Incidence and Prognostic Significance of Thrombocytopenia Developed During Acute Coronary Syndrome in Contemporary Clinical Practice

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Background—Prior studies examining thrombocytopenia among patients with acute coronary syndromes (ACS) evaluated highly selected patients in a clinical trial setting using varying definitions of thrombocytopenia. The incidence, severity, and prognostic significance of acquired thrombocytopenia during ACS in community practice have not been well defined.

Methods and Results—We examined 36,182 patients with non–ST-segment elevation ACS enrolled at 379 US hospitals participating in the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines (CRUSADE) quality improvement initiative between June 2004 and December 2006. Patients with baseline platelet counts \( < 150 \times 10^9/L \) were excluded. Overall, 4,697 patients (13%) developed new thrombocytopenia, defined as nadir platelet count \( < 150 \times 10^9/L \) (referenced lower limit of normal), during their ACS hospitalization. Risks of in-hospital mortality and bleeding correlated directly with severity of thrombocytopenia; even mild thrombocytopenia (nadir 100 to 149 \( \times 10^9/L \)) was associated with increased risks of mortality (adjusted odds ratio [OR], 2.01; 95% CI, 1.69 to 2.38) and bleeding (adjusted OR, 3.76; 95% CI, 3.43 to 4.12). Each 10% drop in platelet count was associated with increased mortality and bleeding risks (adjusted ORs, 1.39 [95% CI, 1.33 to 1.46] and 1.89 [95% CI, 1.83 to 1.95], respectively). A \( \geq 50\% \) drop in platelet count was associated with higher risk of adverse outcomes regardless of the nadir count. A novel combined definition of acquired thrombocytopenia—nadir \( < 150 \times 10^9/L \) or platelet count drop \( \geq 50\% \) in the setting of normal nadir values—is clinically significant. Application of a combined definition for thrombocytopenia using both absolute and relative thresholds permits increased sensitivity for patients at high risk of adverse outcomes. (Circulation. 2009;119:2454-2462.)

Key Words: acute coronary syndrome ■ bleeding ■ thrombocytopenia

Antithrombotic and invasive therapies used in the management of acute coronary syndrome (ACS) contribute to the risk of developing thrombocytopenia during ACS care.1–4 Among patients with non–ST-segment elevation (NSTE) ACS, previous studies have observed a low (1% to 7%) incidence of acute thrombocytopenia.5–7 These studies used a conservative threshold (\( < 100 \times 10^9/L \)) to define thrombocytopenia that is lower than the clinical definition of thrombocytopenia (\( < 150 \times 10^9/L \)). Furthermore, these studies were performed as posthoc analyses of clinical trial databases and were therefore restricted to highly selected patients with less comorbidity than patients treated in routine clinical practice. To date, the incidence, severity, and prognostic significance of acquired thrombocytopenia during ACS in contemporary community practice have not been well established.

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Using data from the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines (CRUSADE) registry, we sought to determine the incidence of thrombocytopenia among unselected community patients treated for NSTE ACS using various definitions of thrombocytopenia, to iden-
tify clinical factors associated with the development of thrombocytopenia, and to characterize the association between the severity of acquired thrombocytopenia and in-hospital outcomes.

Methods

Study Population
CRUSADE is a large, voluntary, national quality improvement registry designed to promote evidence-based treatment of hospitalized patients with NSTE ACS. Enrollment criteria include ischemic symptoms within 24 hours of presentation lasting ≥10 minutes, combined with high-risk features such as ischemic ST-segment ECG changes (ST depression ≥0.5 mm, transient ST elevation of 0.5 to 1.0 mm lasting <10 minutes) and/or positive cardiac biomarkers (troponin I or T and/or creatine kinase-MB higher than the upper limit of normal) within 24 hours of hospital admission. Hospital participation in CRUSADE was voluntary and open to all hospitals in the United States. Participation required approval of the Institutional Review Board of each hospital. Because patient information was collected anonymously without unique patient identifiers, individual informed consent was not required.8

Between June 2004 (when version 2.2 of the CRUSADE data collection was implemented, enabling capture of platelet count data) and December 2006, 64,370 consecutive patients with NSTE ACS were included in the CRUSADE registry. During this time period, the initiative encompassed 394 hospitals of various sizes, teaching status, and interventional or cardiac surgical capabilities across the United States. First, patients with baseline thrombocytopenia (platelet count <150×10^9/L at admission) were excluded (n=3,017). Then, we excluded patients who had non–ACS-related thrombocytopenia; these were patients with in-hospital coronary artery bypass grafting (CABG) who have a high prevalence of cardiopulmonary bypass–associated thrombocytopenia and potential confounding with perioperative bleeding and transfusion needs (n=5,556) and patients who had nadir platelet counts >14 days after their ACS admission (n=158). Finally, patients with missing baseline platelet counts (n=2,681), missing nadir platelet counts (n=16,119), missing timing of platelet counts (n=52), and nadir platelet counts before hospital arrival (n=323) or after hospital discharge (n=282) were excluded. This yielded a final analysis population of 36,182 ACS patients with normal admission platelet counts at the time of hospitalization (Figure 1).

Data Collection and Definitions
Participating hospitals collected detailed information on baseline demographic and clinical characteristics, processes of care, and in-hospital outcomes using a standardized set of data elements and definitions, as previously described.9 Patient data were captured retrospectively via chart review and entered by sites into a Web-based data collection form. Data were screened on entry, and only those meeting predetermined criteria for completeness and accuracy could be saved into the database. In 2002, deidentified records from one quarter of the CRUSADE hospitals (randomly selected) were audited, revealing an overall data accuracy of 95%. The overall degree of missing data averaged 5% across all data elements, with variables such as age and sex missing in <0.5% of all cases. Each quarter, sites received a report summarizing any observed data quality issues, thus iteratively improving the overall quality of the database.

In the present analysis, we investigated the incidence and prognostic significance of thrombocytopenia using several definitions. First, using nadir platelet counts, we defined thrombocytopenia as a nadir below the reference lower limit of normal (150×10^9/L). Patients who developed thrombocytopenia were then further divided into those with mild (100 to 149×10^9/L) or moderate/severe (<100×10^9/L) thrombocytopenia. Second, using the change in platelet count (percent drop from admission to nadir during the hospital stay), we defined thrombocytopenia as a platelet drop ≥50% from admission. Finally, we examined a combined definition for acquired thrombocytopenia, defined as either nadir platelet count <150×10^9/L or platelet count drop ≥50%.

Patients who were transferred out of a CRUSADE hospital were excluded from the outcomes analyses because outcomes data could not be ascertained after transfer as a result of current US privacy laws. Major bleeding was defined as an absolute hematocrit drop of ≥12%, intracranial hemorrhage, retroperitoneal bleeding, red blood cell transfusion with a baseline (admission) hematocrit ≥28%, or red blood cell transfusion with a baseline hematocrit <28%, and witnessed bleeding.

Statistical Methods
Baseline clinical characteristics, in-hospital treatment, and events were compared among patients stratified by nadir platelet count: normal (≥150×10^9/L), mild (100 to 149×10^9/L), and moderate/severe (<100×10^9/L) thrombocytopenia. Continuous variables are presented as medians with interquartile percentiles; categorical variables are expressed as percentages. Univariate comparisons were performed using χ² rank correlation statistics for continuous variables and χ² rank-based group means score statistics for categorical variables.

Multivariable logistic regression with logit link was used to identify factors associated with the development of thrombocytopenia. In addition, the generalized estimating equation method with
exchangeable working correlation structure was used to estimate parameters of the logistic regression model and to calculate empirical (sandwich) SE estimates, accounting for within-hospital clustering because patients at the same hospital are more likely to have similar responses relative to patients in other hospitals (ie, within-center correlation for response). Covariates entered into the model included baseline characteristics (age, sex, race, body mass index, diabetes, hypertension, smoking status, prior myocardial infarction, history of coronary artery disease and dyslipidemia), and use of acute medications (clopidogrel, eptifibatide/abciximab) within the first 24 hours of hospitalization comes were adjusted for baseline characteristics known to increase bleeding risk in the NSTE ACS population, including age, sex, body mass index, renal insufficiency, and signs of heart failure. Covariates included baseline characteristics (age, sex, race, body mass index, renal insufficiency, and signs of heart failure). The relationship between percent change in platelet count and in-hospital adverse events was explored in a similar fashion. Multi-variable logistic regression with the generalized estimating equation also was used to examine the association between thrombocytopenia and in-hospital events. First, patients with mild and moderate/severe thrombocytopenia were compared with patients without thrombocytopenia. Next, risk-adjusted outcomes were examined as a function of percent platelet count change as a continuous variable. Patients whose nadir dropped ≥50% of baseline were then compared with patients with a <50% drop. We used χ² testing to assess the interaction between nadir platelet count and percent platelet count drop in the logistics model. Finally, these outcomes were examined by applying a combined definition of thrombocytopenia: either nadir <150 × 10⁹/L or percent platelet count drop ≥50%. Mortality outcomes were adjusted for the baseline characteristics and presenting features outlined above with the additional variables of family history of coronary artery disease and dyslipidemia. Bleeding outcomes were adjusted for baseline characteristics known to increase bleeding risk in the NSTE ACS population, including age, sex, body mass index, renal insufficiency, and signs of heart failure.

A value of \( P < 0.05 \) was considered statistically significant for all tests. No adjustments were made for multiple comparisons. All analyses were performed with SAS software version 9.1 (SAS Institute, Inc, Cary, NC).

Dr Wang had full access to all of the data in this study and takes responsibility for the integrity of these data and the accuracy of the data analysis.

### Results

#### Baseline Characteristics

Among 36,182 NSTE ACS patients, 4,254 (11.8%) developed nadir platelet counts between 100 and 149 × 10⁹/L (mild
thrombocytopenia), and 443 (1.2%) had nadir platelet counts below 100 \times 10^9/L (moderate/severe thrombocytopenia). The median times from admission to nadir values were 2.1 days for patients with mild thrombocytopenia and 2.9 days for patients with moderate/severe thrombocytopenia. Patients who developed thrombocytopenia were older and more frequently had lower body mass, diabetes, renal insufficiency, and prior cardiovascular disease compared with nonthrombocytopenic patients (Table 1). On admission, these patients had lower blood pressures and more often had signs of heart failure. Of note, they also had significantly lower baseline platelet counts (although still within normal range).

### In-Hospital Treatment

Patients who developed thrombocytopenia were more likely to be treated with unfractionated heparin but were less likely to receive other antithrombotic medications such as low-molecular-weight heparin, aspirin, and clopidogrel (Table 2). These patients also were less likely to receive other guideline-recommended therapies such as β-blockers and statins. Although rates of cardiac catheterization were similar among groups, patients with thrombocytopenia less frequently underwent in-hospital PCI (PCI rates: 65.4% in the normal group, 63.6% in the mild thrombocytopenia group, and 56.8% in the moderate/severe thrombocytopenia group; \( P = 0.006 \)).

### Factors Influencing the Development of Thrombocytopenia

After multivariable modeling, baseline risk factors associated with thrombocytopenia included lower body mass index, female sex, and white race (Table 3). Patients with signs of heart failure, hypotension, or tachycardia on admission; ST-segment depression on ECG; and reduced renal clearance and those with lower baseline platelet counts, even within normal range, also were more likely to develop thrombocytopenia. Among postadmission therapies, in-hospital PCI or cardiac catheterization was most significantly associated with the development of thrombocytopenia.

### In-Hospital Outcomes as a Function of Nadir Platelet Count

As shown in Figure 2A, higher risks of in-hospital death and major bleeding were observed with increasing severity of thrombocytopenia. Almost 1 in every 4 patients with moderate/severe thrombocytopenia died during the ACS hospitalization (Figure 3). Notably, even mild thrombocytopenia was associated with a doubling of mortality risk (adjusted odds ratio [OR], 2.01; 95% CI, 1.69 to 2.38).

Major bleeding rates also rose with the severity of thrombocytopenia, increasing from 10.1% to 23.9% to 53.3% among those with normal, mild, and moderate/severe thrombocytopenia, respectively. After adjustment for differences in clinical risk factors, including differences in baseline platelet counts, patients with thrombocytopenia remained at significantly higher risk of major bleeding (Figure 3).

Patients with thrombocytopenia also were at increased risk of other in-hospital complications (Table 4). Hospital stays progressively lengthened with increased severity of thrombocytopenia; the median lengths of stay were 4 days (interquartile range, 3 to 6 days) in the normal group, 5 days (interquartile range, 3 to 7 days) in the mild thrombocytopenia group, and 7 days (interquartile range, 4 to 11 days) in the

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### Table 2. Use of Acute Medications and Invasive Cardiac Procedures*

<table>
<thead>
<tr>
<th>Variable</th>
<th>No Thrombocytopenia (n=31480), %</th>
<th>Mild Thrombocytopenia (n=4254), %</th>
<th>Moderate/Severe Thrombocytopenia (n=443), %</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute medications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>96.8</td>
<td>95.7</td>
<td>95.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>62.7</td>
<td>61.5</td>
<td>56.9</td>
<td>0.06</td>
</tr>
<tr>
<td>Heparin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>55.4</td>
<td>58.8</td>
<td>62.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Low-molecular-weight heparin</td>
<td>41.0</td>
<td>37.6</td>
<td>35.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Direct thrombin inhibitor</td>
<td>5.6</td>
<td>5.3</td>
<td>4.5</td>
<td>0.27</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIa inhibitor</td>
<td>4.4</td>
<td>4.2</td>
<td>6.3</td>
<td>0.92</td>
</tr>
<tr>
<td>Abciximab</td>
<td>46.4</td>
<td>45.5</td>
<td>48.6</td>
<td>0.49</td>
</tr>
<tr>
<td>Eptifibatide</td>
<td>0.6</td>
<td>0.5</td>
<td>0.3</td>
<td>0.20</td>
</tr>
<tr>
<td>Tiroliban</td>
<td>92.5</td>
<td>91.7</td>
<td>89.2</td>
<td>0.02</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>51.3</td>
<td>50.5</td>
<td>42.7</td>
<td>0.12</td>
</tr>
<tr>
<td>Statin</td>
<td>64.8</td>
<td>63.0</td>
<td>58.3</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>In-hospital procedures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnostic angiography</td>
<td>88.0</td>
<td>87.5</td>
<td>87.3</td>
<td>0.33</td>
</tr>
<tr>
<td>PCI</td>
<td>65.4</td>
<td>63.6</td>
<td>56.8</td>
<td>0.006</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme.

*Acute medications were those given within 24 hours of admission. Percentages were calculated among eligible patients for each therapy (without contraindications).
Table 3. Factors Associated With Thrombocytopenia (<150×10^9/L)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>χ^2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline platelet count (per 10-unit decrease)</td>
<td>1.41</td>
<td>1.39–1.45</td>
<td>1535.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine clearance (per 10-mL/min decrease)</td>
<td>1.12</td>
<td>1.09–1.15</td>
<td>60.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>In-hospital procedure*</td>
<td>1.48</td>
<td>1.33–1.64</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCI</td>
<td>1.64</td>
<td>1.46–1.84</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiac catheterization (without PCI)</td>
<td>1.05</td>
<td>1.03–1.06</td>
<td>47.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Admission systolic blood pressure (per 10-mm Hg decrease)</td>
<td>1.36</td>
<td>1.23–1.50</td>
<td>35.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Signs of heart failure on admission</td>
<td>1.10</td>
<td>1.06–1.14</td>
<td>29.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index (per 5-unit decrease)</td>
<td>1.05</td>
<td>1.03–1.07</td>
<td>21.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Admission heart rate (per 10-bpm increase)</td>
<td>1.17</td>
<td>1.07–1.28</td>
<td>12.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ST depression</td>
<td>1.12</td>
<td>1.01–1.23</td>
<td>5.1</td>
<td>0.03</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.14</td>
<td>1.01–1.29</td>
<td>4.5</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Other variables in the model include age, hypertension, diabetes, prior heart failure, prior myocardial infarction, prior PCI, prior CABG, prior stroke, current/recent smoker, positive cardiac biomarkers, and acute clopidogrel, abciximab, eptifibatide/tirofiban, unfractionated heparin, and low-molecular-weight heparin use before the nadir platelet count. Creatinine clearance was calculated by the Cockroft-Gault equation. Model c index = 0.87.

In-hospital procedures in this table include only those done before the nadir platelet count.

Discussion

The CRUSADE registry provides a unique opportunity to characterize the incidence and prognostic significance of acquired thrombocytopenia among contemporary ACS patients treated in the United States. Thrombocytopenia is a common occurrence among ACS patients, and patients who develop even mild thrombocytopenia incur significantly higher risks of in-hospital mortality and bleeding complications.

Incidence of Thrombocytopenia Varies With Study Population and Definition

To date, the incidence of thrombocytopenia among patients with ACS has been described almost exclusively in the clinical trial setting. In the Platelet Glycoprotein IIb/IIIa in...
Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial, thrombocytopenia, defined as a nadir platelet count <100×10^9/L or <50% of baseline, was observed in 7% of enrolled patients. A similar definition applied by Yeh et al yielded a lower incidence of 2.4% among patients treated with either unfractionated or low-molecular-weight heparin in the Thrombolysis in Myocardial Infarction (TIMI) 11B study. Among patients randomized to either heparin or bivalirudin in the Organization to Assess Strategies for Ischemic Syndromes (OASIS-2) trial, the incidence of thrombocytopenia was only 1%; however, in this study, thrombocytopenia was defined only as nadir platelet count <100×10^9/L. In the ST-elevation myocardial infarction setting, the incidence of thrombocytopenia has been shown to be as high as 16%, primarily in the setting of fibrinolytic use, whereas among those treated with primary PCI, the incidence (2.5%) was similar to that of patients with NSTE ACS. The incidence of thrombocytopenia in routine practice is difficult to extrapolate from these studies because of the restricted criteria for patient inclusion and the lack of a uniform definition of thrombocytopenia across studies.

Although many cardiology studies apply a threshold of 100×10^9/L to define thrombocytopenia, 150×10^9/L is referenced as the lower limit of normal. Some studies further include a relative reduction of ≥50% from baseline in the definition to capture patients with a significant degree of platelet compromise despite a nadir within the normal range. Our study shows that in routine clinical practice, ≈1 in 8 patients with normal platelet counts at baseline developed in-hospital thrombocytopenia (nadir platelet <150×10^9/L) after treatment with contemporary ACS therapies. This rate is significantly higher than previously reported in the cardiology literature owing to the less conservative criteria and broader, unselected study population.

Causes of Thrombocytopenia

Thrombocytopenia that develops in the ACS setting can be related to the treatments received. Immune reactions to heparin, resulting in thrombocytopenia, are paradoxically associated with thrombotic complications, but its incidence in the cardiology population has not been well established because of varying testing patterns, subtypes, and often unclear diagnosis in the presence of concurrent medications. Thrombotic thrombocytopenic purpura associated with thienopyridine therapy is a rare phenomenon that typically occurs within the first 2 weeks of use and should be considered when thrombocytopenia occurs with hemolytic anemia, renal failure, and/or neurological changes. The use of glycoprotein IIb/IIIa inhibitors has previously been associated with thrombocytopenia and should be suspected when platelet counts fall soon after drug initiation. Pseudothrombocytopenia, a platelet artifact, occurs commonly in patients treated with glycoprotein IIb/IIIa inhibitors and may contribute to the incidence of thrombocytopenia in this population. Although heparin-induced thrombocytopenia serologies and peripheral smear data were not captured in this database, none of these acute medications were independently associated with thrombocytopenia (Table 3), which likely reflects the infrequency of these diagnoses.

In-hospital invasive procedures such as cardiac catheterization and PCI were significant independent predictors of thrombocytopenia. This association is not intuitive but may be attributed to procedure-related anticoagulation, hemodilution, or platelet consumption. Patients who underwent in-hospital CABG were excluded from this analysis because of confounding with bleeding outcomes. However, the contribution of mechanical platelet consumption, hemodilution, and filtration in the bypass circuit to the development of thrombocytopenia has been well documented.

Association of Acquired Thrombocytopenia With Outcomes

Although thrombocytopenia developed more frequently among patients who were older with more comorbidities and lower baseline platelet counts, after adjustment for these differences, patients who developed acute thrombocytopenia...
which occurs quite frequently during ACS, is clinically significant. Alternatively, thrombocytopenia may be mediated by interval bleeding; the association between bleeding and downstream risk of mortality and recurrent cardiovascular events has been well established in the observational study; however, the relationship between thrombocytopenia and mortality remains less certain. Platelet activation during their consumption leading to downstream thrombotic events has been hypothesized. Patients who develop thrombocytopenia may, because of perceived bleeding risk, be less likely to receive guideline-recommended therapies and PCI, which further adversely affects downstream outcomes. The effect of thrombocytopenia on mortality may well be mediated by interval bleeding; the association between bleeding and downstream risk of mortality and recurrent cardiovascular events has been well demonstrated in the ACS population.6,13,24 Alternatively, thrombocytopenia may simply be a marker of poor substrate and not necessarily implicated in the causal pathway to death.

Although our findings are congruent with the results of previous studies demonstrating an association between thrombocytopenia and adverse outcomes,5–7,14,15 we further observe that the degree of risk strongly and independently correlates with the severity of thrombocytopenia, whether determined by the absolute nadir value or relative drop from baseline. In Figure 2A, the inflection point for increased bleeding and mortality risks occurs at a nadir platelet count of \( \approx 150 \times 10^9/L \), suggesting that even mild thrombocytopenia, which occurs quite frequently during ACS, is clinically significant.

Previous studies have variably incorporated the severity of platelet count drop into their definitions of thrombocytopenia. Figure 2B shows a mostly linear relationship between degree of drop and adverse outcomes. Interestingly, a significant interaction was observed between nadir platelet count and severity of platelet drop in their association with bleeding outcomes. For patients with mildly impaired or even normal nadir platelet counts, a \( \geq 50\% \) drop in platelet count was associated with significantly increased bleeding rates. Patients who develop thrombocytopenia using a combined definition (platelet count nadir \(< 150 \times 10^9/L \) or platelet count drop \( \geq 50\% \)) have a 2.5-fold higher mortality risk and 4-fold increase in bleeding risk compared with patients without thrombocytopenia. From these results, future studies examining thrombocytopenia in the ACS setting should apply the combined definition of nadir platelet count \(< 150 \times 10^9/L \) or \( \geq 50\% \) relative drop to optimally capture clinically relevant thrombocytopenia.

Almost 2 million patients are hospitalized annually with ACS. Given its sizable incidence, the development of thrombocytopenia in patients with ACS has tremendous clinical and financial consequences. As such, therapeutic strategies to minimize the risk of thrombocytopenia may not only improve associated patient outcomes but also reduce total ACS-related healthcare costs. Further efforts investigating the risk factors that predispose patients to developing thrombocytopenia are warranted. Although applied antiplatelet and antithrombin therapies contribute to the risk of thrombocytopenia via differing mechanisms, it is unclear whether combining these therapies synergistically augments the risk of thrombocytopenia and its attendant poor prognosis or whether novel therapies replacing the heparin/glycoprotein inhibitor anticoagulant combination (eg, bivalirudin, fondaparinux) may be helpful in reducing both thrombocytopenia and bleeding risks.25 Minimization of other medications associated with thrombocytopenia such as nonsteroidal antiinflammatory agents, oral hypoglycemics, or certain antibiotics may help avoid adverse outcomes. Knowledge of these risk factors will allow targeted scrutiny (eg, increased surveillance of platelet counts) in at-risk patients to assist in early identification and may permit more rational selection of therapies.

**Study Limitations**

The observational nature of this study permits an assessment of the risks of thrombocytopenia in routine clinical practice; however, causality between thrombocytopenia and outcomes cannot be established because unmeasured confounding may be present. These data are further limited by only 2 measurements of platelet count (baseline and nadir), so the duration of thrombocytopenia and temporal profile of platelet count drop and recovery cannot be explored. In fact, the bleeding risk associated with thrombocytopenia may be underestimated because bleeding events occurring before the platelet count nadir were excluded, despite the fact that they may have actually occurred after platelet counts had started their downward trend. Patients with missing nadir counts were excluded from the study population, which may have introduced some selection bias. However, comorbidities and presentation features (factors associated with thrombocytopenia develop-
ment) were similar between the analysis and excluded groups. Nadir platelet counts could not be ascertained for the excluded group because (compared with the analysis population) more of these excluded patients either died early or were transferred to another hospital for further ACS care. Given the various mechanisms through which CABG interacts with thrombocytopenia, bleeding definitions, and transfusion requirements, we excluded patients who underwent in-hospital CAGB from our analyses; therefore, our findings cannot be generalized to this population. Other factors that might have contributed to thrombocytopenia such as the use of noncardiac medications associated with thrombocytopenia, presence of antiplatelet antibodies, sepsis, or disseminated intravascular coagulation were not collected; thus, the impact of these diagnoses on treatment patterns (eg, withholding of anti-thrombotic therapies, platelet transfusion) and downstream outcomes cannot be assessed. Finally, the database reports only in-hospital outcomes, so conclusions about long-term consequences of thrombocytopenia cannot be drawn.

Conclusions
The development of thrombocytopenia, even when mild in severity, among patients with ACS is associated with substantial increases in bleeding complications and in-hospital mortality. A combined definition for thrombocytopenia using both an absolute threshold and a relative drop threshold (platelet count drop to <150×10⁹/L or ≥50% of baseline) may optimize the sensitivity for detecting patients with an increased risk of adverse events. Increased vigilance among patients at risk of thrombocytopenia and management strategies that minimize thrombocytopenia risks may significantly improve patient outcomes.

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Disclosures
Dr Wang has been a principal investigator for The Medicines Com and is an investigator for Bristol-Myers Squibb, sanofi-aventis, and Schering-Plough. Dr Roe is an investigator for Daiichi-Sankyo, Eli Lilly, Portola Pharmaceuticals, KAI Pharmaceuticals, Schering-Plough, and sanofi-aventis; a consultant for KAI Pharmaceuticals and Schering-Plough; served on the clinical events adjudication committee for Genentech and Novartis; and on the speakers’ bureau for Schering-Plough. Dr Harrington has been a speaker for Amgen-berg Center for Health Sciences and Bristol-Myers Squibb; a consultant for AstraZeneca, OLG Research, Schering-Plough, Sereidigm, and WebMD/theheart.org; and an advisory board member for Baxter Healthcare, Bayer Pharmaceuticals, Indigo Pharmaceuticals, Nicox, and sanofi-aventis. Dr Ohman has been a consultant for Abiomed, Datoscope, Inovise, Liposcience, Response Biomedical, and The Medicines Co; a principal investigator for Bristol-Myers Squibb, Eli Lilly, Millennium, sanofi-aventis, Schering-Plough, Daiichi-Sankyo, and The Medicines Co; on the speakers’ bureau for CV Therapeutics and The Medicines Co; and a stockholder in Inovise. Dr Gibler has received research grants from EMCREG-International, Millennium, Schering-Plough, sanofi-aventis, and Bristol-Myers Squibb. Dr Peterson has received research grants from Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership, Merck, Schering, and Schering Plough Corp. F-S. Ou reports no conflicts.


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**CLINICAL PERSPECTIVE**

The incidence, severity, and prognostic significance of acquired thrombocytopenia during acute coronary syndromes in community practice have not been well defined. We examined 36,182 patients with non–ST-segment elevation acute coronary syndromes enrolled at 379 US hospitals participating in the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines (CRUSADE) quality improvement initiative between June 2004 and December 2006. Patients with baseline platelet counts <150×10^9/L were excluded. Overall, 13% of patients developed new thrombocytopenia, defined as nadir platelet count <150×10^9/L (referenced lower limit of normal), during their acute coronary syndrome hospitalization. Risks of in-hospital mortality and bleeding correlated directly with severity of thrombocytopenia; even mild thrombocytopenia (nadir, 100 to 149×10^9/L) was associated with increased risks of mortality (adjusted odds ratio [OR], 2.01; 95% CI, 1.69 to 2.38) and bleeding (adjusted OR, 3.76; 95% CI, 3.43 to 4.12). Each 10% drop in platelet count was associated with increased mortality and bleeding risks (adjusted ORs, 1.39 [95% CI, 1.33 to 1.46] and 1.89 [95% CI, 1.83 to 1.95], respectively). A ≥50% drop in platelet count was associated with higher risk of adverse outcomes regardless of the nadir count. A novel combined definition of acquired thrombocytopenia—nadir <150×10^9/L or platelet count drop ≥50%—identifies a population of acute coronary syndrome patients at higher risk of mortality and major bleeding (adjusted ORs, 2.58 [95% CI, 2.23 to 2.98] and 4.32 [95% CI, 3.97 to 4.70], respectively). Application of this combined definition for thrombocytopenia using both absolute and relative thresholds permits increased sensitivity for patients at high risk of adverse outcomes. Increased vigilance among patients at risk of thrombocytopenia and management strategies that minimize thrombocytopenia risks may significantly improve patient outcomes.
Incidence and Prognostic Significance of Thrombocytopenia Developed During Acute Coronary Syndrome in Contemporary Clinical Practice
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