients

	Data
No. of patients	1754
Age, y, mean ± SD	66 ± 18
Sex, no. M/no. F	826/928
Pregnancy, no. (%)	32 (1.8)
Cancer, no. (%)	268 (15.3)
Previous heparin exposure, no. (%)	
More than 3 mo earlier	538 (30.7)
Within the previous 3 mo	60 (3.4)
Setting of treatment, no. (%)	
Entirely in the hospital	816 (46.5)
Primarily at home	938 (53.5)
Indication for LMWH therapy, no. (%)	
Prevention of VTE	452 (25.8)
Treatment of VTE	530 (30.2)
Atrial fibrillation	320 (18.2)
Coronary artery disease	187 (10.7)
Cerebrovascular disease	108 (6.2)
Other	157 (8.9)
LMWH dosage, no. (%)	
Fixed low-dose	376 (21.4)
Therapeutic adjusted-dose	728 (41.5)
Intermediate dose	650 (37.1)
LMWH type, no. (%)	
Nadroparin	880 (45.6)
Enoxaparin	700 (39.9)
Reviparin	67 (3.8)
Dalteparin	64 (3.6)
Parnaparin	43 (2.4)
LMWH duration, d, median (range)	8 (2-30)

at 3 participating centers, had clinical and laboratory surveillance up to 1 month after the discontinuation of LMWH.

Incidence, risk factors, and outcome of HIT

During the study period, 35 patients (2.0%) developed a platelet drop of at least 50%, confirmed by a second determination. In 4 patients, obvious explanations for thrombocytopenia could be found. Two other patients, both affected by advanced cancer, died unexpectedly because of myocardial infarction and pulmonary embolism occurring after 4 and 24 days, respectively, in timely association with their platelet drop. They could not receive the laboratory determination of heparin-dependent antibodies; therefore, the clinical suspicion of HIT could not be confirmed. However, in both patients a cancer-related DIC at the time of their fatal thromboembolic complication could not be excluded. Thus, these 2 patients were considered as unlikely to qualify for HIT development.

The antigen assay was positive in 14 of the 29 patients tested for the presence of heparin-dependent IgG antibodies, the OD being 1.0 or higher in 12 patients. The functional assay was positive in 11 of these 14 patients, and negative in the remaining 15. Hence, the rate of HIT in our cohort was 14 of 1754 (0.80%; 95% CI, 0.43%-1.34%). If the 2 patients who died unexpectedly because of thromboembolic complications, and in whom the search for heparin-dependent antibodies could not be done, are included in the analysis, this rate increases to 0.91% (95% CI, 0.52%-1.48%). However, if among patients who underwent serologic testing the 3 patients with negative functional tests are excluded, then the frequency falls to 0.63% (95% CI, 0.31%-1.12%).

The main features of the 14 patients with HIT are shown in Table 2. In all patients, the platelet drop began or accelerated from the beginning of the fall onward, without a preceding profile of a rising platelet count.

Of the 14 patients who developed HIT, 3 cases occurred in the 376 patients (0.8%) who received low-dose LMWH for prophylactic indications, 6 (0.8%) in the 728 patients who received full doses adjusted to body weight for therapeutic indications, and the remaining 5 (0.8%) in the 650 patients who had intermediate doses of LMWH (nonsignificant differences). Seven cases (0.9%) of HIT occurred in the 816 patients who had in-hospital LMWH treatment and 7 (0.7%) in the 938 who were treated primarily at home (nonsignificant difference). HIT developed in 9 (1.0%) of the 880 patients treated with nadroparin, in 3 (0.4%) of the 700 treated with enoxaparin, in 2 (3.1%) of the 64 treated with dalteparin, and in none of the 110 who were given reviparin or parnaparin.

The previous administration of heparin increased the rate of HIT. This complication occurred in 10 (1.7%) of the 598 patients

Table 2. Main features of the 14 patients with HIT

Patient no.	Age, y	Sex	Cancer present	Previous heparin exposure		Setting	Drug	Dosage	Time to HIT, d	Platelet count, $\times 10^9$/L, baseline/nadir	IgG ELISA OD	HIPA	TE	Time to TE d
				Previous exposure	Time since exposure									
1	73	M	Yes	Yes	4 mo	In hospital	Nadroparin	High	5	259/127	0.8	Negative	No	NA
2	26	M	Yes	No	NA	In hospital	Nadroparin	High	7	249/18	1.3	Positive	No	NA
3	74	M	No	Yes	2 y	In hospital	Nadroparin	High	12	150/32	>2.0	Positive	TIA	14
4	84	F	Yes	Yes	5 wk	In hospital	Enoxaparin	High	2	231/83	>2.0	Positive	No	NA
5	83	F	No	Yes	5 mo	In hospital	Dalteparin	Low	5	209/68	1.8	Positive	No	NA
6	73	M	Yes	Yes	6 mo	In hospital	Nadroparin	Intermediate	9	210/70	>2.0	Positive	Ischemic stroke	12
7	83	M	No	No	NA	In hospital	Nadroparin	Low	12	214/30	1.1	Positive	No	NA
8	63	M	No	Yes	5 mo	At home	Dalteparin	Low	5	186/50	0.9	Negative	No	NA
9	22	M	No	Yes	12 mo	At home	Enoxaparin	Intermediate	9	232/68	1.4	Positive	DVT	11
10	23	M	No	No	NA	At home	Nadroparin	Intermediate	9	248/65	1.2	Positive	No	NA
11	65	F	No	Yes	4 mo	At home	Enoxaparin	Intermediate	4	313/67	1.0	Positive	No	NA
12	44	F	No	Yes	8 mo	At home	Nadroparin	High	6	365/124	1.0	Negative	No	NA
13	38	M	No	No	NA	At home	Nadroparin	Intermediate	13	234/90	1.2	Positive	No	NA
14	72	F	No	Yes	6 mo	At home	Nadroparin	High	5	255/88	>2.0	Positive	Extension of DVT	6

ELISA indicates enzyme-linked immunosorbent assay; TE, thromboembolism; TIA, transitory ischemic attack; NA, not applicable.

who had previous administration of unfractionated or low-molecular-weight heparin (including 1 of the 60 patients who had received either drug in the previous 3 months), as compared with 4 (0.3%) of the 1156 patients who had never been exposed to LMWH (OR = 4.9; 95% CI, 1.5-15.7). After excluding from the analysis the 60 patients who had recently been exposed to LMWH, the OR did not change. HIT developed in a slightly higher proportion of patients with cancer (4 of 268; 1.5%) than noncancer patients (10 of 1486; 0.7%); however, the difference was not statistically significant (OR = 2.2; 95% CI, 0.7-7.2). No cases of HIT were observed among the 32 pregnant patients. Finally, no cases of delayed HIT were observed among the 320 patients who had a prolonged clinical and laboratory observation (0%; 95% CI, 0%-1.15%).

With the exception of the patient who had undergone LMWH treatment less than 3 months earlier (35 days), and developed HIT on day 2, in all remaining patients HIT developed between days 4 and 13: in 6 patients between days 4 and 6, and in additional 7 between days 7 and 13 of LMWH treatment.

The medical treatment of patients who developed HIT was left to the discretion of attending physicians. Ten patients received the intravenous infusion of lepirudin, 2 were treated with danaparoid, and the remaining 2 patients with dermatan sulfate according to either manufacturer's instructions (in case of treatment with lepirudin or danaparoid) or evidence from available literature (in case of treatment with dermatan sulfate).[10] In all 14 patients, the platelet count normalized within 10 days after the discontinuation of LMWH.

Symptomatic thromboembolic complications

Four of the 14 patients (28.6%; 95% CI, 8.4%-58.1%) who developed HIT experienced clinically symptomatic thromboembolic complications in timely association with the occurrence of HIT (proximal DVT in 1, symptomatic extension of ipsilateral DVT in 1, transitory ischemic attack in 1, and stroke resulting in a leg paralysis in 1). All of them belonged to the group of those who had been previously exposed to heparin. Thromboembolic complications were recorded also in 41 of the 1740 patients (2.4%; 95% CI, 1.7%-3.2%) who did not develop HIT (venous thromboembolism in 16, ischemic stroke in 13, acute myocardial infarction in 10, and arterial embolism in 2).

The incidence of thromboembolic events in patients who developed HIT was remarkably higher than that observed in patients who did not, leading to an OR of 16.6 (95% CI, 5.0-55.0). With the exception of the 2 patients described (see "Incidence, risk factors, and outcome of HIT"), in no other patients belonging to the latter group did the platelet count decrease during or following the thromboembolic complication.

Discussion

Because LMWHs are increasingly being used as substitutes for UFH for prophylaxis and treatment of venous and arterial thromboembolic disorders, there is the need to know the true frequency and severity of HIT occurring in medical patients who are candidates for the use of these compounds. In our study, specifically designed to assess the incidence of HIT in medical patients, we checked the development of this complication in 1754 consecutive patients referred to 17 medical departments who were given LMWH for variable periods for prophylactic or therapeutic indications. Of interest, in more than 50% of patients the treatment was conducted primarily on an at-home basis. Using stringent criteria, 14 patients (0.80%; 95% CI, 0.43%-1.34%) developed this complication. This rate is fully consistent with that (0.84%) recently found in a cohort of medical patients treated with UFH, in which similar criteria for HIT detection were adopted.[11] Accordingly, this threatening and potentially fatal complication is to be expected in medical patients treated with LMWH as frequently as in those treated with UFH.

As expected, the risk of thromboembolic complications in patients who developed HIT was high. Four (28.6%) of the 14 patients with HIT experienced either arterial or venous unexpected thromboembolic complications, as compared with 41 (2.4%) of the 1740 patients without HIT, leading to an OR of 16.6 (95% CI, 5.0-55.0). The inclusion of the 2 patients who died unexpectedly because of thromboembolic complications in timely association with the platelet drop and in whom the diagnosis of HIT could not be ruled out with certainty would have increased the OR (26.1; 95% CI, 9.1-75.5) and so would have the exclusion of the 3 patients with negative functional tests for HIT antibodies (23.7; 95% CI, 6.7-84.2). Although the absolute rate was lower than that observed in our recent investigation conducted in medical patients treated with UFH (3 of 5; 60%),[11] the CIs clearly overlap each other. Moreover, this frequency was far higher than that observed in the remaining patients of our cohort. Our data suggest that in those medical patients who develop immune HIT while receiving LMWH treatment, the occurrence of arterial or venous thromboembolic complications is to be expected as often as in patients treated with UFH.

Of interest, no difference in the rate of immune HIT could be detected between patients who had their LMWH treatment conducted entirely in the hospital and those treated primarily on an ambulatory basis. Patients who received LMWH for prevention of venous thromboembolism were as likely to develop HIT and its thrombotic complications as were those who received LMWH for treatment of VTE and those who were given LMWH for prevention or treatment of cardiovascular or cerebrovascular events. Although a higher incidence of HIT was observed in patients treated with dalteparin and, to a smaller extent, with nadroparin than in those treated with enoxaparin, and no cases were observed in patients treated with reviparin or Parnaparin, the lack of a randomized study design and the discrepancy in the number of patients treated with each compound do not allow the conclusion that a true difference exists in the potential of the various LMWHs to produce immune thrombocytopenia. Based on our study results a difference cannot be excluded, and therefore further investigations are needed to clarify this potentially important issue. Of interest, no cases of HIT were observed among the 32 pregnant patients. These considerations suggest that routine platelet count monitoring for HIT is appropriate in all categories of medical patients who are candidates for LMWH treatment irrespective of setting, clinical indication, or heparin type or dosage. Perhaps pregnant patients might remain an important exception, because to our knowledge there has never been a well-documented case of HIT reported in a pregnant patient who was treated exclusively with LMWH.[12]

Surprisingly enough, the incidence of HIT was significantly higher in patients who had a previous (documented or likely) exposure to either UFH or LMWH than in those who had never been exposed to heparin (OR = 4.9; 95% CI, 1.5-15.7), even when the analysis was confined to only the patients who had been treated with LMWH more than 3 months earlier. These findings are in contrast with those from our recent investigation in medical patients treated with UFH,[11] and may account for the relatively

early occurrence of thrombocytopenia (day 4-6) in several patients of our cohort (Table 2). This potentially important issue needs to be confirmed by future investigations.

The temporal pattern of thrombocytopenia reproduced that already described in medical patients treated with UFH.[1,11] In all patients the platelet drop began or accelerated from the beginning of the fall onward, without a preceding profile of a rising platelet count. This makes the behavior of HIT in medical patients substantially different from that usually seen in the surgical setting.[1] As expected, in the only patient with HIT who had received LMWH less than 3 months earlier (35 days), the platelet count fell dramatically 2 days after heparin administration, whereas in all other patients (including those who had been treated with heparin more than 3 months earlier) HIT did not occur before 5 days of LMWH administration (in 6 patients within the first week and in additional 7 within the second week). Finally, of the 320 patients who had a longer follow-up after LMWH discontinuation, none developed delayed-onset HIT (0%; 95% CI, 0%-1.15%). Although the number of patients who had a long-term follow-up was too small to draw reliable conclusions, the rate of delayed-onset HIT in medical patients treated with LMWH may be as low as that occasionally observed in patients treated with UFH.[13,14]

A number of methodologic issues deserve attention. Because we did not perform a baseline search for heparin-dependent antibodies, we cannot exclude that in a number of patients who subsequently developed HIT (especially in those who had previously been exposed to heparin) these antibodies were already present at time of patients' recruitment. In particular, because we were not able to identify among the many patients who had a previous heparin exposure the ones who had been treated with UFH, we cannot exclude that in a number of patients with HIT this complication developed as a result of antibodies produced by prior UFH exposition. In addition, because we did not systematically search for heparin-dependent antibodies in all patients during LMWH treatment, we cannot exclude that the formation of IgG occurred in a proportion of patients higher than that identified.[15] All of these are important issues and need to be addressed in future investigations. However, the purpose of our investigation was to make an estimate of the risk of clinically relevant HIT exhibited by those hospitalized and ambulatory medical patients who are currently treated with LMWH. This is important information for clinicians because every day millions of people receive LMWH for prophylaxis or treatment of thromboembolic disorders. The rate of LMWH-associated HIT we observed is plausible and consistent with that found in other series of medical patients treated with UFH or LMWH.[16] The validity of our approach is confirmed by the high prevalence of unexpected thromboembolic complications among patients labeled as affected by HIT, which fully compares with that observed in patients treated with UFH,[1-5] but contrasts with that observed in the remaining patients of our cohort.

We believe that the results of our study are widely applicable because a large number of consecutive patients with a broad spectrum of medical diseases requiring prophylactic or therapeutic administration of LMWH were included and prospectively followed until heparin discontinuation or later. Confounding factors were minimized by excluding patients suffering from diseases potentially responsible for nonimmune thrombocytopenia. Sensitive and specific criteria were adopted for the definition of HIT. The diagnosis of HIT was indeed accepted only in case of a platelet drop of at least 50% of the pretreatment value, the absence of obvious explanations for thrombocytopenia, and the demonstration of heparin-dependent IgG antibodies obtained using validated antigen and activation assays.[17] Finally, all suspected thromboembolic events were objectively confirmed.

In conclusion, HIT and HIT-related thromboembolic complications are relatively common adverse effects of LMWH treatment in medical patients. They affect especially those patients who have been previously exposed to heparin. Our findings suggest that, at least in medical patients, both the incidence of HIT and the prevalence of thromboembolic complications are consistent with those expected in patients treated with UFH. Because the use of LMWH has largely replaced that of UFH in clinical practice, clinicians should be alerted to and adopt in all patients who are candidates for LMWH those precautions that have long been suggested for prevention and early detection and treatment of immune thrombocytopenia in patients who are candidates for standard heparin therapy, including close clinical and laboratory surveillance at least in the first 2 weeks.

Appendix

In addition to the Writing Committee, the following investigators and institutions participated in the study, all in Italy (in the order of patients contributed to the study): Malattie Tromboemboliche ed Emorragiche, Ematologia con Trapianto, Azienda Ospedaliera Universitaria di Palermo (S. Siragusa, G. Bonifacio, R. Anastasio, A. Malato, L. Lo Coco, V. Abbadessa); Scienze Mediche e Chirurgiche, Clinica Medica II, Università di Padova (P. Prandoni, A. Concolato, M. Perlati, C. Bullo, L. Hartmann, R. Pesavento, A. Pagnan); Medicina Interna e Patologia Clinica, Ospedale di Piacenza (D. Imberti, E. Croci); Azienda Ospedaliera di Cosenza (C. Bova, R. Ricchio); Scienze Mediche e Chirurgiche, Medicina Interna, Università di Padova (F. Fabris, M. Scapin, M. Giannocaro); Medicina Clinica, Università dell'Insubria (W. Ageno, F. Dentali); Medicina Interna ed Angiologia, Azienda Ospedaliera Universitaria di Parma (R. Quintavalla, C. Pattacini); Clinica Medica III, Università di Pavia (C. Balduini, G. Bertolino, E. Venturi); Emostasi e Trombosi, Struttura Operativa di Medicina, Azienda Ospedaliera di Pordenone (P. Tropeano, L. Virgolini); Medicina Generale, Azienda Ospedaliera di Padova (B. Girolami, S. Bottegal, G. Brighenti, G. Baggio); Azienda Alto Vicentino di Thiene, Vicenza (C. Sardella, E. Fongaro, L. Guadagnin); Medicina Interna ed Angiologia, Centro Studi Neurolesi, Messina (S. Rotondo); Oncologia Medica, Ospedale di Taormina (F. Vitale); Angiologia e Chirurgia Vascolare, Trento (A. Bertoldi); Medicina Interna Valdichiana, Ospedale di Cortona (R. Migliacci); Casa di Cura Liotti, Perugia (G. Rosi, A. Lu Priore); and Medicina Generale, Ospedale di Belluno (F. Tremolada, L. Cimarosto).

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