Special Report

Standardized Bleeding Definitions for Cardiovascular Clinical Trials

A Consensus Report From the Bleeding Academic Research Consortium

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Advances in antithrombotic therapy, along with an early invasive strategy, have reduced the incidence of recurrent ischemic events and death in patients with acute coronary syndromes (ACS; unstable angina, non–ST-segment–elevation myocardial infarction [MI], and ST-segment–elevation MI).[1–4] However, the combination of multiple pharmacotherapies, including aspirin, platelet $P2Y_{12}$ inhibitors, heparin plus glycoprotein IIb/IIIa inhibitors, direct thrombin inhibitors, and the increasing use of invasive procedures, has also been associated with an increased risk of bleeding.

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Bleeding complications have been associated with an increased risk of subsequent adverse outcomes, including MI, stroke, stent thrombosis, and death, in patients with ACS and in those undergoing percutaneous coronary intervention (PCI),[5–10] as well as in the long-term antithrombotic setting.[11,12] Thus, balancing the anti-ischemic benefits against the bleeding risk of antithrombotic agents and interventions is of paramount importance in assessing new therapies and in managing patients. Prior randomized trials comparing antithrombotic agents suggest that a reduction in bleeding events is associated with improved survival.[13,14]

Because prevention of major bleeding may represent an important step in improving outcomes by balancing safety and efficacy in the contemporary treatment of ACS, bleeding events have been systematically identified as a crucial end point for the assessment of the safety of drugs during the course of randomized clinical trials, and are an important aspect of the evaluation of new devices and interventional therapies.[15] Unlike ischemic clinical events (eg, cardiac death, MI, stent thrombosis), for which there is now general consensus on end-point definitions,[16,17] there is substantial heterogeneity among the many bleeding definitions currently in use. Lack of standardization makes it difficult to optimally organize key clinical trial processes such as adjudication, and even more difficult to interpret relative safety comparisons of different antithrombotic agents across studies, or even within a given trial, because results may vary according to the definition(s) used for bleeding. Finally, as reflected by the various terms used to describe bleeding (serious, severe, catastrophic, major, life-threatening, etc), the heterogeneity of definitions may undermine the ability of clinical trials to meaningfully define the balance of safety and efficacy in vascular interventions.

In response to the need to develop, disseminate, and ultimately adopt standardized bleeding end-point definitions for patients receiving antithrombotic therapy, the Bleeding Academic Research Consortium (BARC) convened in February 2010 at the US Food and Drug Administration (FDA) headquarters in White Oak, MD. Modeled after the 2006 Academic Research Consortium, which standardized key ischemic end-point definitions in studies aimed at evaluating coronary stents,[17] the BARC effort brought together representatives from academic research organizations, the FDA, the National Institutes of Health, and pharmaceutical and cardiovascular device manufacturers and independent physician thought leaders in the field of cardiovascular disease to develop consensus bleeding definitions that would be useful

The BARC represents a collaboration of independent academic research organizations (Cardialysis, Rotterdam, the Netherlands; Cardiovascular Research Foundation, New York City, NY; Duke Clinical Research Institute, Durham, NC; TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA; Harvard Clinical Research Institute, Boston, MA; Green Lane Coordinating Centre, Auckland, New Zealand; Cleveland Clinic Coordinating Center for Clinical Research, Cleveland, OH; and PERFUSE, Boston, MA), professional societies (European Society of Cardiology, and Society of Cardiac Angiography and Intervention), federal agencies (the US FDA, National Institutes of Health), and independent expert scientists and consultants (Appendix).

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Table 1. Impact of Major Bleeding on Mortality in Registries and Randomized Trials of Patients With Acute Coronary Syndromes or Undergoing Percutaneous Coronary Interventions

					Outcomes in Patients With Major or Severe Bleeding vs No Bleeding			
					Early Deaths (In Hospital or at 30 d)		Deaths up to 1 y	
Study	Setting, Design	Primary Definition*	Patients	Patients With Bleeding, n (%)	Death Rates, %	Adjusted Risk Ratio for Death (95% CI)	Death Rates, %	Adjusted Risk Ratio for Death (95% CI)
Kinnaird et al,[7] 2003	PCI, registry	TIMI	10 974	588 (5.4)	7.5 vs 0.6	3.5 (1.9–6.7)	17.2 vs 5.5	Not significant†
GRACE,[10] 2003	ACS, registry	GRACE	24 045	933 (3.9)	18.6 vs 5.1	1.6 (1.2–2.3)	. . .	. . .
GRACE,[21] 2007	ACS, registry	GRACE	40 087	1140 (2.8)	20.9 vs 5.6	1.9 (1.6–2.2)	7.9 vs 5.2	0.8 (0.6–1.0)
REPLACE-2,[25] 2007	PCI, RCT	REPLACE-2/ ISAR-REACT 3	6001	195 (3.2)	5.1 vs 0.2	. . .	8.7 vs 1.9	2.7 (1.4–4.9)
Rao et al,[6] 2005	NSTE-ACS, meta-analysis of RCTs	GUSTO	26 452	107 (0.4)	25.7 vs 2.9	10.6 (8.3–13.6)	35.1 vs 4.2	7.5 (6.1–9.3)
Eikelboom et al,[5] 2006	NSTE-ACS, meta-analysis of RCTs/registry	CURE	34 146	783 (2.3)	12.8 vs 2.5	9.8 (7.5–12.7)	4.6 vs 2.9‡	1.9 (1.3–2.8)
ACUITY,[9] 2007	NSTE-ACS, RCT	ACUITY	13 819	644 (4.7)	7.3 vs 1.2	7.6 (4.7–12.2)	. . .	3.5 (2.7–4.4)
Ndrepepa et al,[15] 2008	PCI, meta-analysis of RCTs	TIMI	5384	215 (4.0; n=59 major/n=156 minor)	. . .	. . .	12.2 vs 3.3	4.1 (2.1–8.3)
EVENT,[26] 2009	PCI, registry	TIMI	5961	(3.0 overall: 0.7 major, 2.3 minor)	. . .	. . .	15.6 vs 2.4	3.8 (2.5–5.9)
OASIS-5,[27] 2009	NSTE-ACS, RCT	ESSENCE	20 078	990 (4.9): major, 423 (2.1) minor	8.4 vs 2.7	3.5 (2.6–4.6)	14.3 vs 5.4	3.1 (2.6–3.8)
Amlani et al,[28] 2010	STEMI, registry	Protocol defined	1389	152 (10.9)	19.7 vs 8.2	2.8 (1.8–4.3)	. . .	. . .
ISAR-REACT 3,[29] 2010	PCI, RCT	REPLACE-2/ ISAR-REACT 3	4570	555 (12.1) 174 major/381 minor	. . .	. . .	5.2 vs 1.3	4.1 (2.6–6.5)

CI indicates confidence interval; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction; ACS, acute coronary syndrome; GRACE, Global Registry of Acute Coronary Events; RCT, randomized controlled trial; REPLACE-2, Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events; ISAR-REACT 3, Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment; NSTE, non–ST-elevation; GUSTO, Global Use of Strategies to Open Occluded Arteries; CURE, Clopidogrel in Unstable Angina to Prevent Recurrent Events; ACUITY, Acute Catheterization and Urgent Intervention Triage Strategy; EVENT, Evaluation of Drug Eluting Stents and Ischemic Events; and OASIS-5, Organization for the Assessment of Strategies for Ischemic Syndromes.

*For Definitions, please see Table 2.

†Data not provided.

‡Events between 30 days and 6 months.

for cardiovascular clinical trials. Application of these definitions is recommended for both clinical trials and registries.

Importance of Bleeding as an End Point

Hemorrhagic complications occur with a frequency of 1% to 10% during treatment for ACS and after PCI.[18–20] This wide variability in the measured incidence is due to several factors, including differences in patient characteristics, concomitant therapies, timing of event reporting, and definitions across data sets. Regardless of the definition used, several studies have demonstrated that bleeding is associated with an increased risk for short- and long-term adverse outcomes, including death,[18,20] nonfatal MI,[6] stroke,[5] and stent thrombosis.[9] The exact mechanisms underlying this relationship are not known, but may include the cessation of evidence-based therapies, including antiplatelet agents, β-blockers, and/or statin therapies, in patients who suffer bleeding complications,[21,22] the direct effects of blood transfusion used to treat bleeding,[20,23] or greater prevalence of comorbidities in patients who bleed,[21] as well as a deleterious role of anemia.[24]

The relationship between bleeding and morbidity and mortality is underscored by studies demonstrating that bleeding reduction strategies are associated with improved survival in patients with ACS and those undergoing PCI. The data summarized in Table 1 emphasize the importance of bleeding as a common, clinically relevant safety event. To optimize both the end point and its role in clinical trial designs, a consistent approach to collecting bleeding data and adjudicating events is critical.[30] Toward this end, a thoughtful, broadly based consensus definition of what constitutes a bleeding event, similar to what has been done with MI and stent thrombosis, is the objective of BARC efforts.[17]

Bleeding Academic Research Consortium Composition and Goals

An informal collaboration among academic research organizations from the United States and Europe, joined by representatives from the FDA and device manufacturers, led to a consensus document to standardize clinical end points for coronary stent trials.[17] This Academic Research Consortium developed a rapid, scholarly, and clinically relevant process resulting in a portfolio of clinical end-point definitions that

were endorsed by the FDA and broadly incorporated into clinical trial end points.[31,32] The Academic Research Consortium process was a demonstration of effective collaboration among the academic community, FDA, and industry to respond to safety concerns over drug-eluting stents and to improve the conduct of clinical research. This initiative has since been expanded to other clinical domains, including percutaneous valves and peripheral arterial disease, and the effort to establish standardized bleeding definitions presented in this consensus document. These standardized definitions are intended to allow the clinical community to determine the relative safety of different antithrombotic strategies, to provide the industry with a framework in which to evaluate the safety of emerging antithrombotic therapies, and potentially to enhance the regulatory review of new anticoagulant and antiplatelet drugs.

Heterogeneity of Bleeding Definitions Across Trials

Several definitions of bleeding have been used in published clinical trials and registries.[33–35] Table 2 highlights the lack of uniformity in bleeding definitions among recent ACS and PCI clinical trials. Current bleeding definitions consist of both laboratory parameters, such as decreases in hemoglobin and hematocrit scores, and clinical events, including the need for transfusion or surgery, cardiac tamponade, hematomas, and various degrees of bleeding. Each definition incorporates a different combination of these data elements and then rank orders these combinations into severity categories, which vary widely between definitions.

The Thrombolysis in Myocardial Infarction (TIMI) bleeding criteria have been in use for nearly 30 years, and have been reported in most cardiovascular trials. These criteria were developed during the early TIMI trials to define and classify major and minor hemorrhagic events in patients with ST-segment–elevation MI treated with a fibrinolytic drug. The original TIMI definition relies predominantly on laboratory data elements based on decreases in hemoglobin or hematocrit values after adjustment for the effect of blood transfusion.[36] Over time, the definitions have evolved to represent a broader range of bleeding categories and events while specifically defining each individual category.[37–42] The current updated TIMI definition is shown in Table 2.[42,43] Potential limitations of the criteria include that they were developed in the fibrinolytic era, and thus typically characterized severe acute events and difficulties with perception of the nomenclature (eg, many would consider TIMI minor bleeding to hold greater clinical significance than that connoted by the term minor). Common pitfalls that may occur when the TIMI definition is applied are recording hemoglobin drops without clinically overt signs as major bleeding events, as well as uncertainty on the timing of assessing hemoglobin values that may lead to inappropriate peaks and nadirs related to bleeding, therefore obscuring the timing of the bleeding in relation to the intervention. The TIMI criteria also characterize 3 different types of death in relation to bleeding: fatal bleeding, when a bleeding event directly leads to death within 7 days (eg, an intracranial hemorrhage that leads to herniation of the brain and death, hemopericardium that results in death, and a massive gastrointestinal hemorrhage that results in shock, hemodynamic collapse, and death); bleeding contributing to death (ie, a death in which a bleeding event was part of a causal chain of medical events that ultimately led to death within 30 days of the bleed, but bleeding did not directly and/or immediately relate to subject's death; an example is a bleed resulting in discontinuation of antiplatelet therapy followed by stent thrombosis and death); and death unrelated to a bleeding event (the death was unrelated to bleeding because either there was no clinically significant bleeding in the month before death or the bleeding event did not contribute to the subject's death).

The Global Use of Strategies to Open Occluded Arteries (GUSTO) definition of bleeding has also been implemented in a number of trials over the past 2 decades.[44] GUSTO bleeding criteria were initially used to identify significant bleeding in the setting of fibrinolytic therapy for ST-segment–elevation MI. Its various components combine to define bleeding on a graded scale of severity based on clinical acuity and impact. Notably, the GUSTO definition differs from several other definitions in that it does not require changes in hemoglobin, nor does it quantify the amount of blood transfused. Because the GUSTO bleeding criterion is clinically driven, the gradations of bleeding severity track well with risk of death/MI.[45] However, the GUSTO definition also has limitations. In addition to the fact that it was conceived during the fibrinolytic era, adjudication by a clinical events committee is often challenging, given lack of objective standardized criterion. Consequently, outcomes may not be consistent across geographic regions because thresholds for intervention and transfusion vary, depending on local patterns of clinical practice, imaging use, blood banking, etc. Thus, applying this definition requires unique attention to thorough adjudication processes to ensure that outcomes are consistently captured and to statistical analyses to ensure against regional outlier effects.

More recently, bleeding definitions in ACS and PCI trials have combined both laboratory and clinical parameters in an attempt to leverage the strengths and overcome the limitations of the TIMI and GUSTO definitions. Several trials have incorporated a combination of elements from both the TIMI and GUSTO definition,[46,47] have modified these elements,[13,49–53] or have added new parameters.[48,52–54] The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE), Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY), Organization for the Assessment of Strategies for Ischemic Syndromes (OASIS), Safety and Efficacy of Enoxaparin in PCI Patients, an International Randomized Evaluation (STEEPLE), and Platelet Inhibition and Patient Outcomes (PLATO) trials, among others, have used different definitions for major/severe and minor bleeding (Table 2). The ACUITY[48] and Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI)[52] bleeding definitions are identical and were developed by adapting the components of TIMI major and GUSTO severe/moderate bleeding that are relevant to patients undergoing PCI.

Table 2. Heterogeneity in Bleeding Definitions Used in Acute Coronary Syndrome Trials

Trial	Bleeding Definition
TIMI[6,37,38]	Non-CABG related bleeding
	Major
	Any intracranial bleeding (excluding microhemorrhages <10 mm evident only on gradient-echo MRI)
	Clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dL
	Fatal bleeding (bleeding that directly results in death within 7 d)
	Minor
	Clinically overt (including imaging), resulting in hemoglobin drop of 3 to <5 g/dL
	Requiring medical attention
	Any overt sign of hemorrhage that meets one of the following criteria and does not meet criteria for a major or minor bleeding event, as defined above
	Requiring intervention (medical practitioner-guided medical or surgical treatment to stop or treat bleeding, including temporarily or permanently discontinuing or changing the dose of a medication or study drug)
	Leading to or prolonging hospitalization
	Prompting evaluation (leading to an unscheduled visit to a healthcare professional and diagnostic testing, either laboratory or imaging)
	Minimal
	Any overt bleeding event that does not meet the criteria above
	Bleeding in the setting of CABG
	Fatal bleeding (bleeding that directly results in death)
	Perioperative intracranial bleeding
	Reoperation after closure of the sternotomy incision for the purpose of controlling bleeding
	Transfusion of ≥5 U PRBCs or whole blood within a 48-h period; cell saver transfusion will not be counted in calculations of blood products.
	Chest tube output >2 L within a 24-h period
GUSTO[24]	Severe or life-threatening
	Intracerebral hemorrhage
	Resulting in substantial hemodynamic compromise requiring treatment
	Moderate
	Requiring blood transfusion but not resulting in hemodynamic compromise
	Mild
	Bleeding that does not meet above criteria
CURE[5]	Major bleeding
	Life-threatening (fatal, intracranial, requiring surgical intervention, results in substantial hypotension requiring the use of intravenous inotropic agents)
	Hemoglobin decrease ≥5 g/dL or required ≥4 U of blood
	Other major bleeding
	Transfusion of 2–3 U, intraocular
	Minor
	Led to discontinuation of study drug
ACUITY,[28] HORIZONS[32]	Major
	Intracranial or intraocular hemorrhage
	Access-site hemorrhage requiring intervention
	≥5-cm hematoma
	Retroperitoneal
	Reduction in hemoglobin concentration of ≥4 g/dL without an overt source of bleeding
	Reduction in hemoglobin concentration of ≥3 g/dL with an overt source of bleeding
	Reoperation for bleeding
	Use of any blood product transfusion
CURRENT-OASIS 7[33]	Severe
	Requiring transfusion ≥4 U of PRBCs or equivalent whole blood
	Resulting in hemoglobin drop ≥5 g/dL
	Leading to hypotension that requires inotropes
	Requiring surgery
	Symptomatic intracranial hemorrhage
	Fatal

(*Continued*)

Table 2. Continued

Trial	Bleeding Definition
	Other major
	Requiring transfusion of 2 to 3 U
	Significantly disabling, intraocular bleeding leading to significant loss of vision
	Minor
	Other bleeding that leads to modification of drug regimen
	Other
	Bleeding not meeting criteria for major or minor
STEEPLE[31]	Major bleeding
	Fatal bleeding
	Retroperitoneal, intracranial, or intraocular bleeding
	Bleeding that causes hemodynamic compromise requiring specific treatment
	Bleeding that requires intervention (surgical or endoscopic) or decompression of a closed space to stop or control the event
	Clinically overt bleeding, requiring any transfusion of ≥1 U PRBC or whole blood
	Clinically overt bleeding, causing a decrease in hemoglobin of ≥3 g/dL (or, if hemoglobin level is not available, a decrease in hematocrit of ≥10%)
	Minor
	Gross hematuria not associated with trauma (eg, from instrumentation)
	Epistaxis that is prolonged, is repeated, or requires plugging or intervention
	Gastrointestinal hemorrhage
	Hemoptysis
	Subconjunctival hemorrhage
	Hematoma >5 cm or leading to prolonged or new hospitalization
	Clinically overt bleeding, causing a decrease in hemoglobin of 2 to 3 g/dL
	Uncontrolled bleeding requiring protamine sulfate administration
PLATO[34]	Major life-threatening
	Fatal
	Intracranial
	Intrapericardial with cardiac tamponade
	Resulting in hypovolemic shock or severe hypotension that requires pressors or surgery
	Clinically overt or apparent bleeding associated with decrease in hemoglobin >5 g/dL
	Requiring transfusion of ≥4 U whole blood or PRBCs
	Other major
	Significantly disabling (eg, intraocular with permanent vision loss)
	Associated drop in hemoglobin of 3 to 5 g/dL
	Requiring transfusion of 2 to 3 U whole blood or PRBCs
	Any major
	Any one of the above criteria
	Minor
	Requiring medical intervention to stop or treat bleeding (eg, epistaxis requiring visit to medical facility for packing)
	Minimal
	All others (eg, bruising, bleeding gums, oozing from injection sites) not requiring intervention or treatment
GRACE[10,21]	Major
	Requiring a transfusion of ≥2 U PRBCs
	Resulting in a decrease in hematocrit of ≥10%
	Occurring intracerebrally
	Resulting in stroke or death
REPLACE-2/ ISAR-REACT 3[25]	Major
	Intracranial, intraocular, or retroperitoneal
	Overt blood loss with hemoglobin decrease >3 g/dl
	Any hemoglobin decrease >4 g/dL
	Transfusion of ≥2 U blood products

(*Continued*)

Table 2. Continued

Trial	Bleeding Definition
	Minor
	Overt bleeding not meeting criteria for major bleeding
ESSENCE[27]	Major
	Clinically overt bleeding that was fatal (bleeding reported to cause death)
	Symptomatic intracranial hemorrhage
	Retroperitoneal hemorrhage
	Intraocular hemorrhage leading to significant vision loss
	Decrease in hemoglobin of at least 3.0 g/dL (with each blood transfusion unit counting for 1.0 g/dL hemoglobin)
	Bleeding requiring transfusion of ≥2 U RBCs or equivalent of whole blood
	Minor
	All other clinically significant bleeding not meeting the definition for major bleeding and that led to interruption of the study drug for at least 24 h, surgical intervention, or transfusion of ≤1 U blood
Amlani et al[28]	Major
	Hemoglobin drop ≥5 g/dL
	Intracranial hemorrhage
	Bleeding requiring surgery
	Blood transfusion of at least 2 U

TIMI indicates Thrombolysis in Myocardial Infarction; CABG, coronary artery bypass graft; MRI, magnetic resonance imaging; PRBC, packed red blood cell; GUSTO, Global Use of Strategies to Open Occluded Arteries; CURE, Clopidogrel in Unstable Angina to Prevent Recurrent Events; ACUITY, Acute Catheterization and Urgent Intervention Triage Strategy; HORIZONS, Harmonizing Outcomes With Revascularization and Stents; CURRENT-OASIS 7, Clopidogrel optimal loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Interventions; STEEPLE, Safety and Efficacy of Enoxaparin in PCI Patients, an International Randomized Evaluation; PLATO, Platelet Inhibition and Patient Outcomes; GRACE, Global Registry of Acute Coronary Events; REPLACE-2, Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events; ISAR-REACT, Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment; and ESSENCE, Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events.

Challenges to Creating a Universal Bleeding Definition

There are several challenges in creating a universal bleeding definition.[55] It is crucial to first consider the purpose. A comprehensive bleeding classification is required that captures information about the cause (procedural or nonprocedural), site (intraocular, intracranial, visceral, peritoneal, access site, etc), and severity (quantified by impact on laboratory data and clinical status) of bleeding. Such a classification should correlate closely with prognosis and should be able to direct specific diagnostic and treatment protocols. Moreover, the different bleeding categories and the classification system should be carefully considered, whether descriptive such as major or life-threatening or objective using numeric or alphanumeric score. Ideally, a standardized definition should be able to address all these issues. In addition, the definition should be practical and easy to use; ie, it should be based on data that can be readily collected by sites, monitored, and adjudicated.

A key challenge is to maintain an appropriate balance between sensitivity and specificity of criteria to optimize the ability to detect dose response or to discern small variations between therapies while arriving at clinically meaningful conclusions. As noted in the coronary effort,[17] it is generally recognized that no universal definition can be crafted that is perfectly accurate (sensitive and specific) or that is perfect for all applications. The value of a consensus definition that is used consistently across clinical trials is not dependent on perfection.

Nomenclature presents another challenge. Depending on context, the meanings of terms change; if a nuisance bleed encourages a patient to stop taking beneficial medications, it can still have major importance in other senses. Moreover, the site of bleeding affects its relationship with mortality. For example, non–access-site bleeds may have a more significant impact on the likelihood of death/MI than access-site bleeding.[55a] The duration of follow-up also matters, and there may be unmeasured factors. The definitions also change over time. It is not yet known which components of a bleeding definition are predictors of mortality; large groin hematomas, for example, appear less detrimental than TIMI major bleeding or ACUITY major bleeding with or without transfusion.[56] Furthermore, adjudication of bleeding events is a process that does not solely revolve around a definition. Bleeding rates depend on several factors, including how aggressively investigators seek to ascertain information, how definitions are written, and how the definitions are applied. These aspects can complicate the interpretation of safety results from clinical trials, a fact underscored by the complexity of current treatment guidelines.[1,2,57] Short of a comprehensive analysis of very large databases of prospectively acquired detailed bleeding data linking various definitions to subsequent clinical outcomes, which is still lacking, the optimal universal bleeding definition can be arrived at only through expert consensus because the expert consensus process allows weighing and balancing multiple options.

Special Considerations for Coronary Artery Bypass Graft–Related Bleeding Definition

Bleeding after cardiac surgery is a serious complication, and excessive blood loss frequently results in transfusion of allogeneic blood, blood products, or surgical re-exploration.

Most studies have traditionally not considered coronary artery bypass graft (CABG)–related bleeding, but because up to 12% of ACS patients may undergo CABG[58] during the index hospitalization, the BARC group felt that it was important to include CABG-related bleeding in the BARC consensus document. Because CABG surgery is one of the rare instances of surgery performed under full anticoagulation and because transfusion is inherent to cardiopulmonary bypass, it is difficult to define a threshold for bleeding in CABG that would separate the amount of bleeding expected during routine surgery from the unusual or unexpected. It is even more difficult to determine the thresholds for CABG bleeding that are related to a change in prognosis. Mean postoperative chest tube output during the first 24 hours after standard CABG is estimated to be 400±200 mL and up to 1200 mL in patients treated with dual antiplatelet therapy including clopidogrel.[59–62] Bleeding is similar with off-pump CABG and on-pump CABG.[63] Five percent to 7% of patients lose >2 L of blood within the first 24 hours after surgery,[64] and up to 5% require reintervention for bleeding after sternotomy closure.[65]

Both surgical re-exploration and red blood cell transfusion are associated in a dose-dependent and often durable manner with prolonged intensive care and hospital stays and reduced survival rates.[66,67] There are international differences in the threshold for transfusions and probably also for rates of reoperation for bleeding associated with the use of scorecards.[68]

In a pooled analysis of the ACUITY and HORIZONS-AMI trials, CABG-related major ACUITY-graded bleeding in a time-adjusted baseline covariate-adjusted Cox model of 1600 patients did not independently predict subsequent 12-month mortality (hazard ratio, 1.21; 95% confidence interval, 0.81 to 1.80; $P=0.34$).[69]

Rather than developing a specific set of data elements distinct from other types of BARC bleeding (Table 3), BARC was guided with the following principles in developing the definition for BARC type 4 (CABG-related) bleeding. First, BARC CABG-related bleeding definitions must include the same criteria for fatal bleeding, intracranial hemorrhage, need for intervention to control bleeding, and number of transfusions as BARC non–CABG-related bleeding. Second, specific criteria for the amount of chest tube drainage need to be included. Third, if bleeding does not meet the severity criteria for at least a BARC type 3 event, it will not be counted as an event. Fourth, specific time intervals will need to apply for CABG-related events: up to 48 hours for transfusions and intracranial bleeding and within a 24 hour period for excessive chest tube drainage. It is appropriate that there will be no time window for the occurrence of fatal bleeding. It is important to note that the temporal relationship of the bleeding event to the CABG surgery is the primary factor that differentiates type 4 bleeding from type 3 bleeding. Therefore, if a bleeding event occurs during the specified time frame in relation to a CABG procedure but does not meet type 4 severity markers, it will not be adjudicated as a bleeding event. It is also noteworthy to include that only allogenic transfusions are considered transfusions for CABG-related bleeds.

Table 3. Bleeding Academic Research Consortium Definition for Bleeding

Type 0: no bleeding
Type 1: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional
Type 2: any overt, actionable sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation
Type 3
Type 3a
Overt bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided hemoglobin drop is related to bleed)
Any transfusion with overt bleeding
Type 3b
Overt bleeding plus hemoglobin drop ≥5 g/dL* (provided hemoglobin drop is related to bleed)
Cardiac tamponade
Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
Bleeding requiring intravenous vasoactive agents
Type 3c
Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)
Subcategories confirmed by autopsy or imaging or lumbar puncture
Intraocular bleed compromising vision
Type 4: CABG-related bleeding
Perioperative intracranial bleeding within 48 h
Reoperation after closure of sternotomy for the purpose of controlling bleeding
Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period†
Chest tube output ≥2L within a 24-h period
Type 5: fatal bleeding
Type 5a
Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
Type 5b
Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

CABG indicates coronary artery bypass graft. Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes. If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (ie, within a 48-h time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.

*Corrected for transfusion (1 U packed red blood cells or 1 U whole blood=1 g/dL hemoglobin).

†Cell saver products are not counted.

Because CABG-related bleeding is so common, it may overwhelm the incidence of non-CABG bleeding, especially in drug trials. Thus, comparing the effects of treatments on total bleeding rates may not be significantly different between the treatments, even though non-CABG bleeding rates may be significantly different.[70] It is important to report total, CABG-related, and non–CABG-related bleeding separately. In addition, BARC acknowledges that there is a need to know when to stop drugs with a propensity to cause bleeding with CABG (and with other types of surgery). Further research is required to better define the risk associated with CABG bleeding and the effect of components of the definition, particularly transfusions of (different) blood products on subsequent mortality.

In developing a universal bleeding definition, BARC was driven by the following criteria: (1) The definitions should apply in a broad clinical context, and hence will be applicable to cardiovascular clinical trials and/or registries in which bleeding is used as an end point; (2) although CABG-related bleeding may potentially relate to either technical issues or drug effects, BARC acknowledges a need to report CABG-related, non–CABG-related, and total bleeding rates separately and the effects of treatment; and (3) bleeding should be reported in a hierarchical manner characterizing severity with a graded numeric system nomenclature, not with subjective or descriptive terms such as minor or nuisance. Importantly, after a consensus report is proposed, it should result in an end-point definition that will be embraced by the clinical research community, by pharmaceutical and device manufacturers, by regulatory agencies, and ultimately in clinical practice. Finally, the definition should be validated against data sets from several trials.

Proposed Bleeding Definition

- Type 0: no evidence of bleeding.
- Type 1: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional. Examples include, but are not limited to, bruising, hematoma, nosebleeds, or hemorrhoidal bleeding for which the patient does not seek medical attention. Type 1 bleeding may include episodes that lead to discontinuation of medications by the patient because of bleeding without visiting a healthcare provider.
- Type 2: any clinically overt sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that is actionable but does not meet criteria for type 3, type 4 (CABG-related), or type 5 (fatal bleeding) BARC bleeding. The bleeding must require diagnostic studies, hospitalization, or treatment by a healthcare professional. In particular, the bleeding must meet at least one of the following criteria: First, it requires intervention, defined as a healthcare professional–guided medical treatment or percutaneous intervention to stop or treat bleeding, including temporarily or permanently discontinuing a medication or study drug. Examples include, but are not limited to, coiling, compression, use of reversal agents (eg, vitamin K, protamine), local injections to reduce oozing, or a temporary/permanent cessation of antiplatelet, antithrombin, or fibrinolytic therapy. Second, the bleeding leads to hospitalization or an increased level of care, defined as leading to or prolonging hospitalization or transfer to a hospital unit capable of providing a higher level of care. Or third, the bleeding prompts evaluation, defined as leading to an unscheduled visit to a healthcare professional resulting in diagnostic testing (laboratory or imaging). Examples include, but are not limited to, hematocrit testing, hemoccult testing, endoscopy, colonoscopy, computed tomography scanning, or urinalysis. A visit or phone call to a healthcare professional during which neither testing nor treatment is undertaken does not constitute type 2 bleeding.
- Type 3: clinical, laboratory, and/or imaging evidence of bleeding with specific healthcare provider responses, as listed below:
  - Bleeding Academic Research Consortium type 3a bleeding
    - Any transfusion with overt bleeding
    - Overt bleeding plus hemoglobin drop ≥3 to <5 g/dL (provided hemoglobin drop is related to bleeding). Hemoglobin drop should be corrected for intracurrent transfusion in which 1 U packed red blood cells or 1 U whole blood would be expected to increase hemoglobin by 1 g/dL.
  - Bleeding Academic Research Consortium type 3b bleeding
    - Overt bleeding plus hemoglobin drop ≥5 g/dL (provided hemoglobin drop is related to bleed). Hemoglobin drop should be corrected for intracurrent transfusion in which 1 U packed red blood cells or 1 U whole blood would be expected to increase hemoglobin by 1 g/dL.
    - Cardiac tamponade
    - Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
    - Bleeding requiring intravenous vasoactive drugs
  - Bleeding Academic Research Consortium type 3c bleeding
    - Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation; does include intraspinal); subcategories confirmed by autopsy, imaging, or lumbar puncture
    - Intraocular bleed compromising vision
  - Type 4: Coronary Artery Bypass Graft–related bleeding
    - Perioperative intracranial bleeding within 48 hours
    - Reoperation after closure of sternotomy for the purpose of controlling bleeding
    - Transfusion of ≥5 U whole blood or packed red blood cells within a 48-hour period (only allogenic transfusions are considered transfusions for CABG-related bleeds)
    - Chest tube output ≥2 L within a 24-hour period
    - Notes: If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as

not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (ie, within a 48-hour time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.

— Type 5: Fatal bleeding

Fatal bleeding is bleeding that directly causes death with no other explainable cause. BARC fatal bleeding is categorized as either definite or probable as follows:

- Probable fatal bleeding (type 5a) is bleeding that is clinically suspicious as the cause of death, but the bleeding is not directly observed and there is no autopsy or confirmatory imaging.
- Definite fatal bleeding (type 5b) is bleeding that is directly observed (by either clinical specimen [blood, emesis, stool, etc] or imaging) or confirmed on autopsy.
- The site of fatal bleeding is specified as intracranial, gastrointestinal, retroperitoneal, pulmonary, pericardial, genitourinary, or other.
- Bleeding Academic Research Consortium fatal bleeding is meant to capture deaths that are directly due to bleeding with no other cause. The time interval from the bleeding event to the death should be considered with respect to likely causality, but there is no specific time limit proposed. Bleeding that is contributory but not directly causal to death is not classified as fatal bleeding but may be categorized as other forms of bleeding. Bleeding that leads to cessation of antithrombotic or other therapies may be contributory but again would not be classified as fatal bleeding. Bleeding associated with trauma or with surgery may be fatal, depending on whether it was determined to be directly causal or not.
- Examples of potential scenarios consistent with BARC fatal bleeding include the following: (1) A patient who receives a fibrinolytic agent for a small inferior MI loses consciousness and dies; autopsy shows an intracranial hemorrhage with mass effect: definite fatal bleed, intracranial; (2) a patient who receives a fibrinolytic agent for a large anterior MI loses consciousness and develops cardiac arrest; clinical examination immediately earlier showed a dilated left pupil: probable fatal bleed, intracranial; (3) a post-PCI patient on dual antiplatelet therapy who has a witnessed large gastrointestinal bleed becomes hypotensive and dies: definite fatal bleed, gastrointestinal; and (4) a patient develops a gastrointestinal bleed that is successfully cauterized; 3 days later, the gastroenterologist stops dual antiplatelet therapy and the patient has a fatal MI: not a fatal bleed.

Bleeding End-Point Reporting

Bleeding Academic Research Consortium recommends defining the timing of events according to the clinical trial and according to the particular pharmacotherapy or intervention being studied, but at least at 7 days, 30 days, and/or at the end of the trial.

Conclusions

Herein we have proposed a new objective, hierarchically graded, consensus classification for bleeding. After a review of the data and prior definitions, this new BARC categorization was reached by consensus of several groups with experience in considering end points in cardiovascular clinical trials and registries. Validation of these proposed consensus definitions is still needed. We strongly urge trialists and sponsors to begin reporting bleeding events according to BARC definitions in all research efforts from this point forward, even if in conjunction with other definitions. The universality of the definition will overcome the inherent limitations of a consensus-based effort and will allow comprehensive and consistent reporting of bleeding in future clinical investigations.

Appendix

Bleeding Academic Research Consortium Participants

Academic Research Organizations

Cardialysis, Rotterdam, the Netherlands: Pascal Vranckx, MD. Cardiovascular Research Foundation, New York, NY: Adriano Caixeta, MD, PhD; Roxana Mehran, MD; Eugenia Nikolsky, MD, PhD. Cleveland Clinic Coordinating Center for Clinical Research, Cleveland, OH: Venu Menon, MD. Duke Clinical Research Institute, Durham, NC: E. Magnus Ohman, MD; Sunil Rao, MD. Green Lane Coordinating Center, Auckland, New Zealand: Harvey White, MB ChB, DSc. TIMI Study Group, Boston, MA: Deepak L. Bhatt, MD, MPH; Stephen D. Wiviott, MD. Pharmacological/Percutaneous Endoluminal Revascularization for Unstable Syndromes and Its Evaluation (PERFUSE), Boston, MA: C. Michael Gibson, MD.

Physician Society Representatives and Experts

John Eikelboom, MD, McMaster University, Hamilton, ON, Canada; Sanjay Kaul, MD, Cedars-Sinai Medical Center, Los Angeles, CA; Yves Rosenberg, MD, National Heart, Lung, and Blood Institute, Washington, DC; Victor Serebruany, MD, PhD, Johns Hopkins University, Baltimore, MD; Philippe Gabriel Steg, MD, Hopital Bichat, Paris, France; Marco Valgimigli, MD, University of Ferrara, Ferrara, Italy.

US Food and Drug Administration

Ashley B. Boam; Karen Hicks, MD; Bram Zuckerman, MD.

Industry Representatives

Isabela Batsu, MD, sanofi-aventis; Rogelio Braceras, MD, Daiichi-Sankyo; James J. Ferguson, MD, The Medicines Company; Dan M. Jolivette, MD, Medtronic, Inc; Juan Maya, MD, AstraZeneca; Krishnan Ramaswamy, MD, Daiichi-Sankyo; Simona Skerjanec, PharmD, The Medicines Company; Hans Peter Stoll, MD, Cordis Corp, a Johnson & Johnson Co; Paul Underwood, MD, Boston Scientific Corp; Neal Wolff, Bristol-Myers Squibb; Steven Zelenkofske, DO, Regado Biosciences.

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Dr Bhatt has received research grants from AstraZeneca, Bristol-Myers Squibb, Eisai, Sanofi-Aventis, and The Medicines Company. Dr Eikelboom has received research grants from BIHR and The Heart and Stroke Foundation of Canada, as well as honoraria for lectures and/or consultancies from Bristol-Myers Squibb, Sanofi-Aventis, AstraZeneca, and Boehringer-Ingelheim. Dr Gibson has received honoraria for lectures and/or consultancies from Bayer Corp, Johnson & Johnson Corp, Medicure, Portola Pharmaceuticals, Sanofi-Aventis Pharmaceuticals, Schering Plough Corp, The Medicines Company, Daiichi Sankyo, and Eli Lilly. Dr Mehran has received a research grant from the Bristol Myers Squibb/Sanofi-Aventis pharmaceutical partnership, and has served on advisory boards for Abbott Vascular, Accumetrics, AstraZeneca, Cardiva, Cordis, Gilead, Guerbet, Ortho-McNeil, Regado Biosciences, and St. Jude Medical. Dr Nikolsky has served as a consultant for Medtronic Vascular. Dr Rao has received research grants from Cordis Corp, Novartis, Sanofi-Aventis, and Ikaria; has served on the Speaker's Bureau for The Medicines Company, BMS, Sanofi-Aventis, and Terumo Medical; has received honoraria from AstraZeneca, Daiichi-Sankyo/Eli Lilly, and BMS; and has served as a consultant or advisory board member for The Medicines Company, AstraZeneca, BMS, Terumo, and Daiichi-Sankyo/Eli Lilly. Dr Serebruany has received research grants from Bristol-Myers Squibb, Eli Lilly, and Novartis; has served on the speakers' bureau of Boehringer-Ingelheim and Sanofi-Aventis and as a consultant for Merck, Sanofi-Aventis, and Boehringer-Ingelheim; has received honoraria from AstraZeneca and Merck; and holds intellectual property with Eisai, Eli Lilly, and Pfizer. Dr Steg has received a research grant from Servier and honoraria for lectures and/or consultancies from AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, GlaxoSmithKline, Eli Lilly, MSD/Schering Plough, Novartis, Otsuka, Roche, Sanofi-Aventis, Servier, The Medicines Company, Boehringer Ingelheim, and Medtronic. Dr Valgimigli has received research grants from Iroko, Eli Lilly, The Medicines Company, and Medtronic; has received honoraria from Cordis, Johnson & Johnson, Medtronic, Abbott, EISAI, Iroko, Merck, AstraZeneca, Chiesi, Terumo, Accumetrics, and The Medicines Company; and consults for Abbott, Eli Lilly, Choice Pharma, St. Jude, Chiesi, La Roche, CID, Iroko/Cardio, and AstraZeneca. Dr Wiviott has received honoraria for lectures or consultancies from Eli Lilly, Daiichi Sankyo, AstraZeneca, Sanofi-Aventis, Bristol-Myers Squibb, Pfizer, and ARENA and research grants from Eli Lilly/Daiichi Sankyo, Schering-Plough, and Merck. Dr Ohman receives research grant support from Daiichi-Sankyo, Datascope, and Eli Lilly, and has received consulting fees or honoraria from AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead, Liposcience, Merck, Sanofi-Aventis, The Medicines Company, Pozen, and WebMD. Dr White has received research grants from Sanofi-Aventis, Eli Lilly, The Medicines Company, The National Institutes of Health, Pfizer, Roche, Johnson and Johnson, Schering-Plough, MSD, AstraZeneca, GlaxoSmithKline, Daiichi Sankyo, and Bristol-Myers Squibb, and is a consultant for Regado Biosciences. The other authors report no conflicts.

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KEY WORDS: clinical trials ■ hemorrhage ■ outcome ■ pharmacology

SUPPLEMENTAL MATERIAL

Case example #1

A patient enrolled in a clinical trial of a new antithrombotic agent that is to be taken chronically for secondary prevention experiences epistaxis requiring an emergency room visit, nasal packing, and cessation of study drug. There is no associated hypotension and the patient does not require vasopressor support or transfusion. The associated hemoglobin decrease is 2 g/dl.

Meets criteria for Type 2 BARC bleeding, GUSTO mild bleeding, TIMI bleeding requiring medical attention, CURE minor bleeding, PLATO minor bleeding

Case example #2

A patient hospitalized with acute coronary syndrome undergoes percutaneous coronary intervention. Post-procedure, the patient experiences a groin hematoma of 10 cm requiring aggressive manual compression. During the manual compression, she becomes hypotensive, likely due to a vagal reaction from compression of her femoral artery. During this period, she also receives one unit of packed red blood cells. She becomes clinically stable without the need for inotropic support or surgical intervention. There is no decrease in hemoglobin.

This event would require adjudication in order to distinguish hypotension that occurs as a result of brisk bleeding from hypotension that occurs from other causes (like a vagal reaction from manual compression of the femoral access site). This event meets criteria for BARC Type 3a bleeding (any transfusion). Without adjudication, the event would meet criteria for GUSTO severe bleeding (bleeding event with hypotension) and for TIMI Bleeding Requiring Medical Attention.

Standardized Bleeding Definitions for Cardiovascular Clinical Trials: A Consensus Report From the Bleeding Academic Research Consortium

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