

Standardized Bleeding Definitions for Cardiovascular Clinical Trials

A Consensus Report From the Bleeding Academic Research Consortium

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Table 2.

Heterogeneity in Bleeding Definitions Used in Acute Coronary Syndrome Trials

Trial	Bleeding Definition
TIMI ^{6,37,38}	<p>Non-CABG related bleeding</p> <p>Major</p> <ul style="list-style-type: none"> ○ 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) <p>Minor</p> <ul style="list-style-type: none"> ○ Clinically overt (including imaging), resulting in hemoglobin drop of 3 to <5 g/dL <p>Requiring medical attention</p> <ul style="list-style-type: none"> ○ 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

Trial	Bleeding Definition
	<ul style="list-style-type: none"> ○ Prompting evaluation (leading to an unscheduled visit to a healthcare professional and diagnostic testing, either laboratory or imaging) <p>Minimal</p> <ul style="list-style-type: none"> ○ Any overt bleeding event that does not meet the criteria above <p>Bleeding in the setting of CABG</p> <ul style="list-style-type: none"> ○ 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	<p>Severe or life-threatening</p> <ul style="list-style-type: none"> ○ Intracerebral hemorrhage ○ Resulting in substantial hemodynamic compromise requiring treatment <p>Moderate</p> <ul style="list-style-type: none"> ○ Requiring blood transfusion but not resulting in hemodynamic compromise <p>Mild</p> <ul style="list-style-type: none"> ○ Bleeding that does not meet above criteria
CURE ⁵	<p>Major bleeding</p> <ul style="list-style-type: none"> ○ Life-threatening (fatal, intracranial, requiring surgical intervention, results in substantial hypotension requiring the use of intravenous inotropic agents) <ul style="list-style-type: none"> ▪ Hemoglobin decrease ≥ 5 g/dL or required ≥ 4 U of blood ○ Other major bleeding <ul style="list-style-type: none"> ▪ Transfusion of 2–3 U, intraocular <p>Minor</p> <ul style="list-style-type: none"> ○ Led to discontinuation of study drug
ACUITY, ²⁸ HORIZONS ³²	<p>Major</p> <p>Intracranial or intraocular hemorrhage</p>

Trial	Bleeding Definition
	<p>Access-site hemorrhage requiring intervention</p> <p>≥5-cm hematoma</p> <p>Retroperitoneal</p> <p>Reduction in hemoglobin concentration of ≥4 g/dL without an overt source of bleeding</p> <p>Reduction in hemoglobin concentration of ≥3 g/dL with an overt source of bleeding</p> <p>Reoperation for bleeding</p> <p>Use of any blood product transfusion</p>
CURRENT-OASIS 7 ³³	<p>Severe</p> <ul style="list-style-type: none"> ○ 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 <p>Other major</p> <ul style="list-style-type: none"> ○ Requiring transfusion of 2 to 3 U ○ Significantly disabling, intraocular bleeding leading to significant loss of vision <p>Minor</p> <ul style="list-style-type: none"> ○ Other bleeding that leads to modification of drug regimen <p>Other</p> <ul style="list-style-type: none"> ○ Bleeding not meeting criteria for major or minor
STEEPLE ³¹	<p>Major bleeding</p> <ul style="list-style-type: none"> ○ 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%)

Trial	Bleeding Definition
	<p>Minor</p> <ul style="list-style-type: none"> ○ 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	<p>Major life-threatening</p> <ul style="list-style-type: none"> ○ 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 <p>Other major</p> <ul style="list-style-type: none"> ○ 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 <p>Any major</p> <ul style="list-style-type: none"> ○ Any one of the above criteria <p>Minor</p> <ul style="list-style-type: none"> ○ Requiring medical intervention to stop or treat bleeding (eg, epistaxis requiring visit to medical facility for packing) <p>Minimal</p> <ul style="list-style-type: none"> ○ All others (eg, bruising, bleeding gums, oozing from injection sites) not requiring intervention or treatment
GRACE ^{10,21}	Major

Trial	Bleeding Definition
	Requiring a transfusion of ≥ 2 U PRBCs Resulting in a decrease in hematocrit of $\geq 10\%$ Occurring intracerebrally Resulting in stroke or death
REPLACE-2/ISAR-REACT 3 ²⁵	Major <ul style="list-style-type: none"> ○ 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 Minor <ul style="list-style-type: none"> ○ Overt bleeding not meeting criteria for major bleeding
ESSENCE ²⁷	Major <ul style="list-style-type: none"> ○ 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 <ul style="list-style-type: none"> ○ 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 <ul style="list-style-type: none"> ○ 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.