Evaluating the Bite of the BARC

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Therapeutic options for patients with acute coronary syndrome (ACS) and those undergoing percutaneous coronary intervention (PCI) have evolved significantly over the past decade. In the era when there were limited antithrombotic choices, reduction of ischemic events was the primary goal regardless of the risk of bleeding that was associated with the use of antiplatelet and anticoagulant therapies. In the current era, clinicians are faced with 5 oral antiplatelet options (aspirin, ticlopidine, clopidogrel, prasugrel, and ticagrelor), 3 intravenous antiplatelet agents (abciximab, eptifibatide, and tirofiban), 4 anticoagulants (unfractionated heparin, low-molecular-weight heparin, bivalirudin, and fondaparinux), and potentially additional oral anticoagulants for long-term secondary prevention. In general, the iterations in antithrombotic drugs have been directed at achieving robust antithrombotic efficacy but with better safety (ie, lower bleeding risk). The focus on bleeding risk is a relatively new development and is probably driven by the robust literature demonstrating an association between bleeding during the management of ACS or in the setting of PCI and subsequent short- and long-term adverse outcomes, such as myocardial infarction, stroke, stent thrombosis, and death. Given these risks, guidelines for ACS and PCI recommend assessing bleeding risk before starting therapy, ostensibly to identify patients at high risk of bleeding and subsequently to choose therapeutic approaches that are associated with lower bleeding risk. Although this approach appears reasonable, attempting to determine the relative safety of different anticoagulant and antiplatelet options is challenging because of the lack of direct comparative studies and the significant heterogeneity in the way bleeding is defined across clinical trials.

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There are no less than 10 distinct bleeding definitions used in clinical trials and registries of ACS patients. These definitions include various data elements that are then grouped into severity classifications (Figure). These data elements include clinical events, such as blood transfusion or intracranial hemorrhage, laboratory parameters, such as hemoglobin decreases, and consequences such as death. Different trials mixed and matched these elements into bleeding definitions that ostensibly assessed the safety of the experimental therapy relative to control. Although the variation in bleeding definitions across clinical trials of antithrombotic agents was generally accepted, it presented a significant problem as the number of ACS therapies grew. In particular, the lack of a universal bleeding definition made the reporting of bleeding complications subject to gaming. For example, a trial of a new antithrombotic that is more potent than existing therapy might use a very restrictive definition of bleeding. Events that meet this definition might be relatively rare, making the reported rate of bleeding low. On the other hand, a trial of an antithrombotic that is felt to be safer than existing therapy might use a very broad definition of bleeding. Events meeting this definition might be very common, making the reported rate of bleeding high; the difference in bleeding rates between it and control therapy would likely reach statistical significance, thus making the new therapy appear “safer.” Another troubling situation occurs when a trial uses >1 definition to assess bleeding events, which can result in contradictory findings. In the Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial that compared enoxaparin with unfractionated heparin in 10,027 patients with non–ST-segment elevation ACS, safety was evaluated by use of both the Global Use of Strategies to Open occluded arteries (GUSTO) definition of bleeding and the Thrombolysis In Myocardial Infarction (TIMI) definition of bleeding. In the final analysis, the enoxaparin strategy was associated with a significantly higher rate of TIMI major bleeding, but the difference in GUSTO severe bleeding was not statistically different between the 2 arms. Based on these data, determining whether enoxaparin was as safe as unfractionated heparin or was associated with significantly more bleeding depended entirely on which bleeding definition was being used to determine safety. Moreover, the associations between different definitions of bleeding, and even different data elements, and subsequent morbidity and mortality may vary widely.

To address these challenges, a group of representatives from academia (including the authors of this editorial), industry, the National Institutes of Health, and the Food and Drug Administration met in April 2008 to develop a standardized approach to collecting bleeding data for clinical trials. This led to a standardized set of data elements that all trials of new antithrombotic agents should collect to inform the public about the bleeding risks associated with the therapies under study. This consensus recommendation was followed 2 years later by the Bleeding Academic Research Consortium (BARC) meeting that ultimately resulted in the BARC definition of bleeding. BARC bleeding includes data elements from other bleeding definitions, such as transfu-
sions, hemoglobin decreases, and intracranial hemorrhage, but also adds elements such as bleeding leading to discontinuation of antithrombotic medications or requiring surgical intervention to control.

Three aspects of the BARC definition distinguish it from previous definitions. First, it avoids using qualitative terms like “major” or “severe,” and instead uses a numeric system that is somewhat ordinal. Bleeding events are categorized into 6 types (type 0 through 5) that allow for detection of events that may not be captured by use of previous definitions. Second, it includes a special category for coronary artery bypass graft (CABG)-related bleeding. Third, it is designed to rely heavily on adjudication so that hemoglobin decreases that are attributable to bleeding events are the ones that count.

Although the BARC met its goal of developing a definition, the definition itself was ultimately a consensus across clinical trialists and stakeholders. Whether it had prognostic value above and beyond previous definitions was not known. It addition, it was not clear whether the definition could be operationalized in the clinical trial setting and whether it could be adjudicated successfully. In this issue of Circulation, a study by Ndrepepa and colleagues examines the prognostic value of BARC bleeding in a large cohort of patients undergoing PCI. They find that BARC type 2 or greater bleeding is significantly associated with increased 1-year mortality and has a relationship with mortality similar to bleeding defined according to the TIMI or Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE)-2 trial criteria.

Several aspects of this study are worthy of discussion. First, the study demonstrates that the BARC definition can be successfully reconstructed by using data elements that are commonly captured in ACS clinical trials. Moreover, independent personnel reviewed all bleeding events to determine whether each event met criteria for BARC. Hence, not only can BARC be reconstructed, but it can also be successfully adjudicated. Second, the reported rate of bleeding among patients enrolled in the Intracoronary Stenting and Anti-thrombotic Regimen (ISAR) trials using the BARC definition is 3 times higher than the rate with use of either the TIMI or REPLACE-2 criteria. Third, BARC type 2 or greater bleeding is associated with short- and long-term mortality, and this risk is manifest both in the hospital and outpatient setting. Finally, the study shows that there is a dose-response—namely, that there is a progressive increase in the risk of 1-year mortality as the severity of BARC bleeding increased, providing some measure of reassurance that BARC’s ordinal scale appears reasonable.

As 2 physicians involved in developing the BARC bleeding definition, we find a measure of comfort that the work of Ndrepepa validates our efforts. On the other hand, we are not surprised that BARC type 2 or greater bleeding is independently predictive of short- and long-term mortality. Previous studies have demonstrated the association between many of the BARC data elements and morbidity and mortality. Interestingly, the study by Ndrepepa shows that, whereas BARC type 1 was the most common bleeding event that occurred in the study sample, the mortality rate at 30 days and 1 year was not different between patients with type 1 bleeding and patients who did not bleed. In addition, type 4 bleeding (CABG-related bleeding) was very rare (only 8 patients of 1233 that developed bleeding met criteria for type 4 bleeding), and none of these patients died at 30 days or 1 year.

Based on these data, what is the significance of BARC type 1 and type 4 bleeding? The importance of type 1 bleeding is that it considers, to some degree, the patient’s perspective on bleeding events. One of the key underlying mechanisms that explains the association between bleeding and outcomes is the cessation of antithrombotic therapy among patients who develop bleeding. Often, this self-discontinuation of dual antiplatelet therapy places patients at risk for recurrent ischemic events including stent thrombosis. Such information formed the basis for the BARC type 1 bleeding definition. Although it may not be correlated with mortality, measuring the rate of BARC type 1 bleeding may provide unique insights into patient adherence to oral antithrombotic agents, and may be useful in early dose-finding studies of new agents.

The issues surrounding type 4 bleeding are more complex. It is clear that surgical bleeding rates are high in the presence of potent anticoagulants and antiplatelet agents; therefore, quantifying CABG-related bleeding is important when studying ACS patients, because 10% to 15% of them will ultimately require bypass surgery during their hospitalization.

More data on relative rates of type 4 bleeding among antithrombotics may clarify management strategies when CABG is required.

The study by Ndrepepa is a first step—an important one—toward the adoption of a standardized bleeding definition for clinical trials. The next steps must address the
limitations of this study. The patients represented in the analysis all underwent PCI, only 8.4% had elevated troponin levels, and none had ST-segment elevation myocardial infarction. Future studies should assess the prognostic impact of BARC bleeding across the spectrum of ischemic heart disease and across management strategies. In addition, it should be tested in the context of other invasive procedures such as CABG, endovascular procedures, and transcatheter valve procedures. The study by Ndrepepa was partly retrospective in that BARC bleeding was not the primary safety end point of any of the trials included in the analysis; however, the goal of the BARC consensus group was to encourage the prospective use of BARC bleeding as a safety outcome in future clinical trials. To this end, several ongoing clinical trials have adopted BARC as their primary safety end point (ClinicalTrials.gov identifiers NCT01433627 and NCT01406236), which will allow for prospective validation of the definition, and potentially allow for the evaluation of individual data elements so that the definition can be streamlined. Finally, assessment of bleeding not only depends on the definition used, but also on the way in which patients are asked about their signs and symptoms of bleeding. Standardized surveys are used to assess for bleeding complications in patients with hematologic disorders; because antithrombotic therapy for ACS is an iatrogenic disruption of normal hemostatic mechanisms, such standardized questionnaires would add significant value to cardiovascular trials and clinical care. The study by Ndrepepa is the beginning of an important process whose goal is the complete understanding of the risks and benefits of caring for patients with ischemic heart disease, and ultimately finding the appropriate balance in order to further improve outcomes.

Disclosures

Dr Rao received research funding from Cordis Company, Ikaria, Sanofi-aventis; Consulting: Zoll, The Medicines Company, Terumo Medical, and Daiichi Sankyo; Speakers’ bureau/honoraria from Sanofi-aventis; Consulting: Zoll, The Medicines Company, Terumo, and Bristol Myers Squibb. Dr Mehran received research funding from Bristol-Myers Squibb and Daiichi Sankyo Lilly; speakers’ bureau/honoraria from Sanofi-aventis; Consulting: Zoll, The Medicines Company, Terumo, and across management strategies. In addition, it should be tested in the context of other invasive procedures such as CABG, endovascular procedures, and transcatheter valve procedures. The study by Ndrepepa was partly retrospective in that BARC bleeding was not the primary safety end point of any of the trials included in the analysis; however, the goal of the BARC consensus group was to encourage the prospective use of BARC bleeding as a safety outcome in future clinical trials. To this end, several ongoing clinical trials have adopted BARC as their primary safety end point (ClinicalTrials.gov identifiers NCT01433627 and NCT01406236), which will allow for prospective validation of the definition, and potentially allow for the evaluation of individual data elements so that the definition can be streamlined. Finally, assessment of bleeding not only depends on the definition used, but also on the way in which patients are asked about their signs and symptoms of bleeding. Standardized surveys are used to assess for bleeding complications in patients with hematologic disorders; because antithrombotic therapy for ACS is an iatrogenic disruption of normal hemostatic mechanisms, such standardized questionnaires would add significant value to cardiovascular trials and clinical care. The study by Ndrepepa is the beginning of an important process whose goal is the complete understanding of the risks and benefits of caring for patients with ischemic heart disease, and ultimately finding the appropriate balance in order to further improve outcomes.

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