CHEST

Original Research

CRITICAL CARE

Thrombocytopenia in Critically Ill Patients Receiving Thromboprophylaxis

Frequency, Risk Factors, and Outcomes

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Background: **Thrombocytopenia is the most common hemostatic disorder in critically ill patients. The objective of this study was to describe the incidence, risk factors, and outcomes of thrombocytopenia in patients admitted to medical-surgical ICUs.**

Methods: **Three thousand seven hundred forty-six patients in 67 centers were enrolled in a randomized trial in which unfractionated heparin was compared with low-molecular-weight heparin (LMWH) for thromboprophylaxis. Patients who had baseline platelet counts $< 75 \times 10^9$/L or severe coagulopathy at screening were excluded. We analyzed the risk of developing mild (100-149 $\times 10^9$/L), moderate (50-99 $\times 10^9$/L), and severe ($< 50 \times 10^9$/L) thrombocytopenia during an ICU stay. We also assessed independent and time-varying predictors of thrombocytopenia and the effect of thrombocytopenia on major bleeding, transfusions, and death.**

Results: **The incidences of mild, moderate, and severe thrombocytopenia were 15.3%, 5.1%, and 1.6%, respectively. The predictors of each category of thrombocytopenia were APACHE (Acute Physiology and Chronic Health Evaluation) II score, use of inotropes or vasopressors, and renal replacement therapy. The risk of moderate thrombocytopenia was lower in patients who received LMWH thromboprophylaxis but higher in surgical patients and in patients who had liver disease. Each category of thrombocytopenia was associated with subsequent bleeding and transfusions. Moderate and severe thrombocytopenia were associated with increased ICU and hospital mortality.**

Conclusion: **A high severity of illness, prior surgery, use of inotropes or vasopressors, renal replacement therapy, and liver dysfunction are associated with a higher risk of thrombocytopenia developing in the ICU, whereas LMWH thromboprophylaxis is associated with a lower risk. Patients who develop thrombocytopenia in the ICU are more likely to bleed, receive transfusions, and die.**

Trial registry: **ClinicalTrials.gov; No.: NCT00182143; URL: www.clinicaltrials.gov**

CHEST 2013; 144(4):1207–1215

Abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; HIT = heparin-induced thrombocytopenia; HR = hazard ratio; LMWH = low-molecular-weight heparin; PROTECT = Prophylaxis for Thromboembolism in Critical Care Trial; SRA = serotonin release assay; UFH = unfractionated heparin

Thrombocytopenia is the most common hemostatic disorder in critically ill patients[1]; 14% to 44% of these patients develop thrombocytopenia during their ICU stay.[2-7] The cause of thrombocytopenia is often multifactorial and may be attributed to enhanced platelet consumption, reduced platelet production, or hemodilution.[8] Most patients are exposed to heparin during their ICU stay, and heparin-induced thrombocytopenia (HIT) is often suspected, although rarely proven.[2,9,10] Critically ill patients receive other drugs,

such as antibiotics, histamine receptor-2 antagonists, and antiplatelet agents, which have also been associated with thrombocytopenia.[4,11,12] Additional factors that have been associated with the development of thrombocytopenia in studies of critically ill patients include higher APACHE (Acute Physiology and Chronic Health Evaluation) II score, sepsis, and use of dialysis, inotropes, or vasopressors.[13] However, the studies of these risk factors have not been large enough to determine independent associations with severe thrombocytopenia after adjustment for other baseline and time-dependent variables that affect critically ill patients.[2,13]

Thrombocytopenia alters patient management and can prohibit invasive interventions.[14] Thrombocytopenia may also require specific treatments such as platelet transfusions and alternate approaches to thromboprophylaxis and anticoagulation.[15,16] Several studies have evaluated the impact of any (platelet count $< 150 \times 10^9$/L) and severe (platelet count $< 50 \times 10^9$/L) thrombocytopenia on clinical outcomes.[4,5,7,13,17] In general, lower platelet counts have been associated with increased length of stay, need for transfusion of blood products, and increased mortality (ICU and hospital).[13] Physicians are concerned about major bleeding in patients with thrombocytopenia. In a systematic review of observational studies, one study carefully assessed major bleeding, and it found no association with thrombocytopenia.[13] However, most studies that have evaluated the effect of thrombocytopenia on the transfusion of blood products did not adequately adjust for disease severity.[13]

The objectives of this study were to measure the incidence of thrombocytopenia, determine baseline and time-dependent risk factors for the development of thrombocytopenia, and estimate the relation between thrombocytopenia and subsequent major bleeding, transfusion of blood products, length of ICU stay, and ICU mortality in a large cohort of medical-surgical critically ill patients.

Materials and Methods

This study was an a priori analysis based on the Prophylaxis for Thromboembolism in Critical Care Trial (PROTECT) database.[9] PROTECT was a multinational, concealed, stratified, randomized, and blinded trial that enrolled medical-surgical critically ill patients to compare unfractionated heparin (UFH) with low-molecular-weight heparin (LMWH) dalteparin to prevent proximal lower-limb DVT.[9] Patients enrolled in PROTECT were ≥ 18 years old, weighed ≥ 45 kg, and had an expected ICU stay of ≥ 72 h. Reasons for exclusion were major hemorrhage in the previous week; an admission diagnosis of neurosurgery, trauma, orthopedic surgery, or uncontrolled hypertension; ischemic stroke or intracranial hemorrhage in the preceding 3 months; pregnancy; history of HIT; contraindications to blood products; and palliative care or limitation of life support. Patients who had platelet counts $< 75 \times 10^9$/L or severe coagulopathy (international normalized ratio or activated partial thromboplastin time greater than or equal to two times the upper limit of normal) at the time of screening were excluded from the current study. Patients could have received therapeutic anticoagulation or no thromboprophylaxis after randomization if it was required by their medical condition. We collected demographic and baseline clinical information, including age, APACHE II score,[18] admission diagnosis, and comorbid conditions. Data collected daily included CBC counts; administration of blood products (red cells, platelets, plasma, and cryoprecipitate); specific interventions (mechanical ventilation, inotropes or vasopressors, renal replacement therapy, and surgeries); incident DVT and pulmonary embolism; and receipt of antiplatelet agents, anticoagulants, stress ulcer prophylaxis agents, and nonsteroidal antiinflammatory agents.

Major bleeding was evaluated daily and was defined as hemorrhage occurring at a critical site (eg, intracranial hemorrhage) that led to an invasive therapeutic intervention (eg, surgery), caused hemodynamic compromise, required transfusion of at least 2 units of red cells, or caused death.[19] Bleeding was considered minor if it was overt but did not meet the criteria for major bleeding. Two independent, blinded investigators adjudicated bleeding events using a validated tool[9] and found excellent agreement.[20]

Patients were evaluated for HIT with the serotonin release assay (SRA) if their platelet count decreased to $\leq 50 \times 10^9$/L, if there was an otherwise unexplained platelet count decrease to $\leq 50\%$ of the patient's baseline (defined as the first platelet count after enrollment as long as the count was $> 100 \times 10^9$/L), if they developed a symptomatic or asymptomatic thrombotic event, or if HIT was otherwise clinically suspected.

To be included in this study of thrombocytopenia in critical illness, the patients must have had a platelet count measured on the day of enrollment and at least one platelet count after enrollment

Manuscript received February 6, 2013; revision accepted May 23, 2013.

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Funding/Support: The original trial was funded by the Canadian Institutes of Health Research, the Heart and Stroke Foundation of Canada, and the Australian and New Zealand College of Anesthetists Research Foundation.

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DOI: 10.1378/chest.13-0121

but during their ICU stay. We defined three categories of thrombocytopenia according to the lowest platelet count during the ICU stay: mild (100-149 $\times 10^9$/L), moderate (50-99 $\times 10^9$/L), and severe ($< 50 \times 10^9$/L). We classified each category of thrombocytopenia as incident if the platelet count was above one of these three defined thresholds on the day of enrollment and subsequently decreased to one of the categories previously defined at any time during the ICU stay. For example, a patient whose lowest platelet value was 75×10^9/L on days 1 to 5 was categorized as having moderate thrombocytopenia. However, if the patient had a platelet value of 45×10^9/L on day 6, he or she was considered to have severe thrombocytopenia from that day forward. For the survival analysis, we stratified patients according to their lowest platelet count. Each patient who developed thrombocytopenia contributed data to only one model, and patients who did not develop thrombocytopenia contributed data to every model.

We evaluated 15 predictors of mild, moderate, and severe incident thrombocytopenia based on prior reports, scientific plausibility, and availability in the dataset.[13] We included only incident cases per each category in the risk factor analysis. For example, a patient with a platelet count of 120×10^9/L on enrollment was not eligible to be in the risk factor analysis of incident mild thrombocytopenia (100-149 $\times 10^9$/L). However, this patient would be included in the risk factor analysis for the moderate category and could become an incident case if the platelet counts dropped into the moderate category (50-99 $\times 10^9$/L). In the moderate thrombocytopenia analysis, we excluded patients who had severe thrombocytopenia (platelets $< 50 \times 10^9$/L at any point during their ICU stay). In the mild thrombocytopenia analysis, we excluded patients who had moderate or severe thrombocytopenia (platelets $< 100 \times 10^9$/L at any point during their ICU stay). The following baseline demographic variables were evaluated: APACHE II score, medical vs surgical admitting diagnosis, dialysis-dependent end-stage renal disease, sepsis, liver dysfunction (hepatic failure or cirrhosis), and documented cancer (lymphoma, metastatic cancer, leukemia, multiple myeloma, active malignancy, or history of malignancy). We also evaluated the following time-dependent factors in the preceding 3 days: use of inotropes or vasopressors, any dialysis, aspirin or thienopyridines (ticlopidine or clopidogrel), stress ulcer prophylaxis (histamine receptor-2 antagonists or proton-pump inhibitors), prophylactic LMWH, prophylactic UFH, and therapeutic heparin; a new diagnosis of HIT during ICU stay; and incident DVT or pulmonary embolism. Patients with missing predictors were excluded from the risk factor analysis. The protocol and consent forms were approved by each center's research ethics board (e-Table 1).

Statistical Analysis

Continuous data are presented as means and SDs or medians and 25th and 75th percentiles according to distribution. Continuous data were compared using the Wilcoxon rank sum test and the Kruskal-Wallis test for nonnormally distributed data. Dichotomous and categorical data are presented as proportions and were compared using the Fisher exact test. Prevalence and incidence are reported with 95% CIs. Risk factors for mild, moderate, and severe thrombocytopenia were identified using multivariable time-to-event analysis (Cox regression). To adjust for multiple testing, only risk factors that had a strong association ($P < .01$) were considered significant.

We examined the effect of thrombocytopenia on subsequent major bleeding, transfusion of blood products, and mortality using adjusted analyses, in which thrombocytopenia was treated as a time-dependent covariate. The outcomes for these Cox regressions were time to first major or all bleeds, time to first transfusion, and time to death. These analyses were adjusted for age, APACHE II score, use of mechanical ventilation (invasive or noninvasive) at study entry, and use of inotropes or vasopressors at study entry. Hazard ratios (HRs) are presented with 95% CIs. Because HIT is strongly and systematically associated with thrombocytopenia, and the outcomes of HIT-associated thrombocytopenia may differ from those of non-HIT-associated thrombocytopenia, we conducted a sensitivity analysis of the study outcomes excluding patients who had positive SRA tests. Because bleeding and transfusions may be linked events, we also added major bleeding in a separate analysis of the association between thrombocytopenia and transfusions.

Results

The PROTECT trial enrolled 3,746 patients between May 2006 and June 2010. A total of 3,721 patients had a least one platelet count measured beyond the baseline value during the study. The mean age of these patients was 61.4 (SD, 16.5) years, and 56.7% were men. The most common admitting diagnoses were respiratory diseases (45.6%), sepsis (14.8%), and GI diseases (14.0%) (Table 1).

In total, 952 patients of the 3,639 (26.2%) who had a platelet count measured on the day of enrollment had a platelet count $< 150 \times 10^9$/L. Subsequent to enrollment, mild, moderate, and severe thrombocytopenia developed in 417 (15.3%; 95% CI, 14.0-16.7), 140 (5.1%; 95% CI, 4.4-6.0), and 44 (1.6%; 95% CI, 1.2-2.2) patients, respectively (Table 2).

APACHE II score (HR, 1.60; 95% CI, 1.29-1.97 per 10-point increase), receipt of inotropes or vasopressors in the preceding 3 days (HR, 3.32; 95% CI, 2.24-4.91), and renal replacement therapy in the preceding 3 days (HR, 3.62; 95% CI, 2.49-5.27) were associated with the development of severe thrombocytopenia (Table 3). Antiplatelet agents in the preceding 3 days were associated with a decreased risk of severe thrombocytopenia (HR, 0.60; 95% CI, 0.40-0.91). APACHE II score (HR, 1.51; 95% CI, 1.30-1.75 per 10-point increase),

Table 1—*Baseline Demographics*

Demographic	All Patients (N = 3,721)	Incident Thrombocytopenia ($< 150 \times 10^9$/L) (n = 601)
Female	1,611 (43.3)	254 (42.3)
Age, mean (SD), y	61.4 (16.5)	63.6 (15.8)
APACHE II score, mean (SD)	21.5 (7.8)	23.3 (7.6)
Medical admission	3,025 (81.3)	503 (83.7)
Admission diagnosis		
Cardiovascular	336 (9.0)	61 (10.1)
Respiratory	1,697 (45.6)	251 (41.8)
GI	520 (14.0)	82 (13.6)
Renal	65 (1.7)	13 (2.2)
Neurologic	227 (6.1)	34 (5.7)
Sepsis	549 (14.8)	113 (18.8)
Metabolic	144 (3.9)	23 (3.8)
Other (medical)	65 (1.7)	8 (1.3)
Other (surgical)	118 (3.2)	16 (2.7)

Data are given as No. (%) unless otherwise indicated. Table includes all patients with a least one platelet count after baseline and patients who had incident thrombocytopenia. APACHE = Acute Physiology and Chronic Health Evaluation.

Table 2—*Incidence of Thrombocytopenia During ICU Stay (n = 2,725)*

Thrombocytopenia Category (Platelets)	Incidence, No. (%, 95% CI)
None ($\geq 150 \times 10^9$/L)	2,124 (77.9, 76.3-79.5)
Mild (100-149 $\times 10^9$/L)	417 (15.3, 14.0-16.7)
Moderate (50-99 $\times 10^9$/L)	140 (5.1, 4.4-6.0)
Severe ($< 50 \times 10^9$/L)	44 (1.6, 1.2-2.2)

Table includes patients whose platelet count was $\geq 150 \times 10^9$/L on day 1 and with platelet data on day 2 or later. The most severe thrombocytopenia during the ICU stay is reported.

receipt of inotropes or vasopressors (HR, 2.85; 95% CI, 2.20-3.68), and renal replacement therapy (HR, 2.14; 95% CI, 1.56-2.94) were similarly associated with the development of moderate thrombocytopenia, as were a surgical admitting diagnosis (HR, 1.48; 95% CI, 1.11-1.97), a history of liver dysfunction (HR, 3.21; 95% CI, 1.97-5.20), and development of HIT (HR, 10.81; 95%, CI 3.94-29.69). Prophylactic LMWH (compared with UFH or no thromboprophylaxis) administration in the preceding 3 days was associated with a lower risk of moderate thrombocytopenia (HR, 0.62; 95% CI, 0.47-0.84). Mild thrombocytopenia was not associated with any additional predictors of thrombocytopenia; furthermore, sepsis, liver dysfunction, surgical admission, and LMWH administration were not associated with mild thrombocytopenia (Table 3). In addition, there was no association between stress-ulcer prophylaxis, aspirin, or thienopyridines and an increased risk of thrombocytopenia of any severity.

When compared with patients who maintained platelet counts $> 150 \times 10^9$/L throughout their ICU stay, and after adjustment for age, APACHE II score, baseline use of mechanical ventilation, and inotropes or vasopressors, patients who developed severe thrombocytopenia had a significantly increased risk of any subsequent bleeding (HR, 2.57; 95% CI, 1.76-3.75) and major bleeding (HR, 3.54; 95% CI, 2.09-5.99), a significantly increased risk of any blood product transfusion (red cells [HR, 3.42; 95% CI, 2.53-4.63], platelets [HR, 230.71; 95% CI, 104.78-508.00], plasma [HR, 5.07; 95% CI, 3.00-8.57], and cryoprecipitate [HR, 66.66; 95% CI, 12.96-342.87]) and a significantly greater risk of death in the ICU (HR, 2.75; 95% CI, 2.11-3.60) and in hospital (HR, 2.78; 95% CI, 2.20-3.53) (Table 4). In patients who received any transfusion of allogeneic blood products, severe thrombocytopenia was associated with transfusion of a greater number of units of red cells (median, 5 [25th-75th percentile, 2-12] vs median, 2 [25th-75th percentile, 1-3]) and units of plasma (median, 6 [25th-75th percentile, 4-11] vs median, 2 [25th-75th percentile, 2-4]) compared with patients who did not develop thrombocytopenia. Patients who developed severe thrombocytopenia had an increased length of stay in the ICU (17 days [25th-75th percentile, 10-30 days] vs 8 days [25th-75th

Table 3—*Risk Factors for Mild, Moderate, and Severe Thrombocytopenia That Develops in ICU*

Baseline Characteristics	Hazard Ratio (95% CI)		
	Mild Thrombocytopenia (n = 2,539 and 417 events)	Moderate Thrombocytopenia (n = 3,315 and 296 events)	Severe Thrombocytopenia (n = 3,649 and 145 events)
Baseline factors			
APACHE II (per 10-point increase)	1.20 (1.06-1.37)	1.51 (1.30-1.75)	1.60 (1.29-1.97)
Surgical admission	1.13 (0.86-1.48)	1.48 (1.11-1.97)	1.38 (0.92-2.09)
End-stage renal disease	0.79 (0.47-1.31)	0.52 (0.27-1.03)	0.59 (0.28-1.25)
Sepsis	1.28 (0.99-1.66)	1.18 (0.87-1.61)	1.28 (0.85-1.94)
Liver dysfunction	1.35 (0.64-2.86)	3.21 (1.97-5.20)	1.65 (0.77-3.54)
Cancer	1.24 (0.91-1.67)	1.19 (0.84-1.69)	1.50 (0.94-2.40)
Time-dependent factors			
Inotropes/vasopressors	1.64 (1.34-2.01)	2.85 (2.20-3.68)	3.32 (2.24-4.91)
Any dialysis	2.70 (2.01-3.63)	2.14 (1.56-2.94)	3.62 (2.49-5.27)
SRA-positive HIT	10.56 (2.48-45.01)	10.81 (3.94-29.69)	2.40 (0.57-10.11)
Any DVT or PE[a]	0.83 (0.44-1.57)	1.08 (0.60-1.97)	1.91 (1.01-3.63)
Antiplatelet agents[b]	0.94 (0.75-1.17)	0.86 (0.66-1.12)	0.60 (0.40-0.91)
Stress ulcer prophylaxis	0.80 (0.60-1.07)	0.72 (0.51-1.01)	1.08 (0.58-2.00)
Prophylactic LMWH	1.00 (0.79-1.26)	0.62 (0.47-0.84)	0.70 (0.45-1.07)
Prophylactic UFH	0.90 (0.68-1.17)	0.74 (0.53-1.02)	0.80 (0.50-1.27)
Therapeutic heparin	1.20 (0.56-2.57)	0.54 (0.17-1.75)	0.66 (0.16-2.78)

In the mild thrombocytopenia analysis, patients with platelets 100 to 149×10^9/L on d 2 or later were included, and patients with severe or moderate thrombocytopenia (platelets $< 100 \times 10^9$/L at any point during their ICU stay) were excluded. In the moderate thrombocytopenia analysis, patients with platelets 50 to 99×10^9/L on d 2 or later were included, and patients with severe thrombocytopenia (platelets $< 50 \times 10^9$/L at any point during their ICU stay) were excluded. In the severe thrombocytopenia analysis, patients with platelets $< 50 \times 10^9$/L on d 2 or later were included. HIT = heparin-induced thrombocytopenia; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; SRA = serotonin release assay; UFH = unfractionated heparin. See Table 1 legend for expansion of other abbreviation.

[a]Time-dependent factors in the preceding 3 d, except for SRA positivity and any DVT or PE that was on the same day or earlier.

[b]Antiplatelet agents include acetylsalicylic acid or thienopyridine (ticlopidine or clopidogrel).

Table 4—*Clinical Outcomes in Patients Who Developed Mild, Moderate, and Severe ICU-Acquired Thrombocytopenia*

Outcome	Mild TCP vs No TCP		Moderate TCP vs No TCP		Severe TCP vs No TCP	
	Adjusted HR (95% CI)[a]	Adjusted *P* Value	Adjusted HR (95% CI)[a]	Adjusted *P* Value	Adjusted HR (95% CI)[a]	Adjusted *P* Value
Major bleeding	1.96 (1.38-2.78)	< .001	3.52 (2.47-5.04)	< .001	3.54 (2.09-5.99)	< .001
Any bleeding	1.50 (1.21-1.86)	< .001	2.05 (1.61-2.63)	< .001	2.57 (1.76-3.75)	< .001
RBC transfusion	1.43 (1.25-1.63)	< .001	1.91 (1.62-2.25)	< .001	3.42 (2.53-4.63)	< .001
Platelet transfusion	4.79 (2.00-11.45)	< .001	30.26 (14.02-65.32)	< .001	230.71 (104.78-508.00)	< .001
Frozen plasma transfusion	1.98 (1.48-2.65)	< .001	3.89 (2.86-5.28)	< .001	5.07 (3.00-8.57)	< .001
Cryoprecipitate transfusion	9.83 (2.07-46.72)	.004	10.58 (1.98-56.37)	.006	66.66 (12.96-342.87)	< .001
ICU mortality	1.09 (0.88-1.34)	.449	1.60 (1.28-2.00)	< .001	2.75 (2.11-3.60)	< .001
Hospital mortality	1.03 (0.86-1.22)	.767	1.62 (1.35-1.94)	< .001	2.78 (2.20-3.53)	< .001

The outcomes for the Cox regressions are time to first transfusion and time to first bleed. A patient's thrombocytopenia categorization can change throughout his or her ICU stay and this was taken into account in the Cox regressions. HR = hazard ratio; TCP = thrombocytopenia. See Table 1 legend for expansion of other abbreviation.

[a]Adjusted for age, APACHE II score, baseline mechanical ventilation, and inotropes or vasopressors in Cox regression.

percentile, 5-14 days]) and in hospital (31 days [25th-75th percentile, 15-50 days] vs 20 days [25th-75th percentile, 12-36 days]) (Table 5).

After adjustment for age, APACHE II score, baseline mechanical ventilation, and baseline use of inotropes or vasopressors, patients who developed moderate thrombocytopenia were more likely to experience any subsequent bleeding (HR, 2.05; 95% CI, 1.61-2.63) or major bleeding (HR, 3.52; 95% CI, 2.47-5.04) (Table 4) compared with patients who did not develop thrombocytopenia. They were also more likely to be transfused with red cells (HR, 1.91; 95% CI, 1.62-2.25), platelets (HR, 30.26; 95% CI, 14.02-65.32), plasma (HR, 3.89; 95% CI, 2.86-5.28), or cryoprecipitate (HR, 10.58; 95% CI, 1.98-56.37). Adding major bleeding to the transfusion analyses did not significantly modify the HRs. In patients who received any transfusion of allogeneic blood products, those who developed moderate thrombocytopenia received more units of red cells (3 [25th-75th percentile, 2-7] vs 2 [25th-75th percentile, 1-3]) and units of plasma (4 [25th-75th percentile, 2-7] vs 2 [25th-75th percentile, 2-4]) compared with patients without thrombocytopenia. Moderate thrombocytopenia was also associated with increased ICU (HR, 1.60; 95% CI, 1.28-2.00) and hospital (HR, 1.62; 95% CI, 1.35-1.94) mortality. Length of stay in the ICU (11 days [25th-75th percentile, 7-21 days] vs 8 days [25th-75th percentile, 5-14 days]) and hospital (25 days [25th-75th percentile, 14-50 days] vs 20 days [25th-75th percentile, 12-36 days]) was greater in patients who developed moderate thrombocytopenia compared with those who did not develop thrombocytopenia (Table 5).

Mild thrombocytopenia was associated with an increase in major or any bleeding, blood product transfusions, and length of stay (Table 4). However, there was no association between mild thrombocytopenia and ICU or hospital mortality compared with patients who did not develop thrombocytopenia. Figure 1 shows Kaplan-Meier curves for the different levels of thrombocytopenia categories. In a sensitivity analysis that excluded patients who had positive SRA tests (n = 17),

Table 5—*Transfusion of Blood Products and Duration of Mechanical Ventilation and Hospital and ICU Stay Stratified by Lowest Platelet Count During ICU stay*

Outcome	Most Severe Thrombocytopenia Throughout Entire ICU Stay				
	Mild (100 to < 150 × 10^9/L) (n = 914)	Moderate (50 to < 100 × 10^9/L) (n = 488)	Severe (< 50 × 10^9/L) (n = 151)	None (≥ 150 × 10^9/L) (n = 2,168)	Unadjusted *P* Value[a]
Units of RBCs transfused (ever)[b]	2 (1-5)	3 (2-7)	5 (2-12)	2 (1-3)	< .001
Unit of platelets transfused (ever)[b]	3.5 (1-5)	5 (2-6)	5 (2-11)	1.5 (1-3.5)	.065
Units of frozen plasma transfused (ever)[b]	3 (2-4)	4 (2-7)	6 (4-11)	2 (2-4)	< .001
Units of cryoprecipitate transfused (ever)[b]	8 (5-10)	5 (4-6)	10 (2-10)	8 (8-8)[c]	.834
Duration of invasive mechanical ventilation, d	6 (3-12)	7 (3-16)	14 (7-26)	4 (2-9)	< .001
Duration of ICU stay, d	10 (6-17)	11 (7-21)	17 (10-30)	8 (5-14)	< .001
Duration of hospital stay, d	23 (14-44)	25 (14-50)	31 (15-50)	20 (12-36)	< .001

Data are presented as median (interquartile range).

[a]Kruskal-Wallis test.

[b]The number of transfused products are among those patients who had transfusions.

[c]One patient only.

all associations with outcomes identified previously remained significantly associated with mild, moderate, and severe thrombocytopenia, including the lower risk of moderate thrombocytopenia observed with LMWH (HR, 0.63; 95% CI, 0.47-0.84).

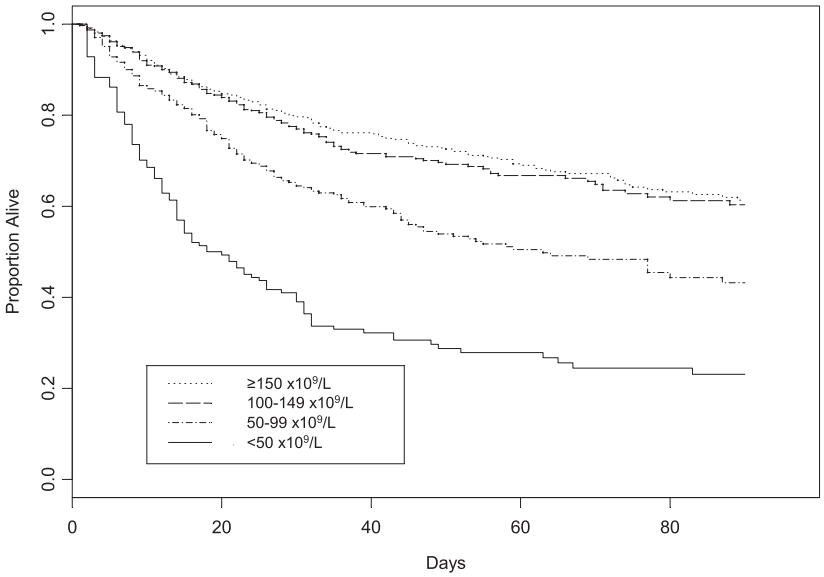
Discussion

In this study, we found that the prevalence of thrombocytopenia was 26.2%. In addition, the incidences of mild (platelet count $< 100 \times 10^9$/L), moderate ($50\text{-}99 \times 10^9$/L), and severe ($< 50 \times 109$/L) thrombocytopenia in the ICU were 15.3%, 5.1%, and 1.6%, respectively. Similar studies of patients in a medical-surgical ICU have reported a prevalence of thrombocytopenia (platelet count $< 150 \times 10^9$/L) of 23.7% to 44.0% and an incidence of thrombocytopenia of 14.3% to 27.0%, respectively.[4,5,21]

We identified several independent risk factors for mild, moderate, and severe thrombocytopenia. Most of these risk factors were nonmodifiable, including illness severity, admission diagnosis (eg, sepsis), use of advanced life support (eg, inotropes or vasopressors, dialysis), and organ dysfunction (liver or renal dysfunction at admission). HIT diagnosis, as determined by a positive SRA test, was also strongly predictive of both mild and moderate but not severe thrombocytopenia, consistent with the natural history of HIT.[22]

Thromboprophylaxis with LMWH was the only modifiable factor associated with a decreased risk of moderate thrombocytopenia. This finding was also suggested in a meta-analysis of 7,287 medical and surgical patients in which LMWH was associated with a trend toward a lower odds of thrombocytopenia in comparison with UFH (OR, 0.47; 95% CI, 0.22-1.02; $P = .06$).[23] Antiplatelet agents were the only factor associated with a decreased risk of severe thrombocytopenia. This finding could be secondary to indication bias, preemptive discontinuation of antiplatelet agents in patients with worsening thrombocytopenia, or a true protective effect of antiplatelet agents. One study in patients undergoing angioplasty reported a protective effect of aspirin use for the development of thrombocytopenia.[24]

In contrast to other studies, we did not confirm an association between either stress-ulcer prophylaxis or antiplatelet agents and thrombocytopenia.[12] Differences in patient populations and individual predictors included in risk factor analyses between the current and previous studies may account for this difference in findings. A causal relation between these drug classes and thrombocytopenia cannot be excluded completely, although previously identified associations may be have been due to unmeasured confounders (eg, severity of illness, comorbid conditions, age, sex, and admission diagnosis).



No. at risk					
≥150 x10⁹/L	2769	922	385	210	119
100-149 x10⁹/L	705	456	210	124	77
50-99 x10⁹/L	241	256	131	80	41
<50 x10⁹/L	6	71	41	28	18

Figure 1. Unadjusted Kaplan-Meier curves for hospital mortality. Patients categorized per thrombocytopenia definition according to their lowest platelet count up to each point in time.

Previous studies of patients in the medical-surgical ICU found an association between thrombocytopenia and bleeding in univariate analyses, but these studies did not adjust for confounding factors.[1,2,5,7] In a study of patients undergoing liver transplants, Ben Hamida et al[25] found no association between severe thrombocytopenia and major bleeding, after adjusting for disease severity. We found that all three levels of thrombocytopenia were associated with an increased risk of major bleeding, after adjusting for confounding factors. In addition, the association was stronger for the categories of lower platelet counts. Interestingly, moderate and severe thrombocytopenia were associated with similar risks of major bleeding.

We also found a significant and independent association between all three categories of thrombocytopenia and transfusion of allogeneic blood products (platelets, red cells, plasma, and cryoprecipitate). Previous studies have also suggested associations between thrombocytopenia and platelet transfusions[4,5,7,25-27] or red cell transfusions,[2,25,26,28,29] but these studies did not adjust for confounding factors. One exception is a case-control study that matched 36 patients by APACHE II score, primary diagnosis, and length of stay, and found an increase in blood product transfusion in patients who had severe thrombocytopenia (OR, 1.52; 95% CI, 1.05-2.20).[29] Our findings raise the question of blood product use and efficacy in patients with thrombocytopenia. Further assessment of platelet transfusion effectiveness in preventing bleeding in patients with thrombocytopenia is warranted.

In this study, hospital and ICU mortality were independently associated with moderate and severe thrombocytopenia but not mild thrombocytopenia. A study of thrombocytopenia in patients admitted to the ICU for community-acquired pneumonia also reported an independent association between mortality and severe thrombocytopenia and but not mild thrombocytopenia.[30]

The strengths of this study include the multicenter design, standardized comprehensive data collection, and centralized adjudication of bleeding in duplicate using a validated tool[19] with excellent agreement.[20] We conducted rigorous statistical analyses of risk factors and outcome, and adjusted for confounders and time-dependent covariates using Cox regression analysis. However, the length of stay analyses were not adjusted. The large sample size minimizes the possibility of random error and increases the precision of our results compared with earlier studies in this population.[2,4,5,7,27] However, this study was conducted using a randomized thromboprophylaxis trial database. Therefore, the inclusion and exclusion criteria, which do not necessarily reflect all critically ill patients, need to be considered in interpreting these results. In particular, patients who had a platelet count $< 75 \times 10^9$/L at the time of screening were excluded. For this reason, the rates of severe and critical thrombocytopenia are likely to have been underestimated. Furthermore, because few patients developed critical thrombocytopenia with platelet counts $< 20 \times 10^9$/L, we were unable to further analyze this condition. Finally, this study was not designed to evaluate other bleeding risk factors; we have examined the rates, determinants, and outcomes of major bleeding in a separate publication.[31]

This study suggests that thrombocytopenia is an independent predictor of poor outcomes in medical-surgical critically ill patients. Whether attempting to correct the thrombocytopenia (with platelet transfusions or thrombopoietic agents) or preventing thrombocytopenia can improve these outcomes in critically ill patients remains unknown.

Conclusion

In critically ill medical and surgical patients who receive thromboprophylaxis, the incidence of mild to moderate thrombocytopenia is high, whereas the incidence of severe thrombocytopenia is low. A high illness severity score, surgical diagnosis, use of vasopressors or inotropes, renal replacement therapy, and liver dysfunction are associated with the development of thrombocytopenia. Compared with patients who do not develop thrombocytopenia, critically ill patients who develop thrombocytopenia are more likely to have subsequent bleeding, receive transfusions, and die in the ICU or hospital.

Acknowledgments

Author contributions: Mr Williamson is the guarantor of the paper and takes responsibility for the integrity of the work as a whole, from inception to the published article.

Mr Williamson: contributed to the conception, design, and interpretation of the data and drafting of the submitted article.

Dr Albert: contributed to the conception, design, and interpretation of the data; critical revision of the manuscript; and final approval of the version to be published.

Ms Heels-Ansdell: contributed to the analysis and interpretation of the data, critical revision of the manuscript, and final approval of the version to be published.

Dr Arnold: contributed to the interpretation of the data, critical revision of the manuscript, and final approval of the version to be published.

Dr Lauzier: contributed to the interpretation of the data, critical revision of the manuscript, and final approval of the version to be published.

Dr Zarychanski: contributed to the interpretation of the data, critical revision of the manuscript, and final approval of the version to be published.

Dr Crowther: contributed to the interpretation of the data, critical revision of the manuscript, and final approval of the version to be published.

Dr Warkentin: contributed to the interpretation of the data, critical revision of the manuscript, and final approval of the version to be published.

Dr Dodek: contributed to the interpretation of the data, critical revision of the manuscript, and final approval of the version to be published.
Dr Cade: contributed to the interpretation of the data, critical revision of the manuscript, and final approval of the version to be published.
Dr Lesur: contributed to the interpretation of the data, critical revision of the manuscript, and final approval of the version to be published.
Dr Lim: contributed to the interpretation of the data, critical revision of the manuscript, and final approval of the version to be published.
Dr Fowler: contributed to the interpretation of the data, critical revision of the manuscript, and final approval of the version to be published.
Dr Lamontagne: contributed to the interpretation of the data, critical revision of the manuscript, and final approval of the version to be published.
Dr Langevin: contributed to the interpretation of the data, critical revision of the manuscript, and final approval of the version to be published.
Dr Freitag: contributed to the interpretation of the data, critical revision of the manuscript, and final approval of the version to be published.
Dr Muscedere: contributed to the interpretation of the data, critical revision of the manuscript, and final approval of the version to be published.
Dr Friedrich: contributed to the interpretation of the data, critical revision of the manuscript, and final approval of the version to be published.
Dr Geerts: contributed to the interpretation of the data, critical revision of the manuscript, and final approval of the version to be published.
Dr Burry: contributed to the interpretation of the data, critical revision of the manuscript, and final approval of the version to be published.
Dr Alhashemi: contributed to the interpretation of the data, critical revision of the manuscript, and final approval of the version to be published.
Dr Cook: contributed to the conception, design, and interpretation of the data; critical revision of the manuscript; and final approval of the version to be published.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following conflicts of interest: Mr Williamson has received speaker honoraria from Boeringher-Ingleheim GmbH and Pfizer, Inc. He is a recipient of a doctoral training award for applicants with a professional degree from the Fonds de la recherche du Québec-Santé (FRQ-S). Dr Arnold holds a New Investigator Award from the Canadian Institutes of Health Research (CIHR) in partnership with Hoffmann-La Roche Ltd. Dr Lauzier is a recipient of a research career award from the FRQ-S. Dr Zarychanski receives salary support from CIHR as part of a randomized controlled trial Mentoring Award. Dr Crowther has sat on advisory boards for Leo Pharma Inc; Pfizer, Inc; Bayer; Boehringer-Ingelheim GmbH; Alexion; CSL Behring; and Artisan Pharma, Inc. He has prepared educational materials for Pfizer, Inc; Octapharma AG; and CSL Behring, and has provided expert testimony for Bayer. Dr Crowther's institution has received funding for research projects from Boehringer-Ingelheim GmbH; Octapharma AG; Pfizer, Inc; and Leo Pharma Inc. Dr Warkentin has served as a consultant and/or has received honoraria for speaking on behalf of companies that manufacture low-molecular-weight heparin (Pfizer Canada Inc, and Sanofi SA), heparin-coated grafts (W.L. Gore & Associates, Inc), heparin-like molecules (ParinGenix, Inc), and nonheparin anticoagulants for the management of HIT (Canyon Pharmaceuticals and GlaxoSmithKline). His institution has received funding from GlaxoSmithKline and Instrumentation Laboratory, as well as from the Heart and Stroke Foundation of Ontario for research related to HIT. Dr Warkentin has also received royalties from Informa plc for a book, entitled *Heparin-Induced Thrombocytopenia*. He receives compensation for medicolegal consultation and testimony regarding thrombocytopenic disorders, including HIT. Dr Crowther holds a Career Investigator Award from the Heart and Stroke Foundation of Ontario and the Leo Pharma Chair in Thromboembolism Research at McMaster University and St. Joseph's Healthcare, Hamilton, ON, Canada. Dr Fowler holds a Clinician Scientist Award from the Heart and Stroke Foundation of Ontario. Dr Lamontagne is a recipient of a research career award from the FRQ-S and a CIHR RCT Mentoring Award. Dr Friedrich holds a Clinician Scientist Award from the CIHR. Dr Cook is a research chair of the CIHR. The remaining authors have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.
Role of sponsors: The sponsors had no role in the design of the study, the collection and analysis of the data, or in the preparation of the manuscript.
Other contributions: The study drug, prophylactic dalteparin, was provided for international use by Pfizer Inc, and by Eisai, Inc, in the United States. We are grateful to the patients and families contributing to the PROTECT trial, and thank the research coordinators and bedside staff for their participation.
Additional information: The e-Table and e-Appendix can be found in the "Supplemental Materials" area of the online article.

References

1. Chakraverty R, Davidson S, Peggs K, Stross P, Garrard C, Littlewood TJ. The incidence and cause of coagulopathies in an intensive care population. *Br J Haematol*. 1996;93(2):460-463.
2. Shalansky SJ, Verma AK, Levine M, Spinelli JJ, Dodek PM. Risk markers for thrombocytopenia in critically ill patients: a prospective analysis. *Pharmacotherapy*. 2002;22(7):803-813.
3. Akca S, Haji-Michael P, de Mendonça A, Suter P, Levi M, Vincent JL. Time course of platelet counts in critically ill patients. *Crit Care Med*. 2002;30(4):753-756.
4. Crowther MA, Cook DJ, Meade MO, et al. Thrombocytopenia in medical-surgical critically ill patients: prevalence, incidence, and risk factors. *J Crit Care*. 2005;20(4):348-353.
5. Vanderschueren S, De Weerdt A, Malbrain M, et al. Thrombocytopenia and prognosis in intensive care. *Crit Care Med*. 2000;28(6):1871-1876.
6. Vandijck DM, Blot SI, De Waele JJ, Hoste EA, Vandewoude KH, Decruyenaere JM. Thrombocytopenia and outcome in critically ill patients with bloodstream infection. *Heart Lung*. 2010;39(1):21-26.
7. Strauss R, Wehler M, Mehler K, Kreutzer D, Koebnick C, Hahn EG. Thrombocytopenia in patients in the medical intensive care unit: bleeding prevalence, transfusion requirements, and outcome. *Crit Care Med*. 2002;30(8):1765-1771.
8. Wang HL, Aguilera C, Knopf KB, Chen TM, Maslove DM, Kuschner WG. Thrombocytopenia in the intensive care unit [published online ahead of print January 9, 2012]. *J Intensive Care Med*. doi:10.1177/0885066611431551.
9. Cook D, Meade M, Guyatt G, et al; PROTECT Investigators for the Canadian Critical Care Trials Group and the Australian and New Zealand Intensive Care Society Clinical Trials Group. Dalteparin versus unfractionated heparin in critically ill patients. *N Engl J Med*. 2011;364(14):1305-1314.
10. Crowther MA, Cook DJ, Albert M, et al; Canadian Critical Care Trials Group. The 4Ts scoring system for heparin-induced thrombocytopenia in medical-surgical intensive care unit patients. *J Crit Care*. 2010;25(2):287-293.
11. Bennett CL, Connors JM, Carwile JM, et al. Thrombotic thrombocytopenic purpura associated with clopidogrel. *N Engl J Med*. 2000;342(24):1773-1777.
12. Ecker RD, Wijdicks EF, Wix K, McClelland R. Does famotidine induce thrombocytopenia in neurosurgical patients? *J Neurosurg Anesthesiol*. 2004;16(4):291-293.
13. Hui P, Cook DJ, Lim W, Fraser GA, Arnold DM. The frequency and clinical significance of thrombocytopenia complicating critical illness: a systematic review. *Chest*. 2011;139(2):271-278.

14. Greinacher A, Selleng K. Thrombocytopenia in the intensive care unit patient. *Hematology Am Soc Hematol Educ Program*. 2010:135-143.
15. Arnold DM, Crowther MA, Cook RJ, et al. Utilization of platelet transfusions in the intensive care unit: indications, transfusion triggers, and platelet count responses. *Transfusion*. 2006;46(8):1286-1291.
16. Selleng K, Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia in intensive care patients. *Crit Care Med*. 2007;35(4):1165-1176.
17. Moreau D, Timsit JF, Vesin A, et al. Platelet count decline: an early prognostic marker in critically ill patients with prolonged ICU stays. *Chest*. 2007;131(6):1735-1741.
18. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985;13(10):818-829.
19. Arnold DM, Donahoe L, Clarke FJ, et al. Bleeding during critical illness: a prospective cohort study using a new measurement tool. *Clin Invest Med*. 2007;30(2):E93-E102.
20. Arnold DM, Lauzier M, Rabbat C, et al. Adjudication of bleeding outcomes in an international thromboprophylaxis trial in critical illness. *Thromb Res*. 2013;131(3):204-209.
21. Masrouki S, Mebazaa MS, Mestiri T, Ben Ammar MS. Risk factors of mortality in critically ill patients with thrombocytopenia [in French]. *Ann Fr Anesth Reanim*. 2004;23(8):783-787.
22. Warkentin TE. Clinical presentation of heparin-induced thrombocytopenia. *Semin Hematol*. 1998; 35(4)(suppl 5):9-16.
23. Martel N, Lee J, Wells PS. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. *Blood*. 2005; 106(8):2710-2715.
24. Nikolsky E, Sadeghi HM, Effron MB, et al. Impact of in-hospital acquired thrombocytopenia in patients undergoing primary angioplasty for acute myocardial infarction. *Am J Cardiol*. 2005;96(4):474-481.
25. Ben Hamida C, Lauzet JY, Rézaiguia-Delclaux S, et al. Effect of severe thrombocytopenia on patient outcome after liver transplantation. *Intensive Care Med*. 2003;29(5):756-762.
26. Hanes SD, Quarles DA, Boucher BA. Incidence and risk factors of thrombocytopenia in critically ill trauma patients. *Ann Pharmacother*. 1997;31(3):285-289.
27. Stéphan F, Hollande J, Richard O, Cheffi A, Maier-Redelsperger M, Flahault A. Thrombocytopenia in a surgical ICU. *Chest*. 1999;115(5):1363-1370.
28. Baughman RP, Lower EE, Flessa HC, Tollerud DJ. Thrombocytopenia in the intensive care unit. *Chest*. 1993;104(4): 1243-1247.
29. Stephan F, Montblanc Jd, Cheffi A, Bonnet F. Thrombocytopenia in critically ill surgical patients: a case-control study evaluating attributable mortality and transfusion requirements. *Crit Care*. 1999;3(6):151-158.
30. Brogly N, Devos P, Boussekey N, Georges H, Chiche A, Leroy O. Impact of thrombocytopenia on outcome of patients admitted to ICU for severe community-acquired pneumonia. *J Infect*. 2007;55(2):136-140.
31. Lauzier F, Arnold D, Rabbat C, et al. In medical-surgical ICU patients, major bleeding is common but independent of heparin prophylaxis. *Crit Care*. 2012;16(suppl 1):435.