E xcessive bleeding is a hazard that has been noted throughout history. As early as the 12th century, physicians identified males who died of uncontrollable bleeding and noted familial relationships. Although hemophilia was probably the source, over the past decade there has been a therapy-induced increase in hemorrhagic disorders. Until recently, treatment for obstructive cardiovascular disease has primarily focused on vessel patency and relief of the thrombosis. Although bleeding has been the accepted primary side effect of antithrombotics, the success and proliferation of novel antiplatelet and antithrombin therapies has tipped the hemorrhage-thrombosis scale. As has been appreciated in many recent clinical trials, the risk of bleeding has now limited efficacy for many of these therapies, leading to a reexamination of new and combinatorial therapeutic uses for antithrombotics.

Although it seems evident that adding more powerful antithrombotic therapies would lead to greater bleeding, the increase in hemorrhage was not entirely anticipated. New antithrombotics typically have favorable bleeding/thrombotic profiles in preclinical models and are primarily evaluated singularly and, therefore, may or may not be directly applicable to clinical use.1 For example, warfarin treatment is associated with hematoma expansion after intracerebral hemorrhage, and it was hoped that direct thrombin inhibitors would mitigate this side effect. In the use of different animal models of intracerebral hemorrhage, warfarin-treated animals had enlarged cerebral hematomas and bleeding, but no difference was found between oral thrombin inhibitor–treated animals and controls.2 Although this is similar to clinical observations,3 other therapies have not had the same consistency in bleeding with preclinical trials.4 Potential inconsistencies between preclinical and clinical studies have made the development of new and safer antithrombotics increasingly challenging.

The use of a wide variety of antiplatelet and antithrombotic agents has been associated with additive bleeding risk with multidrug use. Although often studied in isolation, because these therapies have been increasingly used in combination, the absolute risk may need to be redefined. For instance, the use of low-dose aspirin is associated with an almost 2-fold increase in the risk of upper gastrointestinal bleeding in comparison with none, and this risk is increased further in individuals taking low-dose aspirin with clopidogrel, oral anticoagulants, nonsteroidal anti-inflammatory drugs, or high-dose oral corticosteroids.5 There has also been reevaluation of the frequency and correlates of bleeding with dual-antiplatelet therapy, in particular, over an extended period in a stable population. In the 15 603 patients enrolled in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial,6 long-term clopidogrel (75 mg/d) was compared with placebo in patients receiving daily aspirin (75–162 mg). Severe bleeding occurred in 1.7% of the clopidogrel group versus 1.3% on placebo (P=0.087); moderate bleeding occurred in 2.1% versus 1.3%, respectively. Importantly, the risk of bleeding was greatest the first year, and patients without moderate or severe bleeding during the first year were no more likely than placebo-treated patients to have bleeding thereafter. In addition, even moderate bleeding was strongly associated with mortality.6

As the appreciation for bleeding risk has grown, so has the need for consistency in the interpretation of existing data and planned studies. This has been particularly important for the assessment of bleeding risk, because in many existing trials the quantification/definition of bleeding has varied widely. Analyses have been performed to identify baseline characteristics that independently predict bleeding and to determine how bleeding events impact mortality. In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38),4 bleeding rates were examined in 13 420 patients with acute coronary syndromes. In this study, 534 (4.0%) experienced a serious bleeding event. Variables with the highest strength of association with risk of serious bleeding were female sex, use of a glycoprotein IIb/IIIa inhibitor, duration of intervention, age, assignment to prasugrel, regional characteristics, admission diagnosis of ST-elevation myocardial infarction, femoral access for angiography, creatinine clearance, hypercholesterolemia, and arterial hypertension. Serious bleeding was associated with a significantly increased adjusted hazard ratio for mortality. Although not surprising, the major predictors of serious bleeding were a combination of patient and procedural characteristics and antiplatelet therapies. Also, although serious bleeding was strongly associated with mortality within the first month of the bleeding event, this association was not significant beyond 40 days.4

With the use of existing data, assessments for bleeding risk are being developed with a goal of baseline prediction of bleeding risk complementing ischemic risk prediction for optimization of cardiovascular event care. By use of the community-treated patients with non–ST-elevation acute
myocardial infarction enrolled in the Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines (CRUSADE) Quality Improvement Initiative, a model that identified 8 independent baseline predictors of in-hospital major bleeding was developed (n=71 277) and validated (n=17 857). The CRUSADE bleeding score (range, 1–100 points) was created by assignment of weighted integers that corresponded to the coefficient of each variable. The rate of major bleeding increased by bleeding risk score quintiles, and this score successfully quantified risk for in-hospital major bleeding across all postadmission treatments. The CRUSADE bleeding score was subsequently tested in an independent population of patients hospitalized for non–ST-segment elevation acute myocardial infarction. In this group of 782 consecutive patients, the CRUSADE risk score was generally validated and found to be useful in the cohort of patients who underwent cardiac catheterization, although no conclusions could be drawn in regard to those treated with antithrombotics who did not undergo cardiac catheterization.

Several definitions of bleeding have been used in published clinical trials and registries, and the differences emphasize the lack of uniformity in bleeding definitions. These bleeding definitions may comprise laboratory parameters, clinical events, need for transfusion, and various degrees of bleeding. To address this problem, a Special Report was recently published to standardize bleeding definitions for cardiovascular clinical trials and became a consensus report from the Bleeding Academic Research Consortium. This pivotal report delineated a new objective, hierarchically graded, consensus classification for bleeding that used existing trials, data, and prior definitions. As highlighted by an accompanying editorial by The Center for Drug Evaluation and Research of the Food and Drug Administration, the Bleeding Academic Research Consortium 5-tiered assessment strategy is a step in the right direction, but it remains to be validated, and a comprehensive analysis of extensive databases of prospectively acquired bleeding data linking these definitions to clinical outcomes would be optimal.

As noted by these recent studies, the issue of bleeding is evolving beyond well-established risk factors. In addition to defining risk with medications traditionally thought of as antithrombotics, other medications need to be considered that may be reported to have off-target effects on platelets or the coagulation system. There has been a concern in regard to statins; however, a recent study found no evidence that statins were associated with intracerebral hemorrhage, and, if such a risk is present, its absolute magnitude is likely to be small and outweighed by the other cardiovascular benefits of these drugs. Conversely, some nutritional supplements and vitamins have been shown to alter platelet function and increase bleeding and hemorrhagic stroke. In addition, other clinical factors may contribute to bleeding. For instance, the association between white blood cell count and bleeding was noted in patients with ST-segment elevation acute myocardial infarction treated with percutaneous coronary intervention. The use of these therapies alone and in combination will continue to evolve. The establishment of consistent models of risk prediction is a strong step forward. These models may evolve as additional risk factors are defined, including genetic parameters that may predict risk of bleeding. Bleeding has been associated with an increased risk of subsequent adverse outcomes, including myocardial infarction, stroke, stent thrombosis, and death, in patients with coronary syndromes, stroke, and peripheral interventions; therefore, the ability to balance the anti-ischemic benefits with the bleeding risk of antithrombotic agents will continue to be of central importance in treating patients and evaluating new therapies.

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References
8. Abu-Assi E, Gracia-Acuna JM, Ferreira-Gonzalez I, Pena-Gil C, Gayoso-Diez P, Gonzalez-Juanatey JR. Evaluating the performance of the can rapid risk stratification of unstable angina patients suppress adverse


Appreciating and Mitigating Bleeding Risk
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