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EDITORIAL COMMENT

Deconstructing the Language of Bleeding*

Harold L. Dauerman, MD

Burlington, Vermont

In the beginning, there was 1 definition of bleeding complications. The TIMI (Thrombolysis In Myocardial Infarction) definition of bleeding was designed to analyze the safety of 2 different thrombolytic regimens in the context of a landmark ST-segment elevation myocardial infarction (STEMI) reperfusion trial (1). The TIMI definition is simple: major and minor bleeding classes are defined according to hemoglobin decrease or the presence of intracranial bleeding. As studies of acute myocardial infarction progressed, trial-specific definitions for bleeding added nuance in measurement (e.g., transfusion requirements, hemodynamic instability, organ-specific bleeding) and inconsistency in language (e.g., major, minor, moderate, severe, mild, nuisance). Bleeding discussions became a source of endless controversy: 9 different definitions of bleeding were used in 13 trials of antithrombotic therapy, with significant implications for interpretations of drug safety (2).

See page 1866

In 2008, the ABC (Academic Bleeding Consensus) Multidisciplinary Group convened "with the goal of developing a consensus approach to measure the incidence and severity of hemorrhagic complications" (3). This group developed a uniform framework for collecting data but decided against returning to the halcyon days of a single definition of bleeding. The framework strategy is noncontroversial: all trials should collect the same data. This fully deconstructed bleeding approach encouraged trial researchers to customize significant bleeding according to the clinical syndrome being studied: "As an alternative to using a single standard bleeding definition, the consensus group recommended standardized collection and reporting of bleeding-related data elements that describe the timing and site of bleeding, the direct consequences of bleeding (e.g., discontinuation of study medications and transfusions), and outcomes after bleeding (e.g., bleeding leading to death)."

Two years later, BARC (Bleeding Academic Research Consortium) convened; their goal was to "…to develop, disseminate and ultimately adopt standardized bleeding end point definitions for patients receiving antithrombotic therapy" (4). The BARC group gave us a partially deconstructed definition of bleeding: qualitative terms such as major and minor were discarded and replaced with a 5-tiered system (Fig. 1). As stated in a commentary by the U.S. Food and Drug Administration: "The FDA supports the use of standardized endpoint definitions that have been validated and properly reflect clinical outcomes" (5). In this issue of the *Journal*, Kikkert et al. (6), from the University of Amsterdam, provide us with insight into the BARC bleeding definitions as they relate to the clinical outcome of 1-year mortality after percutaneous coronary intervention (PCI) for STEMI.

Toward a unified definition of bleeding. The analysis by Kikkert et al. (6) is the second study to validate the BARC bleeding definition, and it focused on patients undergoing PCI for STEMI. A previous study by Ndrepepa et al. (7) used a validation set consisting of 6 of the ISAR (Intracoronary Stenting and Antithrombotic Regimen) clinical trials focused on patients undergoing lower risk PCI. Both studies validate the risk of PCI-related BARC bleeding on 1-year mortality. These 2 important studies are both disparate and complimentary (Table 1). For example, the study by Ndrepepa et al. (7) addressed BARC bleeding prognosis in a clinical trial population that was largely stable and relatively lower risk; the Kikkert et al. (6) study focuses on a registry group with STEMI only. Thus, it is not surprising that the 2 studies do not agree on even the most basic question: how often does BARC bleeding occur? The 3-fold variation in the incidence of BARC type 2 and 3 bleeding is likely due to differences in patient populations. However, one cannot exclude the possibility that retrospectively assessing the elements of BARC bleeding may be challenging and that variations may be due to errors of retrospection. The retrospective application of BARC bleeding classifications seems to be especially challenging at the extremes: the Kikkert et al. (6) analysis chose to exclude the BARC type 1 bleeding class, recognizing the difficulty of retrospectively assessing "bleeding that is not actionable." The analysis by Ndrepepa et al. (7) chose to exclude BARC type 5 bleeding and reassign each of these bleeds to a lower tier to avoid the circular reasoning of determining the impact of fatal bleeds on 1-year mortality.

There is a more glaring concern: the prognostic value of BARC bleeding classes is not necessarily consistent. The authors of both groups used multivariable Cox proportional hazards models to assess independent correlates of 1-year mortality, including BARC bleeding. The ISAR group found BARC type $\geq$2 or $\geq$3 bleeding events had an independent 2- to 3-fold increased hazard of 1-year death (7). The study by Kikkert et al. (6) used similar multivariable regression analysis

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From the University of Vermont College of Medicine, Burlington, Vermont. Dr. Dauerman is a consultant for Medtronic and The Medicines Company; and has received research grants from Abbott Vascular and Medtronic.

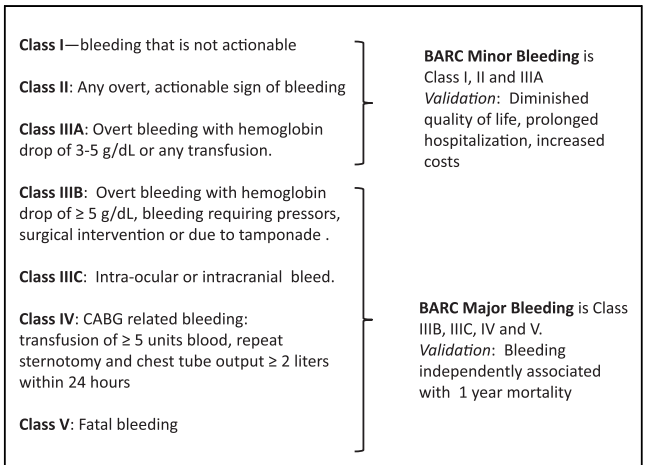

Figure 1 **BARC Bleeding: From Unified Trial Definitions to Unified Clinical Decision Making**

BARC (Bleeding Academic Research Consortium) is a partially deconstructed bleeding definition with up to 7 different classes of bleeding. A simplification into major and minor bleeding groups may provide clinical guidelines as well as specific validation endpoints. CABG = coronary artery bypass graft.

but reached an entirely different conclusion: BARC type 2 and 3a bleeding did not increase the adjusted hazard ratio for 1-year mortality, and only the sum of BARC type 3b + 3c bleeding increased the mortality risk. Comparing these discordant outcomes is difficult because the analyses used BARC bleeding either inclusively (BARC type ≥2) or ordinately (equal to BARC type 2). We are left with 2 potentially disturbing conclusions: BARC bleeding reflects clinical outcomes only in selected patient populations or variations in statistical analyses make comparisons across studies once again challenging. Either way, the unified demonstration of BARC clinical relevance is unclear based on the 1-year mortality analyses of these 2 groups.

The TIMI definition of bleeding is far from perfect. Thus, it is worthwhile that the investigators compare the relative value of multiple bleeding scales in predicting 1-year mortality. In the analysis by Ndrepepa et al. (7), 3 bleeding scales provide independent predictive value with respect to 1-year mortality: REPLACE (Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events) 2 major bleeding, 3.1-fold increased risk; TIMI major + minor bleeding, 3.6-fold increased risk; and BARC type ≥2 bleeding, 2.7-fold increased risk. The analysis by Kikkert et al. (6) uses TIMI, ISTH (International Society on Thrombosis and Haemostasis), and GUSTO (Global Use of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) as comparators to BARC. Patients having a TIMI major bleed have a 2-fold increased hazard of 1-year death; patients having a BARC type 3b + 3c bleed have a 1.84-fold increased hazard of 1-year death. Once again, we are left with an unclear comparison between the 2 studies, but what is clear is the apparent lack of superiority of the new bleeding scale. Thus, BARC can neither provide uniform predictive value nor demonstrate clear superiority compared with previous definitions.

Bleeding for clinicians. In light of these grey areas in applying the BARC bleeding definitions, the original purpose of the BARC and ABC consensus groups should be reconsidered. All bleeding scales have been created for federal agencies, industry, academia, and clinical trials. However, times have changed: the connection between bleeding events and morbidity/mortality is no longer emphasized only in labeling decisions by the U.S. Food and Drug Administration. According to the 2011 American College of Cardiology/American Heart Association Guidelines for PCI, bleeding assessment is part of our routine clinical practice: All patients should be evaluated for risk of bleeding before PCI (Class I, Level of Evidence: C) (8). To allow cardiologists to meet the guideline recommendation, we need a unified definition for bleeding that is clinically meaningful and easy to use.

The BARC consensus group is to be congratulated for bringing forth a new classification of bleeding that could provide uniformity for clinical trials. This classification is potentially superior to any other definition of bleeding: it includes clinically and laboratory-measured bleeding, has organ-specific nuance, and includes post-bypass surgery bleeding parameters. BARC importantly highlights the need to collect data on softer bleeding endpoints (BARC

Table 1 **Validation of the BARC Bleeding Definitions According to 1-Year Mortality**

	ISAR: Ndrepepa et al. (7) (N = 12,459)	Amsterdam: Kikkert et al. (6) (N = 2,002)	Summary (N = 14,461)
Timing of bleeding episode	Index hospitalization for PCI	Index hospitalization for PCI	Uniform time interval analysis
Patient population	6 Pooled clinical trials	Single-center registry	Different patient populations
Clinical spectrum	PCI for angina, UA, and NSTEMI	PCI for STEMI, including cardiogenic shock	Different clinical spectrums
Incidence of BARC type 2	1.4%	4.4%	More than 3-fold variation in incidence
Incidence of BARC type 3	3.9%	14.2%	More than 3-fold variation in incidence
Incidence of BARC type 3c	0.08%	0.04%	Cranial/ocular bleeds are very rare
BARC type 2: risk of 1-year death	HR = 2.72*	HR = 0.96†	Potentially discordant
BARC type 3: risk of 1-year death	HR = 3.19*	Type 3a: HR = 0.97† Type 3b + 3c: HR = 1.84†	Potentially discordant

*Adjusted hazard ratio (HR) using Cox model for BARC (Bleeding Academic Research Consortium) type ≥2 or ≥3 bleeding. †Adjusted HR using Cox model for BARC type 2 and BARC type 3 bleeding. ISAR = Intracoronary Stenting and Antithrombotic Regimen; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; UA = unstable angina.

type 1): such previously understudied bleeding events may not predict mortality but will affect the patient's quality of life (9,10). In deconstructing the language of bleeding to its element parts or to a hierarchical tier, something has been gained: uniformity. However, something vital has also been lost: words like major, minor, moderate, and severe are confusing in their inconsistency but critical in their connection to actual decision making. The 5 tiers and 3 subclasses of BARC bleeding are a memory challenge that most of us will fail. Can a practicing cardiologist be expected to choose a treatment strategy weighing the risk of stent thrombosis against a hazard of BARC type 3b + 3c bleeding? Conversely, weighing a 50% decrease in stent thrombosis compared with a doubling of minor bleeding is a clinical language that resonates.

Validation and memory. The difficulty in finding clear proof of BARC's superiority provides a chance to revisit the definition to find a simpler scale that brings back descriptive terms that provide relative meaning (Fig. 1). From 7 different classes of bleeding, we need to find intrinsic meaning and less memorization by rediscovering words like major and minor. Second, we need to remove fatal bleeding as a class; fatal bleeding clearly fits the clinical meaning of the term "major." Third, we need to address a concern of the regulatory agencies: what is the reason to classify coronary artery bypass graft–related bleeding as prognostically different from PCI-related bleeds (5)? One definition could apply to all pharmacological studies, clinical syndromes, and invasive cardiac procedures. Fourth, we need to embrace the softer definitions created by BARC (9): there are now 2 groups that have validated the BARC bleeding scale with respect to a single endpoint (1-year mortality) (6,7). However, nonfatal bleeding complications are of significant interest to clinicians and patients; prolonged hospitalization, increased hospital costs, and diminished quality of life matter (11). Thus, we should set goals for a clinical bleeding scale accordingly. For minor bleeding, the scale must predict events that are nonfatal; for major bleeding events, the scale must predict 1-year mortality.

As we reconstruct the language of bleeding, we need to meet the needs of those having the conversation; that group is no longer simply trialists and federal agencies. The bleeding conversation now includes all of us who are taking care of cardiology patients. A unified, translatable bleeding scale that validates minor and major concerns across the spectrum of both bleeding events and cardiovascular clinical trials is worthy of further effort: after the ABC, BARC, ISAR, and Amsterdam analyses, we are getting closer.

Reprint requests and correspondence to: Dr. Harold L. Dauerman, Division of Cardiology, McClure 1, Fletcher Allen Health Care, University of Vermont, 111 Colchester Avenue, Burlington, Vermont 05401. E-mail: harold.dauerman@vtmednet.org.

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