In this issue of Circulation, Wang and colleagues demonstrate that even mild thrombocytopenia (platelet count nadir <150×10⁹/L) developing in patients with acute coronary syndrome (ACS) is associated with bleeding and death. Similar observations have been made in other settings. Critically ill patients with thrombocytopenia have increased duration of mechanical ventilation and risk of death. An increased risk of death also has been reported in thrombocytopenic patients (platelet count nadir <100×10⁹/L) with non–ST-segment elevation ACS (odds ratio [OR], 6.7; 95% confidence interval [CI], 1.9 to 25; P=0.003). Patients receiving heparin in diverse clinical settings who develop thrombocytopenia also have an increased risk of death (OR, 3.4; 95% CI, 2.1 to 5.6; P<0.001); the risk is highest in patients with the greatest decrease in platelet count.4

Wang and colleagues found that specific pharmacological agents infrequently triggered or exacerbated thrombocytopenia. Of course, exceptions exist to the general rule that thrombocytopenia is due to factors other than drug therapy. Those few patients who develop heparin-induced thrombocytopenia (HIT) can die as a direct consequence of this prothrombotic condition. Even in patients suspected to have HIT, thrombocytopenia is a powerful predictor of adverse events; in 1 study of thrombocytopenic patients investigated for HIT, the mortality of those patients with confirmed HIT was actually lower than in the control subjects who tested negative for antibodies or who only had non–platelet-activating heparin-dependent antibodies detected.6 Clearly, thrombocytopenia represents a more relevant risk for mortality than even a well-defined adverse drug reaction such as HIT, for which reasonably effective therapies are available.

How should we now interpret the results of the study by Wang and coworkers? This study analyzed the prognostic significance of thrombocytopenia reported 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) registry, which included data from 64 370 patients in 394 US hospitals. This study excluded non–ST-segment elevation ACS patients who had baseline thrombocytopenia, who underwent cardiac surgery, whose platelet count data (or its timing) were unavailable. Nevertheless, 36 182 patients with non–ST-segment elevation ACS who had a normal admission platelet count remained available for analysis.

Thrombocytopenia was defined as a platelet count nadir <150×10⁹/L and was further subclassified as mild (100 to 149×10⁹/L) or moderate/severe (<100×10⁹/L). The authors also analyzed patients with large platelet count declines (≥50% from baseline) regardless of whether absolute thrombocytopenia occurred.

Baseline clinical characteristics, in-hospital treatment, and events were compared among patients stratified by nadir platelet count. Covariates entered into the model included (among many others) the use of acute medications such as clopidogrel, unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and glycoprotein IIb/IIIa antagonists (eptifibatide, tirofiban, abciximab) within the first 24 hours of hospitalization.

Thirteen percent (4697 of 36 182) of the study patients developed thrombocytopenia, mostly mild (11.8%) rather
than moderate/severe (1.2%). The platelet count nadir occurred at day 2.1 for patients with exclusively mild thrombocytopenia and at day 2.9 for patients with moderate/severe thrombocytopenia. This temporal pattern of early platelet count decline resembles that seen in patients with perioperative thrombocytopenia and nonimmune UFH-induced platelet count declines (discussed later).8

The patients who developed thrombocytopenia were older and more frequently had lower body mass, diabetes, renal insufficiency, prior cardiovascular disease, lower blood pressures, and signs of heart failure. They also had significantly lower baseline platelet counts. Through multivariable modeling, baseline risk factors associated with thrombocytopenia included lower body mass index, female sex, white race, signs of heart failure, hypotension, tachycardia on admission, ST-segment depression on ECG, and reduced renal function. Patients with lower baseline platelet counts (within the normal range) also were more likely to develop thrombocytopenia.

These observations may help to explain why some patients developed thrombocytopenia and why they may also have died more often. The smaller body mass index and impaired renal function may suggest an enhanced risk of circulatory overload. Moreover, the strong association between a lower baseline platelet count and subsequent thrombocytopenia is consistent with the view that greater illness acuity—as an independent risk factor for platelet count reduction—predisposes to evolution to frank thrombocytopenia over the first few days after admission.

This impact of a low-normal baseline platelet count value as a risk factor for subsequent thrombocytopenia was particularly powerful. Although the adjusted OR for this risk factor (OR, 1.41; 95% CI, 1.39 to 1.45 for every 10×10^9/L decrease in platelet count) might seem small at first glance, it nonetheless implies that a patient whose admission platelet count was 180×10^9/L (ie, near the median baseline value of patients who subsequently developed thrombocytopenia) is far more likely to develop thrombocytopenia than someone whose baseline platelet count was 260×10^9/L (ie, the median value among patients in CRUSADE who never developed thrombocytopenia), with an estimated OR of 15.6 (1.41^8 for a difference in platelet count of 80×10^9/L). Most likely, therefore, initial illness severity—itself predisposing to low-normal baseline platelet counts—is the main factor accounting for subsequent thrombocytopenia.

What is the risk of death in patients who develop thrombocytopenia? Wang and colleagues found that almost 1 in every 4 patients who developed moderate/severe thrombocytopenia died during hospitalization. Notably, even mild thrombocytopenia was associated with a doubling of mortality risk (adjusted OR, 2.01; 95% CI, 1.69 to 2.38). Other events that occurred more frequently in patients with thrombocytopenia included major bleeding and prolonged hospital stay.

What role did medications, particularly antithrombotic agents (UFH, LMWH, or glycoprotein IIb/IIIa antagonists), play in predicting thrombocytopenia? Preceding UFH use was more common in patients with thrombocytopenia (of any degree) compared with patients without thrombocytopenia; in contrast, the opposite was seen with LMWH use (the Table). UFH, but not LMWH, causes platelet aggregation, which may predispose to thrombocytopenia temporally associated with its use. This effect is known as nonimmune heparin-associated thrombocytopenia (formerly type 1 HIT).8 It would be attractive to hypothesize that this UFH-induced platelet proaggregatory effect (which reaches its maximum 2 to 3 days after heparin administration) could explain the thrombocytopenia—and perhaps enhanced mortality—observed in CRUSADE. However, multivariable logistic regression analysis (per the legend of Table 3 in the Wang et al article) failed to identify a relationship between any medication (including UFH and LMWH) and mortality.

So, what should be made of these data? It appears that thrombocytopenia does predict mortality. However, this is not likely to be a direct drug effect (eg, mediated through platelet proaggregatory effects or as a result of bleeding). Rather, lower platelet counts at the time of development of ACS and the development of frank thrombocytopenia during treatment for ACS should be regarded as a general marker of illness acuity or severity. That thrombocytopenia is not linked to pharmacological agents suggests that clinicians should be cautious about expecting that newer antithrombotic agents might achieve lower mortality through reduced risk of thrombocytopenia (although a new agent could improve mortality for other reasons). Indeed, in a study reported by Eikelboom and colleagues,3 it did not matter whether the patient received UFH (a drug that predisposes to thrombocytopenia through immune and nonimmune mechanisms) or hirudin (an agent that does not); with either agent, thrombocytopenia predicted increased mortality.

The study of Wang and colleagues, together with existing literature, engenders a feeling of physician helplessness: We know that thrombocytopenia is bad, but we do not think we can do anything about it.

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References

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