Incidence and Prognostic Significance of Thrombocytopenia in Patients Treated With Prolonged Heparin Therapy

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Background: Despite widespread heparin use in clinical practice, the associated development of thrombocytopenia is an underrecognized and undertreated complication.

Methods: We analyzed data from consecutive hospitalized patients treated with heparin (unfractionated or low molecular weight) for 4 days or longer to determine the incidence, predictors, prognostic significance, and management of “thrombocytopenia,” defined as a platelet count less than $150 \times 10^9/L$, reduction in platelet count of 50% or more from the admission level, or both.

Results: We enrolled 2420 patients (median age, 65.2 years; 43.8% women) in 48 US hospitals. Thrombocytopenia occurred in 881 patients (36.4%; 95% confidence interval [CI], 34.5%-38.3%). Of those who developed thrombocytopenia, 5.1% died, compared with 1.6% of those without thrombocytopenia (odds ratio [OR], 3.4; 95% CI, 2.1-5.6; P <.001). Thrombocytopenia was also associated with greater risk of myocardial infarction (OR, 2.1; 95% CI, 1.5-2.8; P <.001) and congestive heart failure (OR, 1.3; 95% CI, 1.1-1.6; P = .01). After adjustment for important covariates, thrombocytopenia remained an independent predictor of thrombotic and hemorrhagic events. A relative reduction in platelet count of more than 70% was the strongest independent predictor of death (OR, 13.4; 95% CI, 6.5-27.6; P < .001), followed by a relative reduction in platelet count of 50% to 70%, worse Killip class, occurrence of thromboembolic complications, older age, and longer duration of heparin therapy.

Conclusions: Thrombocytopenia occurs frequently after prolonged heparin therapy and is strongly associated with worse short-term clinical outcome. The relative reduction in platelet count is a powerful independent predictor of all-cause mortality in hospitalized patients.

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THE CLINICAL USE OF HEPARIN AS AN ANTICOAGULANT BEGAN IN THE 1930S. WITH TIME, IT HAS STEADILY BECOME A STANDARD THERAPY FOR BOTH PREVENTING AND TREATING THROMBOTIC DISORDERS, WITH ESTIMATES (REPORTED IN 1995) OF 1 TRILLION UNITS BEING ADMINISTERED TO AS MANY AS 12 MILLION PATIENTS IN THE UNITED STATES.1

In patients receiving heparin compounds, thrombocytopenia can be defined as an absolute reduction in platelet count to less than $150 \times 10^9/L$, a relative reduction of 50% or more from the baseline level (baseline), or both. Patients with acute coronary syndrome and those undergoing percutaneous coronary intervention who receive heparin therapy and subsequently develop thrombocytopenia are at risk of adverse outcomes.2,3 However, the relationship of thrombocytopenia and outcome in an unselected population of hospitalized patients receiving heparin therapy has not been carefully studied. In this large prospective registry of unselected hospitalized patients, we sought to determine the incidence, predictors, prognostic significance, and current management of thrombocytopenia in hospitalized patients receiving therapy with either unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH).

METHODS

COMPLICATIONS AFTER THROMBOCYTOPENIA CAUSED BY HEPARIN REGISTRY: OVERALL POPULATION

The rationale and design of the Complications After Thrombocytopenia Caused by Heparin (CATCH) Registry have been published...
In brief, the CATCH trial was a prospective observational study of patients treated with heparin. Overall inclusion criteria were as follows: age older than 18 years; treatment with UFH by either the subcutaneous or intravenous route, LMWH, or both; and identification as being at risk for heparin-induced thrombocytopenia (HIT) according to prespecified definitions for 3 strata. Patients receiving heparin for 4 days or longer were consecutively identified and screened through computerized pharmacy records, and these patients were enrolled in the prolonged heparin stratum. Patients with cardiac disorders admitted to cardiac or intensive care units, being treated with any type of heparin, and who developed thrombocytopenia were enrolled in the cardiac thrombocytopenia stratum. Patients who underwent serologic testing for evaluation of immune-mediated HIT were enrolled in the serologic studies stratum. This prespecified approach enabled inclusion of patients with and without cardiac disorders from both medical and surgical settings.

Selected baseline patient characteristics, clinical variables and procedures during hospitalization, previous and in-hospital use of medications, standard laboratory measures, and clinical outcomes were captured electronically with patient identities blinded. Exclusion criteria used before the index admission included chronic (>30 days) thrombocytopenia, hematologic cancers, and receipt of antineoplastic agents known to affect the bone marrow. Where required, investigators received approval from their local institutional review board, and patients provided informed consent to participate. Forty-eight hospitals in the United States participated.

**THROMBOCYTOPENIA AND SEROLOGIC TESTING FOR HIT: DEFINITIONS**

Baseline and nadir platelet counts were collected for all patients enrolled in the CATCH Registry. To assess current clinical practices, local investigators determined the frequency of platelet count monitoring during the index hospitalization, the decision about which patients should be screened for immune-mediated HIT, and the type of serologic tests that should be used. The definition of thrombocytopenia was prespecified as an absolute reduction in platelet count on at least 1 measure to less than 150×10^9/L, a relative reduction of 50% or greater from baseline, or both. For serologic screening for HIT, we collected the type and number of tests that were performed to document the presence of HIT antibodies. We also evaluated the respective intervals between initial heparin administration, development of thrombocytopenia, first mention of suspicion of HIT in the medical record, ordering of serologic tests, and the availability of serologic test results, which were qualitatively expressed as positive, negative, or not performed.

**CLINICAL OUTCOMES**

All patients were followed up until hospital discharge or death, whichever occurred first. Clinical events that occurred from hospital admission through discharge were documented, including death from cardiovascular or noncardiovascular causes and thromboembolic events such as myocardial infarction (MI), stroke, transient ischemic attack, arterial embolism, deep venous thrombosis, and pulmonary embolism.

**ADDITIONAL MANAGEMENT INFORMATION**

We also collected the frequency of thrombocytopenia in which there was documentation of a suspicion of HIT (based on a thorough review of full patient medical records), presence of hematologic consultation, performance of additional hematologic tests, use of alternative anticoagulant agents including direct thrombin inhibitors, blood product transfusions, and discharge diagnoses of HIT or HIT associated with thrombosis.

**STATISTICAL ANALYSIS**

All data were analyzed at the Duke Clinical Research Institute, Durham, North Carolina. The distributions of continuous variables are expressed as medians (25th and 75th percentiles). Distributions of continuous variables were compared using the Wilcoxon rank sum test (Mann-Whitney test). Discrete variables are reported as frequencies (n = absolute number of patients) and percentages, and were tested using the χ^2 test. Multiple logistic regression analyses were performed to develop models for identifying independent predictors of thrombocytopenia development and death during the index hospitalization. We selected candidate variables on the basis of results of previous studies and clinical input. The final model variables were based on a backward variable selection process. Plots of platelet count decrease compared with mortality risk were developed using spline methods to describe continuous relationships that required polynomial fitting. All tests were 2-sided and considered significant at α < .05. However, because of the multiple comparisons and exploratory nature of these analyses, all results are considered hypothesis generating. Data analysis was performed with commercially available software (SAS version 8.2; SAS Institute Inc, Cary, North Carolina).

**RESULTS**

**PATIENT POPULATION**

A total of 3617 patients were enrolled in the CATCH Registry from March 1, 2003, to April 30, 2004. Of these, 2420 patients were placed in the prolonged heparin stratum after receiving heparin therapy for 4 days or longer.

**BASELINE CHARACTERISTICS**

Patients who developed thrombocytopenia were older, more often male, more likely to be white, and had a lower body mass index compared with those who did not develop thrombocytopenia (Table 1). Patients with thrombocytopenia more frequently had a history of renal dysfunction, MI, and percutaneous coronary intervention. There was no significant difference between patients who did or did not develop thrombocytopenia insofar as smoking status, history of diabetes mellitus, hypertension, peripheral vascular disease, congestive heart failure, stroke, or transient ischemic attack.

Patients who developed thrombocytopenia were more often admitted for treatment of a cardiovascular disorder. For example, an initial admission for cardiac surgery was 6 times more common among patients who subsequently developed thrombocytopenia. The median baseline platelet count was significantly lower in patients who developed thrombocytopenia compared with those who did not (184 × 10^9/L vs 261 × 10^9/L; P < .001). Overall, 70% of patients received heparin for venous thromboembolism prophylaxis. Acute coronary syndrome was the primary indication for heparin therapy in 13% of patients. Less than 10% of patients had received heparin therapy within 120 days of hospitalization.
Overall, 881 patients (36.4%; 95% confidence interval [CI], 34.5%-38.3%) developed thrombocytopenia (Figure 1).

The most common diagnostic criterion met was an absolute reduction in platelet count to less than 150 × 10^9/L, with 512 patients (58.1%) fitting this category alone. A relative reduction of 50% or more from the baseline platelet count (without a reduction to <150 × 10^9/L) was observed in 56 patients (6.4%), and 313 patients (35.5%) met both criteria for thrombocytopenia. Using a threshold of less than 100 000, 3.93% of the population had a low platelet count, and 19.2% of the population had a platelet count less than 100 000 or a decrease of 50% or more.

### Table 1. Baseline Characteristics According to Development of Thrombocytopenia

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall</th>
<th>With Thrombocytopenia</th>
<th>With No Thrombocytopenia</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>2420 (100)</td>
<td>881 (36.4)</td>
<td>1539 (63.6)</td>
<td>.001</td>
</tr>
<tr>
<td>Age (Q1, Q3), y</td>
<td>65.2 (54.4, 75.9)</td>
<td>66.9 (56.3, 76.3)</td>
<td>64.0 (53.3, 75.5)</td>
<td>.001</td>
</tr>
<tr>
<td>Female sex</td>
<td>1059 (43.8)</td>
<td>390 (43.4)</td>
<td>669 (43.4)</td>
<td>.27</td>
</tr>
<tr>
<td>White race</td>
<td>1894 (78.5)</td>
<td>724 (82.3)</td>
<td>1170 (76.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI (Q1, Q3)</td>
<td>27.8 (23.9, 33.1)</td>
<td>27.4 (23.6, 32.1)</td>
<td>28.2 (24.2, 33.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Platelet count (Q1, Q3), × 10^9/L</td>
<td>237 (187, 303)</td>
<td>184 (147, 246)</td>
<td>261 (217, 326)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Killip class II or higher</td>
<td>390 (16.1)</td>
<td>171 (19.4)</td>
<td>219 (14.2)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

### Medical history

- Previous MI: 413 (17.1) | 176 (20.0) | 237 (15.4) | .04 |
- Previous PCI: 257 (10.6) | 117 (13.3) | 140 (9.1) | .001 |
- Previous CABG: 347 (14.3) | 138 (15.7) | 209 (13.6) | .16 |
- Diabetes mellitus: 824 (34.1) | 339 (38.5) | 485 (31.5) | <.001 |
- Hypertension: 1478 (61.1) | 554 (63.0) | 924 (60.0) | .01 |
- Heart failure: 596 (24.7) | 232 (26.3) | 366 (23.8) | .01 |
- Renal insufficiency: 431 (17.9) | 179 (20.4) | 252 (16.4) | .01 |
- Previous heparin exposure: 226 (9.3) | 76 (8.6) | 150 (9.8) | .36 |
- Current smoker: 509 (21.1) | 176 (20.1) | 333 (21.8) | .01 |
- Alcohol abuse: 264 (10.9) | 103 (11.7) | 161 (10.5) | .36 |

### Primary reason for hospitalization

- Noncardiac disorder: 1590 (65.7) | 511 (58.0) | 1079 (70.1) | <.001 |
- Venous thrombosis: 71 (4.5) | 20 (2.6) | 51 (4.7) | .64 |
- Stroke/TIA: 52 (3.3) | 13 (2.6) | 39 (2.6) | .16 |
- Hip fracture and orthopedic or other noncardiovascular surgery: 1231 (77.5) | 395 (77.5) | 836 (77.5) | <.001 |
- Pneumonia/COPD: 179 (11.3) | 50 (9.8) | 129 (12.0) | .01 |
- Vascular surgery: 56 (3.5) | 32 (6.3) | 24 (2.2) | .01 |
- Cardiac disorder: 830 (34.3) | 370 (42.0) | 460 (29.9) | .01 |
- ACS: 163 (19.7) | 77 (20.8) | 86 (18.7) | .01 |
- MI: 139 (16.8) | 59 (16.0) | 80 (17.4) | .01 |
- Heart failure: 204 (24.6) | 64 (17.3) | 140 (30.5) | .01 |
- Arrhythmia: 116 (14.0) | 48 (13.0) | 68 (14.8) | .01 |
- Cardiac surgery: 83 (10.0) | 70 (18.9) | 13 (2.8) | .01 |

### Primary indication for heparin therapy

- ACS: 325 (13.4) | 152 (17.3) | 173 (11.2) | <.001 |
- Atrial fibrillation: 150 (6.2) | 63 (7.2) | 87 (5.7) | <.001 |
- Venous thromboembolism prophylaxis: 1689 (69.8) | 575 (65.3) | 1114 (72.4) | <.001 |
- Venous thromboembolism treatment: 127 (5.3) | 40 (4.5) | 87 (5.7) | .01 |

Abbreviations: ACS, acute coronary syndromes; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; Q1 and Q3, quartile 1 and quartile 3, respectively; TIA, transient ischemic attack.

*Thrombocytopenia is defined as an absolute nadir platelet count less than 150 × 10^9/L or a relative reduction of 50% or more from the baseline platelet count.

bKillip class I, no evidence of heart failure; II, mild heart failure with limited rales; III, heart failure with more extensive rales; IV, cardiogenic shock with systolic blood pressure less than 90 mm Hg.

cWithin the last 3 months.

**INCIDENCE OF THROMBOCYTOPENIA**

Overall, 881 patients (36.4%; 95% confidence interval [CI], 34.5%-38.3%) developed thrombocytopenia (Figure 1). The most common diagnostic criterion met was an absolute reduction in platelet count to less than 150 × 10^9/L, with 512 patients (58.1%) fitting this category alone. A relative reduction of 50% or more from the baseline platelet count (without a reduction to <150 × 10^9/L) was observed in 56 patients (6.4%), and 313 patients (35.5%) met both criteria for thrombocytopenia. Using a threshold of less than 100 000, 3.93% of the population had a low platelet count, and 19.2% of the population had a platelet count less than 100 000 or a decrease of 50% or more.
patients who developed thrombocytopenia by the main study criteria, the median absolute nadir platelet count was $117 \times 10^9/L$ and the median time from initial heparin exposure to any threshold for defining thrombocytopenia was 55 hours.

The incidence of thrombocytopenia varied according to the type and duration of heparin therapy. Among 366 patients treated with only LMWH for fewer than 7 days, 18.3% developed thrombocytopenia, in contrast to 28.3% of 513 patients treated with only UFH and 55.8% of 68 patients who received both types of heparin. A similar pattern of association was observed among patients treated with heparin for 7 days or longer.

**ANTICOAGULATION THERAPY DURING HOSPITALIZATION**

Overall, 40.3% of patients were treated with LMWH alone (99.3%, enoxaparin) and 51.9% were treated with UFH alone (Table 2). Significantly fewer patients who subsequently developed thrombocytopenia received LMWH alone than did those who did not (35.6% vs 42.9%, respectively; $P < .001$). In contrast, there was no significant difference in the use of UFH alone between patients who developed thrombocytopenia and those who did not (52.9% vs 51.3%, respectively; $P = .44$). Compared with patients without thrombocytopenia, those who developed thrombocytopenia had been exposed to UFH longer and more frequently received it intravenously. Similarly, those who developed thrombocytopenia had been exposed to any heparin therapy longer than those patients who had not (median duration, 8.5 vs 7.5 days; $P = .003$).

**SUSPECTED HIT, SEROLOGIC SCREENING, AND USE OF ALTERNATIVE THERAPIES**

Heparin-induced thrombocytopenia was clinically suspected in 76 patients (8.6%) who met at least 1 of the predefined criteria for thrombocytopenia (Table 3). The diagnosis was suspected a median of 2 days after 1 or both criteria for thrombocytopenia were met. Hematologic consultation was performed in 53 patients (6.0%) on average 4 days after development of thrombocytopenia.

Serologic screening for HIT was performed in 78 patients with thrombocytopenia (8.9%), a median of 2 days after thrombocytopenia developed. The most common tests were the platelet factor 4 enzyme-linked immunosorbent assay, which was performed in 60 patients (6.8%), followed by the heparin-induced platelet aggregation assay in 30 patients (3.4%). The carbon 14–serotonin release assay was performed in only 4 patients (0.5%). Results of serologic studies for HIT were abnormal (at least 1 abnormal result) in 17 patients, or 22% of patients tested.

A direct thrombin inhibitor was administered in 20 patients (2.3%) and was begun a median of 27 hours after suspicion of HIT. Anticoagulation with warfarin sodium was used in 262 patients with thrombocytopenia (30%);...
however, only 14 patients (1.5%) received it as an overlapping therapy with a direct thrombin inhibitor. We also found that in 95 patients with thrombocytopenia (10.8%) who received warfarin sodium, the therapy was initiated after platelet count recovery. A platelet glycoprotein IIb or IIIa receptor inhibitor was administered in 5.7% of patients with thrombocytopenia, with no significant differences in use between patients with or without thrombocytopenia. Aspirin was given to 453 patients with thrombocytopenia (51.5%), and clopidogrel bisulfate to 154 (17.5%).

**RELATIONSHIP BETWEEN THROMBOCYTOPENIA AND CLINICAL OUTCOMES**

Patients who developed thrombocytopenia during the index hospitalization more frequently experienced adverse outcomes (Figure 2). At all time points after initial heparin exposure, the incidence of major cardiovascular events, including death, MI, and congestive heart failure, was significantly higher in patients who developed thrombocytopenia compared with those who did not.

We examined the relationship between thrombocytopenia and all-cause mortality by analyzing the absolute and relative reductions in platelet count in patients who received any heparin therapy for 4 days or longer. We found an inverse relationship between the nadir platelet count and in-hospital death, the risk of death increasing progressively with decreasing nadir platelet count beyond the inflection point of 150×10^9/L (Figure 3A). We found a direct relationship between the relative reduction from baseline platelet count and in-hospital death, the risk significantly increasing at the point of 50% reduction. There was a major increase in the risk of death beyond the inflection point of a 70% decrease in platelet count (Figure 3B).

**PREDICTING THROMBOCYTOPENIA AND IN-HOSPITAL DEATH**

The multivariable models for predicting thrombocytopenia and in-hospital outcomes are given in Table 4 and

![Figure 2. In-hospital outcomes insofar as development of thrombocytopenia. MI indicates myocardial infarction; CHF, congestive heart failure.](image)

![Figure 3. Relationship of absolute reduction (nadir) and relative reduction (percentage from baseline) in platelet count and in-hospital death in the overall cohort of patients treated with heparin for 4 days or longer. A, Nadir platelet count vs death. B, Percent decrease in platelet count vs risk of death.](image)

**Table 5.** Baseline platelet count was independently associated with the development of thrombocytopenia. We observed a strong and graded association between admission platelet count and risk of developing thrombocytopenia during hospitalization (odds ratio [OR], 4.8; 95% CI, 3.6-6.3; P<.001 for baseline platelet count less than 200×10^9/L, and OR, 1.7; 95% CI, 1.3-2.3; P<.001 for baseline platelet counts ranging from 200×10^9/L to 250×10^9/L [reference category of baseline platelet count >250×10^9/L]). Other factors strongly and independently associated with thrombocytopenia were admission for cardiac or vascular surgery and management of acute coronary syndrome, as well as the use of intravenous UFH or both UFH and LMWH. Duration of heparin therapy was an independent predictor of thrombocytopenia, the risk increasing 4% per 1-day increment...
in the duration of heparin exposure. In addition, the risk of developing thrombocytopenia increased 2% per 1-U decrease in body mass index and increased 10% per 10-mm Hg decrement in diastolic blood pressure. A history of thrombocytopenia while receiving heparin therapy was independently associated with a higher risk of developing thrombocytopenia. Variables in this model that were not independent predictors included age, male sex, white race, presence of diabetes or hypertension, systolic blood pressure, Killip class II or higher, previous MI, previous percutaneous coronary intervention, and use of eptifibatide therapy.

We identified 5 independent predictors of inhospital death (Table 5). The relative reduction in platelet count was the strongest variable, with a graded association between the magnitude of reduction and the risk of in-hospital death (OR, 13.4; 95% CI, 6.5-27.6; P < .001 for >70% reduction; and OR, 4.0; 95% CI, 2.1-7.5; P < .001 for 50%-70% reduction). Internal validation showed no overfitting of the model, with the original model c-index of 0.81 and bootstrap bias-corrected c-index of 0.80. Other independent predictors of death were older age, duration of heparin therapy, occurrence of thromboembolic complications, and Killip class. The multivariable model results did not change substantially when excluding patients who had undergone coronary artery bypass grafting. We used the model described in Table 4 as a propensity score to adjust for factors that predict thrombocytopenia, and this did not significantly change the results.

**COMMENT**

We found a surprisingly high incidence of thrombocytopenia, occurring in more than one-third of patients treated with heparin for at least 4 days. This is higher than previously reported in retrospective studies of selected patient populations. The development of thrombocytopenia, in particular, a greater than 70% decrease in platelet count from baseline values during heparin administration, was independently associated with thrombotic and hemorrhagic events. Of concern, thrombocytopenia infrequently prompted a timely diagnostic evaluation for HIT, and when the diagnosis was considered, management strategies were delayed and rarely followed published guidelines.

Thrombocytopenia is a clinically important phenomenon in patients treated with heparin for several reasons. First, it can represent a drug-related immunohematologic reaction that develops in patients exposed to a widely used pharmaceutical agent. Second, life-threatening thrombotic events occur frequently. Third, despite wide-scale recognition, thrombocytopenia remains underdiagnosed and improperly treated, placing patients at unacceptable risk for adverse (potentially preventable) outcomes.

Guidelines for the recognition, treatment, and prevention of HIT set forth by the American College of Chest Physicians and the Hemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology underscore the importance of platelet count monitoring in patients receiving heparin therapy who are deemed at risk for HIT. Current guidelines emphasize the timely evaluation of suspected HIT when thrombocytopenia develops in a temporal pattern consistent with heparin-induced immunization; they also recommend the prophylactic use of a nonheparin anticoagulant and avoid-
ance of vitamin K antagonists in patients in whom the diagnosis is either strongly suspected or confirmed.12-15

Patients enrolled in the CATCH Registry received heparin for 4 days or longer. Yet, among those developing thrombocytopenia, fewer than 10% were suspected of having HIT, and even when HIT was suspected, there were significant delays in diagnostic testing, evaluation by a hematology specialist, heparin cessation, and the initiation of an alternative anticoagulant such as lepirudin, argatroban, or bivalirudin. Of added concern, vitamin K antagonists were used frequently before platelet count recovery and without an appropriate overlap with the direct thrombin inhibitor. Collectively, our observations identify a serious gap between published guidelines and clinical practice in the United States.12

THROMBOCYTOPENIA IN CONTEMPORARY CLINICAL PRACTICE

We observed a higher incidence of thrombocytopenia among patients being treated with UFH or LMWH than previously reported.5,16-18 There are several possible explanations for this finding. The definition of thrombocytopenia has not been applied uniformly across studies. We used an absolute nadir platelet count of less than 150 x 10^9/L, which represents a common lower limit of normal in most clinical laboratories and a less conservative threshold than studies using a 100 x 10^9/L threshold. We also included in our definition a relative reduction of 50% or more from the baseline platelet count, which might include platelet counts within the normal range. These are recommended criteria for a diagnosis of thrombocytopenia in patients treated with heparin,19,20 and they offer both a sensitive measure and a high pretest predictor of a clinically significant condition.21 In contrast to randomized clinical trials in acute coronary syndrome and venous thromboembolism prophylaxis after elective hip surgery, we included a broad and unselected population of patients who required heparin for cardiac as well as noncardiac illnesses in both medical and surgical settings.

Patients who developed thrombocytopenia had a lower baseline platelet count and a lower body mass index, and also were more likely to be admitted because of acute coronary syndrome or for cardiovascular surgery. Factors previously reported as independently associated with thrombocytopenia such as older age, female sex, and use of eptifibatide or any glycoprotein IIb or IIIa inhibitor therapy were not predictive in our patient cohort.26 We also found a direct and consistent relationship between the type, route, and duration of heparin therapy and the likelihood of thrombocytopenia. Although we did not collect information about the amount of heparin given to all patients, we found evidence of both dose- and preparation-response relationships between heparin therapy and risk of developing thrombocytopenia. Patients given UFH intravenously were at higher risk than those who received UFH or LMWH subcutaneously. The development of thrombocytopenia during a course of LMWH therapy, even in medical patients, should not be underestimated or assumed to be unrelated, in particular, if there has been previous exposure to UFH.27 The risk increased with longer heparin exposure, 4% per 1-day increment beyond 4 days of heparin therapy. This observation has important implications for routine clinical practice.

Few studies have reported detailed information on the time course of thrombocytopenia with heparin therapy. Patients with immune-mediated HIT typically have a decrease in platelet count 5 to 10 days after initiation of treatment. In patients in the CATCH trial, the median time from initial heparin administration to a diagnosis of thrombocytopenia was 55 hours. Therefore, while a significant percentage of patients developed thrombocytopenia within a time frame consistent with classic-onset HIT, others experienced an accelerated-course onset. Approximately 10% of patients had received heparin therapy within 90 days of their index hospitalization.10 Although we prespecified in the enrollment criteria that both baseline and nadir platelet counts be documented, as well as whether a relative or an absolute reduction in platelet count occurred, we did not specify the frequency of platelet count testing. Because relatively few patients who developed thrombocytopenia underwent serologic testing for HIT, we could not establish a diagnosis of immune-mediated HIT in most cases; however, among those who were tested, nearly one-third were found to have either heparin–platelet factor 4 antibodies, heparin-induced platelet aggregation, or heparin-induced serotonin release. If one extrapolates this prevalence to the total population, the overall incidence of HIT could be in the range of 10%. Thus, a decrease in platelet count should trigger heightened patient surveillance and, when indicated, further diagnostic evaluation.

After adjustment for important covariates, we found that thrombocytopenia, in particular, a greater than 70% reduction in platelet count from baseline, remained independently associated with adverse short-term clinical outcomes. We demonstrated a strong, direct, and graded increase in the risk of death according to the magnitude of the relative reduction in platelet count. Although the mechanisms underlying this association are unknown, unmeasured severity of illness, bone marrow suppression, and more intense platelet activation may be relevant contributors.

LIMITATIONS

While sites were instructed to enroll sequential patients, because some required informed consent, the study may have selectively enrolled healthier patients. The time frame and frequency of platelet count monitoring were left entirely to the investigator’s discretion to define current practice around monitoring, diagnostic evaluation, and management of thrombocytopenia. Accordingly, the temporal relationship between thrombocytopenia and the occurrence of nonfatal events may have been incompletely defined. Some of the outcomes, including MI and congestive heart failure, might have occurred before thrombocytopenia was documented in the medical records of participating sites. Although our study demonstrated a clear association between the development of thrombocytopenia and adverse short-term clinical outcomes, it has limitations inherent to all observational studies, in which unmeasured factors may have confounded 1 or more observed associations.
Thrombocytopenia is common in hospitalized patients receiving heparin for treatment of medical or surgical illness and is an independent marker of risk of death and life-threatening events. The currently practiced diagnostic approach and management of patients with thrombocytopenia at risk for HIT, as documented in the CATCH study, raises serious concerns and should prompt action to narrow the gap between guidelines and clinical practice in the United States.

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REFERENCES


