Standardized Definitions for End Point Events in Cardiovascular Trials

The Standardized Data Collection for Cardiovascular Trials Initiative is a working group composed of academicians, professional societies, Clinical Data Interchange Standards Consortium (CDISC), Health Level 7, Clinical Trials Transformation Initiative (CTTI), industry, and the Food and Drug Administration (FDA). The goal of this working group is to improve the quality and efficiency of cardiovascular trials.

The purpose of this document is to propose definitions for cardiovascular end points that could be used as a framework to design clinical trials. End point definitions are necessary in clinical trials so that events are clearly characterized by objective criteria and reported uniformly. If uniformly defined, events in drug development programs or among different clinical trials may be analyzed more easily and trends and other safety signals may be identified.

Please share with us any comments you have about the Introduction or these definitions. With respect to comments, please cite the end point name, chapter, page number(s), section number, and line number(s) first, and then add your comments and rationale.

In addition to creating these definitions to simplify the conduct of clinical trials, other goals for the working group include creating standardized case report forms for these end point events that investigators can download from the CDISC website, integrating these standardization processes with CDISC and HL7, and creating a data warehouse of cardiovascular trials.

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Introduction

The purpose of this document is to provide a framework of definitions for cardiovascular end points in clinical trials. These definitions are based on clinical and research expertise, published guidelines and definitions, and our current understanding of the specific laboratory tests, diagnostic tests, and imaging techniques used in clinical practice to diagnose these events.

It is recognized that definitions of cardiovascular end points may change over time, as new biomarkers or other diagnostic tests become available, or as standards evolve and perceptions of clinical importance become modified.

End point definitions are necessary in clinical trials so that events are clearly characterized by objective criteria and reported uniformly. However, some events may be complex and may not neatly fulfill the specified criteria. Furthermore, within a large-scale, multicenter, international study, some results may not be available because they were never measured by the physician responsible for their care at the time, because the test was not available locally, or because the results can no longer be found. In all cases, clinical judgment should be used to determine the most likely cause of an event. Where the person performing the adjudication of an event is blind to the treatment allocation, any errors will be random, rather than systematic. As a consequence, any noise introduced by slight misclassifications of events will not bias the result towards one arm or another, but may mask a true difference in effectiveness or safety or increase the chance of concluding non-inferiority.

Advances in database technologies and statistical methodologies have created opportunities to aggregate large trial datasets. If uniformly defined, events in drug development programs or among different clinical trials may be analyzed more easily and trends and other safety signals may be identified. More consistent definitions could improve the ability to estimate event rates in a contemplated clinical trial.

All definitions have limitations and will not seem satisfactory for every case. The goal of this document is to propose definitions that will be suitable for study end points in cardiovascular trials and as events of interest in assessing cardiovascular safety.

Keeping in mind the value and limitations of any type of standardization, the following definitions are proposed to simplify the conduct of cardiovascular trials and to form a basis on which to design clinical trials. Flexibility in these definitions may be necessary to address the particulars of a drug product, clinical trial, or study population.

This document includes eleven chapters and one appendix. Each chapter provides the definition for a particular cardiovascular event.

CHAPTER 1. Definition of Cardiovascular Death

The determination of the specific cause of cardiovascular death is complicated by the fact that we are particularly interested in one underlying cause of death (acute myocardial infarction (AMI)) and several modes of death (arrhythmia and heart failure/low output). It is noted that heart attack-related deaths are manifested as sudden death or heart failure, so these events need to be carefully defined.

Cardiovascular death includes death resulting from an acute myocardial infarction, sudden cardiac death, death due to heart failure, death due to stroke, and death due to other cardiovascular causes, as follows:

1. **Death due to Acute Myocardial Infarction** refers to a death by any mechanism (arrhythmia, heart failure, low output) within 30 days after a myocardial infarction (MI) related to the immediate consequences of the myocardial infarction, such as progressive congestive heart failure (CHF), inadequate cardiac output, or recalcitrant arrhythmia. If these events occur after a "break" (e.g., a CHF and arrhythmia free period of at least a week), they should be designated by the immediate cause, even though the MI may have increased the risk of that event (e.g., late arrhythmic death becomes more likely after an acute myocardial infarction (AMI)). The acute myocardial infarction should be verified to the extent possible by the diagnostic criteria outlined for acute myocardial infarction or by autopsy findings showing recent myocardial infarction or recent coronary thrombus. Sudden cardiac death, if accompanied by symptoms suggestive of myocardial ischemia, new ST elevation, new LBBB, or evidence of fresh thrombus by coronary angiography and/or at autopsy should be considered death resulting from an acute myocardial infarction, even if death occurs before blood samples or 12-lead electrocardiogram (ECG) could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.

   Death resulting from a procedure to treat a myocardial infarction (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG), or to treat a complication resulting from myocardial infarction, should also be considered death due to acute MI.

   Death resulting from a procedure to treat myocardial ischemia (angina) or death due to a myocardial infarction that occurs as a direct consequence of a cardiovascular investigation/procedure/operation should be considered as a death due to other cardiovascular causes.

2. **Sudden Cardiac Death** refers to a death that occurs unexpectedly, not following an acute AMI, and includes the following deaths:

   a. Death witnessed and instantaneous without new or worsening symptoms

   b. Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest AMI

   c. Death witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review)

   d. Death after unsuccessful resuscitation from cardiac arrest

   e. Death after successful resuscitation from cardiac arrest and without identification of a non-cardiac etiology (Post-Cardiac Arrest Syndrome)

   f. Unwitnessed death without other cause of death (information regarding the patient's clinical status preceding death should be provided, if available)

General Considerations

- A subject seen alive and clinically stable 12-24 hours prior to being found dead without any evidence or information of a specific cause of death should be classified as "sudden cardiac death." Typical scenarios include
  - Subject well the previous day but found dead in bed the next day
  - Subject found dead at home on the couch with the television on

- Deaths for which there is no information beyond "Patient found dead at home" may be classified as "death due to other cardiovascular causes" or in some trials, "undetermined cause of death." Please see Chapter 3, Definition of Undetermined Cause of Death, for full details.

3. **Death due to Heart Failure or Cardiogenic Shock** refers to a death occurring in the context of clinically worsening symptoms and/or signs of heart failure (see Chapter 7) without evidence of another cause of death and not following an AMI. Note that deaths due to heart failure can have various etiologies, including one or more AMIs (late effect), ischemic or non-ischemic cardiomyopathy, or valve disease.

   Death due to Heart Failure or Cardiogenic shock should include sudden death occurring during an admission for worsening heart failure as well as death from progressive heart failure or cardiogenic shock following implantation of a mechanical assist device.

   New or worsening signs and/or symptoms of congestive heart failure (CHF) include any of the following:

   a. New or increasing symptoms and/or signs of heart failure requiring the initiation of, or an increase in, treatment directed at heart failure or occurring in a patient already receiving maximal therapy for heart failure

   b. Heart failure symptoms or signs requiring continuous intravenous therapy or chronic oxygen administration for hypoxia due to pulmonary edema

   c. Confinement to bed predominantly due to heart failure symptoms

   d. Pulmonary edema sufficient to cause tachypnea and distress **not** occurring in the context of an acute myocardial infarction, worsening renal function, or as the consequence of an arrhythmia occurring in the absence of worsening heart failure

   e. Cardiogenic shock **not** occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure

      Cardiogenic shock is defined as systolic blood pressure (SBP) < 90 mm Hg for greater than 1 hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypoperfusion:

      - Cool, clammy skin ***or***
      - Oliguria (urine output < 30 mL/hour) ***or***
      - Altered sensorium ***or***
      - Cardiac index < 2.2 L/min/m^2

      Cardiogenic shock can also be defined if SBP < 90 mm Hg and increases to ≥ 90 mm Hg in less than 1 hour with positive inotropic or vasopressor agents alone and/or with mechanical support.

General Considerations

Heart failure may have a number of underlying causes, including acute or chronic ischemia, structural heart disease (e.g. hypertrophic cardiomyopathy), and valvular heart disease. Where treatments are likely to have specific effects, and it is likely to be possible to distinguish between the various causes, then it may be reasonable to separate out the relevant treatment effects. For example, obesity drugs such as fenfluramine (pondimin) and dexfenfluramine (redux) were found to be associated with the development of valvular heart disease and pulmonary hypertension. In other cases, the aggregation implied by the definition above may be more appropriate.

4. **Death due to Stroke** refers to death occurring up to 30 days after a stroke that is either due to the stroke or caused by a complication of the stroke.

5. **Death due to Other Cardiovascular Causes** refers to a cardiovascular death not included in the above categories (e.g. dysrhythmia unrelated to sudden cardiac death, pulmonary embolism, cardiovascular intervention (other than one related to an AMI), aortic aneurysm rupture, or peripheral arterial disease). Mortal complications of cardiac surgery or non-surgical revascularization should be classified as cardiovascular deaths.

CHAPTER 2. Definition of Non-Cardiovascular Death

Non-cardiovascular death is defined as any death that is not thought to be due to a cardiovascular cause. Detailed recommendations on the classification of non-cardiovascular causes of death are beyond the scope of this document. The level of detail required and the optimum classification will depend on the nature of the study population and the anticipated number and type of non-cardiovascular deaths. Any specific anticipated safety concern should be included as a separate cause of death. The following is a suggested list of non-cardiovascular* causes of death:

Non-Malignant Causes

- Pulmonary
- Renal
- Gastrointestinal
- Hepatobiliary
- Pancreatic
- Infection (includes sepsis)
- Non-infectious (e.g., systemic inflammatory response syndrome (SIRS))
- Hemorrhage, not intracranial
- Non-cardiovascular system organ failure (e.g., hepatic failure)
- Non-cardiovascular surgery
- Other non-cardiovascular, specify: _____
- Accidental/Trauma
- Suicide
- Drug Overdose

*Death due to a gastrointestinal bleed should **not** be considered a cardiovascular death.

Malignant Causes

Malignancy should be coded as the cause of death if:

- Death results directly from the cancer; or
- Death results from a complication of the cancer (e.g. infection, complication of surgery / chemotherapy / radiotherapy); or
- Death results from withdrawal of other therapies because of concerns relating to the poor prognosis associated with the cancer

Cancer deaths may arise from cancers that were present prior to randomization or which developed subsequently. It may be helpful to distinguish these two scenarios (i.e. worsening of prior malignancy; new malignancy).

Suggested categorization includes common organ systems, hematologic, or unknown.

CHAPTER 3. Definition of Undetermined Cause of Death

Undetermined Cause of Death refers to a death not attributable to one of the above categories of cardiovascular death or to a non-cardiovascular cause. Inability to classify the cause of death may be due to lack of information (e.g., the only available information is "patient died") or when there is insufficient supporting information or detail to assign the cause of death. In general, the use of this category of death should be discouraged and should apply to a minimal number of patients in well-run clinical trials.

A common analytic approach for cause of death analyses is to assume that all undetermined cases are included in the cardiovascular category (e.g., presumed cardiovascular death, specifically "death due to other cardiovascular causes"). Nevertheless, the appropriate classification and analysis of undetermined causes of death depends on the population, the intervention under investigation, and the disease process. The approach should be prespecified and described in the protocol and other trial documentation such as the end point adjudication procedures and/or the statistical analysis plan.

CHAPTER 4. Definition of Myocardial Infarction

1. General Considerations

The term myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia.

In general, the diagnosis of MI requires the combination of:

- Evidence of myocardial necrosis (either changes in cardiac biomarkers or post-mortem pathological findings); and
- Supporting information derived from the clinical presentation, electrocardiographic changes, or the results of myocardial or coronary artery imaging

The totality of the clinical, electrocardiographic, and cardiac biomarker information should be considered to determine whether or not a MI has occurred. Specifically, timing and trends in cardiac biomarkers and electrocardiographic information require careful analysis. The adjudication of MI should also take into account the clinical setting in which the event occurs. MI may be adjudicated for an event that has characteristics of a MI but which does not meet the strict definition because biomarker or electrocardiographic results are not available.

2. Criteria for Myocardial Infarction

a. Clinical Presentation

The clinical presentation should be consistent with diagnosis of myocardial ischemia and infarction. Other findings that might support the diagnosis of MI should be taken into account because a number of conditions are associated with elevations in cardiac biomarkers (e.g., trauma, surgery, pacing, ablation, congestive heart failure, hypertrophic cardiomyopathy, pulmonary embolism, severe pulmonary hypertension, stroke or subarachnoid hemorrhage, infiltrative and inflammatory disorders of cardiac muscle, drug toxicity, burns, critical illness, extreme exertion, and chronic kidney disease). Supporting information can also be considered from myocardial imaging and coronary imaging. The totality of the data may help differentiate acute MI from the background disease process.

b. Biomarker Elevations

For cardiac biomarkers, laboratories should report an upper reference limit (URL). If the 99th percentile of the upper reference limit (URL) from the respective laboratory performing the assay is not available, then the URL for myocardial necrosis from the laboratory should be used. If the 99th percentile of the URL or the URL for myocardial necrosis is not available, the MI decision limit for the particular laboratory should be used as the URL. Laboratories can also report both the 99th percentile of the upper reference limit and the MI decision limit. Reference limits from the laboratory performing the assay are preferred over the manufacturer's listed reference limits in an

assay's instructions for use. CK-MB and troponin are preferred, but CK may be used in the absence of CK-MB and troponin.

For MI subtypes, different biomarker elevations for CK, CK-MB, or troponin will be required. The specific criteria will be referenced to the URL.

In many studies, particularly those in which patients present acutely to hospitals which are not participating sites, it is not practical to stipulate the use of a single biomarker or assay, and the locally available results are to be used as the basis for adjudication. However, if possible, using the same cardiac biomarker assay and preferably, a core laboratory, for all measurements reduces inter-assay variability.

Since the prognostic significance of different types of myocardial infarctions (e.g., periprocedural myocardial infarction versus spontaneous myocardial infarction) may be different, consider evaluating outcomes for these subsets of patients separately.

c. Electrocardiogram (ECG) Changes

Electrocardiographic changes can be used to support or confirm a MI. Supporting evidence may be ischemic changes and confirmatory information may be new Q waves.

- **Criteria for acute myocardial ischemia (in absence of left ventricular hypertrophy (LVH) and left bundle branch block (LBBB)):**

  - ST elevation
    New ST elevation at the J point in two anatomically contiguous leads with the cut-off points: ≥ 0.2 mV in men (> 0.25 mV in men < 40 years) or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads.

  - ST depression and T-wave changes
    New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or new T inversion ≥ 0.1 mV in two contiguous leads.

  The above ECG criteria illustrate patterns consistent with myocardial ischemia. In patients with abnormal biomarkers, it is recognized that lesser ECG abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings.

- **Criteria for pathological Q-wave**

  - Any Q-wave in leads V2-V3 ≥ 0.02 seconds or QS complex in leads V2 and V3
  - Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III, and aVF)[a]

  [a]The same criteria are used for supplemental leads V7-V9, and for the Cabrera frontal plane lead grouping.

- **Criteria for Prior Myocardial Infarction**

  - Pathological Q-waves, as defined above
  - R-wave ≥ 0.04 seconds in V1-V2 and R/S ≥ 1 with a concordant positive T-wave in the absence of a conduction defect

3. Myocardial Infarction Subtypes

Several MI subtypes are commonly reported in clinical investigations and each are defined below:

a. Spontaneous MI

1. Detection of rise and/or fall of cardiac biomarkers with at least one value above the URL with at least one of the following:

   - Clinical presentation consistent with ischemia
   - ECG evidence of acute myocardial ischemia
   - New pathological Q waves
   - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
   - Autopsy evidence of acute MI

2. If biomarkers are elevated from a prior infarction, then a spontaneous myocardial infarction is defined as:

   a. One of the following:
      - Clinical presentation consistent with ischemia
      - ECG evidence of acute myocardial ischemia
      - New pathological Q waves
      - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
      - Autopsy evidence of acute MI

   AND

   b. Both of the following:
      - Evidence that cardiac biomarker values were decreasing (e.g., two samples 3-6 hours apart) prior to the suspected MI*
      - ≥ 20% increase (and > URL) in troponin or CK-MB between a measurement made at the time of the initial presentation and a further sample taken 3-6 hours later

   *If biomarkers are increasing or peak is not reached, then a definite diagnosis of recurrent MI is generally not possible.

b. Percutaneous Coronary Intervention-Related Myocardial Infarction

Peri-PCI MI is defined by any of the following criteria. Symptoms of cardiac ischemia are not required.

1. Biomarker elevations within 48 hours of PCI:

   - Troponin or CK-MB (preferred) > 3 x URL ***and***
   - No evidence that cardiac biomarkers were elevated prior to the procedure;

   OR

   - Both of the following must be true:
     - ≥ 50%[1] increase in the cardiac biomarker result
     - Evidence that cardiac biomarker values were decreasing (e.g., two samples 3-6 hours apart) prior to the suspected MI

2. New pathological Q waves

3. Autopsy evidence of acute MI

c. Coronary Artery Bypass Grafting-Related Myocardial Infarction

Peri-coronary artery bypass graft surgery (CABG) MI is defined by the following criteria. Symptoms of cardiac ischemia are not required.

1. Biomarker elevations within 72 hours of CABG:

   - Troponin or CK-MB (preferred) > 5 x URL ***and***
   - No evidence that cardiac biomarkers were elevated prior to the procedure;

   OR

   - Both of the following must be true:
     - ≥ 50%[2] increase in the cardiac biomarker result
     - Evidence that cardiac biomarker values were decreasing (e.g., two samples 3-6 hours apart) prior to the suspected MI.

AND

[1] **Data should be collected in such a way that analyses using ≥ 20% or ≥ 50% could both be performed.**
[2] **Data should be collected in such a way that analyses using ≥ 20% or ≥ 50% could both be performed.**

2. One of the following:

- New pathological Q-waves persistent through 30 days
- New persistent non-rate-related LBBB
- Angiographically documented new graft or native coronary artery occlusion
- Other complication in the operating room resulting in loss of myocardium
- Imaging evidence of new loss of viable myocardium

OR

3. Autopsy evidence of acute MI

d. Silent Myocardial Infarction

Silent MI is defined by the following:

1. No evidence of acute myocardial infarction

AND

2. Any one of the following criteria:

- New pathological Q-waves. A confirmatory ECG is recommended if there have been no clinical symptoms or history of myocardial infarction.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause
- Autopsy evidence of a healed or healing MI

APPENDIX 1. Common Classification Schemes for Myocardial Infarction Categories

For some trials, categorization of MI end points may be helpful or necessary using one or more of the classification schemes below:

1. By the Universal MI Definition:

a. Clinical Classification of Different Types of Myocardial Infarction

- **Type 1**
  Spontaneous myocardial infarction related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection

- **Type 2**
  Myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply, e.g., coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension

- **Type 3**
  Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood

- **Type 4a**
  Myocardial infarction associated with PCI

- **Type 4b**
  Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy

- **Type 5**
  Myocardial infarction associated with CABG

b. Sample Clinical Trial Tabulation of Randomized Patients by Types of Myocardial Infarction

Types of MI	Treatment A Number of patients (N =)	Treatment B Number of patients (N =)
MI Type 1	n, %	n, %
MI Type 2	n, %	n, %
MI Type 3	n, %	n, %
MI Type 4	n, %	n, %
MI Type 5	n, %	n, %
Total number	n, %	n, %
N = total number of patients; n = number of patients with a particular MI.		

2. By Electrocardiographic Features:

- **ST-Elevation MI (STEMI)**
  - Additional subcategories may include:
    - Q-wave
    - Non-Q-wave
    - Unknown (no ECG or ECG not interpretable)

- **Non-ST-Elevation MI (NSTEMI)**
  - Additional subcategories may include:
    - Q-wave
    - Non-Q-wave
    - Unknown (no ECG or ECG not interpretable)

- **Unknown (no ECG or ECG not interpretable)**

3. By Biomarker Elevation (per Universal MI Definition):

The magnitude of cardiac biomarker elevation can be calculated as a ratio of the peak biomarker value divided by the 99th percentile URL.

The biomarker elevation can be provided for various MI subtypes, as shown in the example below.

Classification of the Different Types of Myocardial Infarction According to Multiples of the 99th Percentile URL of the Applied Cardiac Biomarker

Multiples X 99 %	MI Type 1 (spontaneous)	MI Type 2 (secondary)	MI Type 3* (sudden death)	MI Type 4 ** (PCI)	MI Type 5** (CABG)	Total Number
1-2 X						
>2-3 X						
>3-5 X						
>5-10 X						
>10 X						
Total number						

*Biomarkers are not available for this type of myocardial infarction since the patients expired before biomarker determination could be performed.

**For the sake of completeness, the total distribution of biomarker values should be reported. The hatched areas represent biomarker elevations below the decision limit used for these types of myocardial infarction.

CHAPTER 5. Definition of Hospitalization for Unstable Angina

Unstable angina requiring hospitalization is defined as

1. Symptoms of myocardial ischemia at rest (chest pain or equivalent) or an accelerating pattern of angina with frequent episodes associated with progressively decreased exercise capacity

AND

2. Prompting an unscheduled visit to a healthcare facility and hospitalization (including chest pain observation units) **within 24 hours** of the most recent symptoms

AND

3. At least one of the following:

   a. New or worsening ST or T wave changes on resting ECG
      - ST elevation
        New ST elevation at the J point in two anatomically contiguous leads with the cut-off points: ≥ 0.2 mV in men (> 0.25 mV in men < 40 years) or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads.

      - ST depression and T-wave changes
        New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or new T inversion ≥ 0.1 mV in two contiguous leads.

      The above ECG criteria illustrate patterns consistent with myocardial ischemia. It is recognized that lesser ECG abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings.

   b. Definite evidence of myocardial ischemia on myocardial scintigraphy (clear reversible perfusion defect), stress echocardiography (reversible wall motion abnormality), or MRI (myocardial perfusion deficit under pharmacologic stress) that is believed to be responsible for the myocardial ischemic symptoms/signs

   c. Angiographic evidence of ≥ 70% lesion and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischemic symptoms/signs

   d. Need for coronary revascularization procedure (PCI or CABG) during the same hospital stay. This criterion would be fulfilled if the admission for myocardial ischemia led to transfer to another institution for the revascularization procedure without interceding home discharge

AND

4. No evidence of acute myocardial infarction

General Considerations

1. Escalation of pharmacotherapy for ischemia, such as intravenous nitrates or increasing dosages of β-blockers, should be considered supportive of the diagnosis of unstable angina. However, a typical presentation and admission to the hospital with escalation of pharmacotherapy, without any of the additional findings listed under category 3, would be insufficient alone to support classification as hospitalization for unstable angina.

2. If subjects are admitted with suspected unstable angina, and subsequent testing reveals a non-cardiac or non-ischemic etiology, this event should not be recorded as hospitalization for unstable angina. Potential ischemic events meeting the criteria for myocardial infarction should not be adjudicated as unstable angina.

3. Planned rehospitalization for performance of an elective revascularization in the absence of symptoms at rest prompting admission should not be considered a hospitalization for unstable angina. For example, a patient with stable exertional angina whose admission for coronary angiography and PCI is prompted by a positive outpatient stress test should not be considered a hospitalization for unstable angina.

4. A patient who undergoes an elective catheterization where incidental coronary artery disease is found and who subsequently undergoes coronary revascularization will not be considered as meeting the hospitalization for unstable angina end point.

CHAPTER 6. Definition of Transient Ischemic Attack and Stroke

Introduction

These definitions of Transient Ischemic Attack and Stroke apply to a wide range of clinical trials. They are general, overarching, and widely applicable definitions combined with a specific clinical measurement of disability. They are flexible in their application and consistent with contemporary understanding of the pathophysiology of stroke. This approach enables clinical trials to assess the clinically relevant consequences of vascular brain injury for determining the safety or effectiveness of an intervention.

Transient Ischemic Attack

Transient ischemic attack (TIA) is defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, *without* acute infarction.

Stroke

Stroke is defined as an acute episode of neurological dysfunction caused by focal or global brain, spinal cord, or retinal vascular injury.

Classification:

A. Ischemic Stroke

Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue.

Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.

B. Hemorrhagic Stroke

Hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by a nontraumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage.

C. Undetermined Stroke

Undetermined stroke is defined as a stroke with insufficient information to allow categorization as A or B.

2. Stroke Disability

Stroke disability should be measured by a reliable and valid scale in all cases. For example, the modified Rankin Scale may be used to address this requirement:

Scale	Disability
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

Additional Considerations

In trials involving patients with stroke, evidence of vascular central nervous system injury without recognized neurological dysfunction may be observed. Examples include microhemorrhage, silent infarction, and silent hemorrhage. When encountered, the clinical relevance of these findings may be unclear. If appropriate for a given clinical trial, however, they should be precisely defined and categorized.

The distinction between a Transient Ischemic Attack and an Ischemic Stroke is the presence of infarction, not the transience of the symptoms. In addition to laboratory documentation of infarction, persistence of symptoms is an acceptable indicator of infarction. Thus, symptom transience should be defined for any clinical trial in which it will be used to distinguish between transient ischemia and infarction.

CHAPTER 7. Definition of Heart Failure Requiring Hospitalization

Heart failure (HF) requiring hospitalization is defined as an event that meets the following criteria:

a. Requires hospitalization defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 24* hour stay (or a date change if the time of admission/discharge is not available).

*For this end point in any given clinical trial, there should be some flexibility in the required duration of stay, depending on the population and the adverse event profile of the drug to be studied. For example, a clinical trial studying patients with NYHA Class III/IV heart failure may not wish to capture hospitalizations less than 24 hours in duration, because this population may have frequent hospital visits requiring short-term therapy. On the contrary, clinical trials in patients with NYHA Class I/II heart failure may wish to capture shorter hospitalizations that may be predictive of subsequent decompensation.

AND

b. Clinical symptoms of heart failure, including at least one of the following:
New or worsening
- dyspnea
- orthopnea
- paroxysmal nocturnal dyspnea
- increasing fatigue/worsening exercise tolerance

AND

c. Physical signs of heart failure, including at least two of the following:
1. edema (greater than 2+ lower extremity)
2. pulmonary crackles greater than basilar (pulmonary edema must be sufficient to cause tachypnea and distress **not** occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure)
3. jugular venous distension
4. tachypnea (respiratory rate > 20 breaths/minute)
5. rapid weight gain
6. S3 gallop
7. increasing abdominal distension or ascites
8. hepatojugular reflux
9. radiological evidence of worsening heart failure
10. A right heart catheterization within 24 hours of admission showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥ 18 mm Hg or a cardiac output < 2.2 L/min/m^2

NOTE: Biomarker results (e.g., brain natriuretic peptide (BNP)) consistent with congestive heart failure will be supportive of this diagnosis, but the elevation in BNP cannot be due to other conditions such as cor pulmonale, pulmonary embolus, primary pulmonary hypertension, or congenital heart disease. Increasing levels of BNP, although not exceeding the ULN, may also be supportive of the diagnosis of congestive heart failure in selected cases (e.g. morbid obesity).

AND

d. Need for additional/increased therapy
   1. Initiation of, or an increase in, treatment directed at heart failure or occurring in a patient already receiving maximal therapy for heart failure and including at least one of the following:
      - Initiation of or a significant augmentation in oral therapy for the treatment of congestive heart failure
      - Initiation of intravenous diuretic, inotrope, or vasodilator therapy
      - Uptitration of intravenous therapy, if already on therapy
      - Initiation of mechanical or surgical intervention (mechanical circulatory support, heart transplantation or ventricular pacing to improve cardiac function), or the use of ultrafiltration, hemofiltration, or dialysis that is specifically directed at treatment of heart failure.

AND

e. No other non-cardiac etiology (such as chronic obstructive pulmonary disease, hepatic cirrhosis, acute renal failure, or venous insufficiency) and no other cardiac etiology (such as pulmonary embolus, cor pulmonale, primary pulmonary hypertension, or congenital heart disease) for signs or symptoms is identified.

NOTE: It is recognized that some patients may have multiple simultaneous disease processes. Nevertheless, for the end point event of heart failure requiring hospitalization, the diagnosis of congestive heart failure would need to be the primary disease process accounting for the above signs and symptoms.

CHAPTER 8. Interventional Cardiology Definitions

1. **Coronary Revascularization Procedure:** A coronary revascularization procedure is a catheter-based or open surgical procedure designed to improve myocardial blood flow. Catheter-based tools (e.g., balloon catheters, cutting balloons, atherectomy devices, lasers, bare metal stents, and drug-eluting stents) improve myocardial blood flow by increasing the luminal area at a site of an obstructive coronary lesion. Bypass grafts (arterial, venous, or synthetic) improve myocardial blood flow by providing a conduit for blood flow distal to an obstructive coronary lesion. Insertion of a guidewire through a coronary guide catheter into a coronary vessel or bypass graft for the purpose of percutaneous coronary intervention (PCI) is considered intention for PCI. However, in the assessment of the severity of intermediate lesions with the use of intravascular ultrasound, Doppler flow velocity, or fractional flow reserve, insertion of a guidewire will NOT be considered PCI.

2. **Procedural Success:** Achievement of <30 % residual diameter stenosis of the target lesion assessed by visual inspection or quantitative coronary angiography (QCA) and no in-hospital major adverse cardiac events (MACE, a composite of death, MI, or repeat coronary revascularization of the target lesion). Ideally, the assessment of the residual stenosis at the end of the procedure should be performed by an angiographic core laboratory.

   Comment: *For some devices or clinical settings (e.g., plain old balloon angioplasty (POBA) for patients undergoing non-cardiac surgery), achievement of < 50% diameter stenosis by visual inspection is an acceptable definition for procedural success.*

3. **Elective and Non-elective Procedures:**

   Elective: An elective procedure is one performed on a patient with stable cardiac function in the days or weeks prior to the procedure. Elective cases are usually scheduled at least 1 day prior to the procedure.

   Non-Elective: A non-elective procedure is one performed on a patient who has been stabilized following initial treatment of acute coronary ischemia, and there is clinical consensus that the procedure should occur within the next 24 hours.

   OR

   A procedure that is performed without delay on a patient with evidence of ongoing refractory ischemia with or without hemodynamic instability.

4. **Target Lesion:** A target lesion is any lesion treated or attempted to be treated during the trial procedure with the study device. The target lesion is the treated segment starting 5 mm proximal and ending 5 mm distal to the study device (stent, in most cases).

5. **Target Vessel:** A target vessel is any native coronary vessel (e.g., left main coronary artery (LMCA), left anterior descending coronary artery (LAD), left circumflex coronary artery (LCX), or right coronary artery (RCA)) or bypass graft to the LAD, LCX, or RCA containing the target lesion. The target vessel includes the target lesion as well as segments of the vessel that are upstream and downstream to the target lesion, including side branches (native vessel).

6. **Non-Target Lesion:** A non-target lesion is one for which revascularization is not attempted or one in which revascularization is performed using a non-study device.

7. **Non-Target Vessel:** A non-target vessel is one for which revascularization is not attempted or one in which revascularization is performed using a non-study device.

8. **Target Vessel, Non-Target Lesion:** Any lesion or revascularization of a lesion in the target vessel other than the target lesion.

9. **Target Lesion Revascularization (TLR):** Target lesion revascularization is any repeat percutaneous intervention of the target lesion (including 5 mm proximal and distal to the target lesion) or surgical bypass of the target vessel performed for restenosis or other complication involving the target lesion. In the assessment of TLR, angiograms should be assessed by an angiographic core laboratory (if designated) and made available to the Clinical End Points Committee (CEC) for review.

10. **Target Vessel Revascularization (TVR):** Target vessel revascularization is any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. In the assessment of TVR, angiograms should be assessed by an angiographic core laboratory (if designated) and made available to the CEC for review.

11. **Clinically-Driven Target Lesion Revascularization:** Revascularization is clinically-driven if the subject has a target lesion diameter stenosis ≥ 50% by QCA and clinical or functional ischemia which cannot be explained by another native coronary or bypass graft lesion. Clinical or functional ischemia includes any of the following:

    a. A history of angina pectoris, presumably related to the target vessel
    b. Objective signs of ischemia at rest (ECG changes) or during exercise test (or equivalent), presumably related to the target vessel
    c. Abnormal results of any invasive functional diagnostic test (e.g., Doppler flow velocity reserve or fractional flow reserve (FFR))
    d. A diameter stenosis ≥70% by QCA even in the absence of the above signs or symptoms.

Comment: *In the absence of QCA data or if a <50% stenosis is present, TLR may be considered clinically-driven by the CEC if severe ischemic signs and symptoms attributed to the target lesion are present.*

CHAPTER 9. Definition of Peripheral Arterial Revascularization Procedure

1. **Peripheral Arterial Revascularization Procedure:** A peripheral arterial revascularization procedure is a catheter-based or open surgical procedure designed to improve peripheral arterial blood flow. This procedure may include thrombectomy, embolectomy, atherectomy, dissection repair, angioplasty, and stent placement.

   The intention to perform percutaneous peripheral arterial intervention is denoted by the insertion of a guidewire through a guide catheter into a peripheral artery.

   The target vessel(s) should be specified (e.g., aorta, renal, mesenteric, iliac, femoral, tibial) and recorded as well as the type of revascularization procedure (e.g., surgical, angioplasty, stent placement, thromboembolectomy). For simplicity, this definition applies to non-cardiac and non-cerebrovascular vessels, including the aorta, but does not address aortic aneurysm repair.

2. **Procedural Success:** In the case of percutaneous intervention for obstructive lesions, procedural success is defined as the achievement of a final residual diameter stenosis < 30% by angiography at the end of the procedure (and without flow limiting arterial dissection and hemodynamically significant translesional pressure gradient) without any in-hospital major adverse events (death, acute onset of limb ischemia, need for urgent/emergent vascular surgery). The balloon inflation and/or stent placement may be preceded by use of adjunctive devices (e.g., percutaneous mechanical thrombectomy, directional or rotational atherectomy, laser, chronic total occlusion crossing device).

3. **Elective and Non-Elective Procedures:**

   Elective: An elective procedure is one that is scheduled and is performed on a patient with stable peripheral arterial disease.

   Non-Elective: A non-elective procedure is one performed on a patient who has been stabilized following initial treatment of acute peripheral limb ischemia, and there is clinical consensus that the procedure should occur within the next 24 hours.

   OR

   A procedure that is performed without delay because of urgency of the medical condition (e.g., acute limb ischemia, acute aortic dissection).

4. **Target Lesion:** A target lesion is any lesion treated or attempted to be treated during the trial procedure with the index device. The target lesion is the treated segment starting 5 mm proximal and ending 5 mm distal to the index device (stent, in most cases).

5. **Target Vessel**: A target vessel is any vessel (e.g., non-cardiac or non-cerebrovascular vessel) that contains the target lesion treated with the study device. The target vessel includes the target lesion as well as the entire vessel upstream and downstream to the target lesion, including side branches (native vessel).

6. **Non-Target Lesion:** A non-target lesion is one for which revascularization is not attempted or one in which revascularization is performed using a non-study device.

7. **Non-Target Vessel**: A non-target vessel is one for which revascularization is not attempted or one in which revascularization is performed using a non-study device.

8. **Target Vessel, Non-Target Lesion:** Any lesion or revascularization of a lesion in the target vessel other than the target lesion.

9. **Target Lesion Revascularization (TLR):** Target lesion revascularization is any repeat percutaneous intervention of the target lesions (including 5 mm proximal and distal to the index device) or surgical bypass of the target vessel performed for restenosis or other complication involving the target lesion. In the assessment of TLR, angiograms should be assessed by an angiographic core laboratory (if designated) and made available to the Clinical End Points Committee (CEC) for review.

10. **Target Vessel Revascularization (TVR):** Target vessel revascularization is any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. In the assessment of TVR, angiograms should be assessed by an angiographic core laboratory (if designated) and made available to the CEC for review.

11. **Clinically-Driven Target Lesion Revascularization:** Clinically-driven target lesion revascularization is a target lesion revascularization prompted by recurrent ipsilateral limb symptoms (intermittent claudication, critical limb ischemia) or objective imaging evidence of target lesion restenosis (i.e., most commonly with duplex ultrasonography). In the assessment of clinically driven TLR based on duplex ultrasonography, ultrasonographic images should be assessed by a duplex ultrasound core laboratory (if designated) and made available to the CEC for review.

CHAPTER 10. Definition of Stent Thrombosis

Stent Thrombosis: Timing

Stent thrombosis should be reported as a cumulative value over time and at the various individual time points as specified below. Time 0 is defined as the time point after the guiding catheter has been removed and the subject has left the cardiac catheterization laboratory.

Stent Thrombosis: Timing

Acute stent thrombosis[1]	0-24 hours post stent implantation
Subacute stent thrombosis[1]	> 24 hours – 30 days post stent implantation
Late stent thrombosis[2]	> 30 days – 1 year post stent implantation
Very late stent thrombosis[2]	> 1 year post stent implantation

[1]Acute or subacute can also be replaced by the term early stent thrombosis. Early stent thrombosis (0-30 days) will be used herein.
[2]Includes "primary" as well as "secondary" late stent thrombosis; "secondary" late stent thrombosis is a stent thrombosis after a target lesion revascularization.

Stent Thrombosis: Categories

We propose three categories of evidence to define stent thrombosis, as follows:

1. Definite Stent Thrombosis

Definite stent thrombosis is considered to have occurred by *either* angiographic or pathologic confirmation:

a. Angiographic confirmation of stent thrombosis[a]

- Thrombolysis in Myocardial Infarction (TIMI) flow is:
  - TIMI flow grade 0 with occlusion originating in the stent or in the segment 5 mm proximal or distal to the stent region in the presence of a thrombus[b,c] ***OR***
  - TIMI flow grade 1, 2, or 3 originating in the stent or in the segment 5 mm proximal or distal to the stent region in the presence of a thrombus[b,c]

AND at least one of the following criteria has been fulfilled within a 48 hour time window:

- New acute onset of ischemic symptoms at rest (typical chest pain with duration > 20 minutes)
- New ischemic ECG changes suggestive of acute ischemia
- Typical rise and fall in cardiac biomarkers (See definition of non-procedural-related MI (i.e. spontaneous MI) in Chapter 4.

[a]The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion)

[b]Non-occlusive thrombus: Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) non-calcified filling defect or lucency surrounded by contrast material (on three sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream

[c]Occlusive thrombus: TIMI 0 or TIMI 1 flow intra-stent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originating from the side branch)

b. Pathologic Confirmation of Stent Thrombosis

Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy.

2. Probable Stent Thrombosis

Probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:

a. Any unexplained death within the first 30 days**§**

b. Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause

[§]In patients undergoing PCI for ST-elevation myocardial infarction (STEMI), one may consider excluding unexplained death within 30 days of the procedure as evidence of probable stent thrombosis.

3. Possible Stent Thrombosis

Possible stent thrombosis is considered to have occurred with any unexplained death from 30 days following intracoronary stenting until end of trial follow-up.

CHAPTER 11. Bleeding Definitions

1. GUSTO

a. Severe or Life Threatening

Either intracranial hemorrhage or bleeding that causes hemodynamic compromise and requires intervention

b. Moderate

Bleeding that requires blood transfusion but does not result in hemodynamic compromise

c. Mild

Bleeding that does not meet the criteria for severe or moderate

2. TIMI

a. Types of TIMI Bleeding

1. Major

- Any intracranial bleeding

OR

- Clinically overt signs of hemorrhage associated with a drop in hemoglobin (Hgb) of ≥ 5 g/dL.

2. Minor

Any clinically overt signs of hemorrhage (including imaging) that is associated with a fall in Hgb of 3 to < 5 g/dL

3. Medical Attention:

Any overt sign of hemorrhage that requires medical evaluation, medical treatment (including discontinuation of medications), or surgical treatment, and that does not meet criteria for a major or minor bleeding event, as defined above.

4. Minimal

Any overt bleeding event that does not meet the criteria above

NOTE: To account for transfusions, Hgb measurements will be adjusted for any packed red blood cells (PRBCs) or whole blood given between baseline and post-transfusion measurements. A transfusion of one unit of blood will be assumed to result in an increase by 1 gm/dL in Hgb. Thus, to calculate the true change in hemoglobin, if there has been an intervening transfusion between two blood measurements, the following

calculations should be performed: Δ Hgb = [Baseline Hgb – Post transfusion Hgb] + [# transfused units].

b. Relationship of Bleeding to Death

1. Fatal Bleeding

Death in which a bleeding event directly led to death within 7 days. Examples of fatal bleeding events are an intracranial hemorrhage that led to herniation of the brain and death within 24 hours, and a massive gastrointestinal hemorrhage that results in shock, hemodynamic collapse, and death. If a bleeding event is considered fatal, then the cause of death must be either intracranial or non-intracranial bleeding.

2. Bleeding Contributed to Death

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 was not directly and/or immediately related to the subject's death. An example of bleeding contributing to death is a large retroperitoneal bleed that leads to surgical evacuation, development of a subsequent abscess in the area of bleeding that leads to sepsis, multiorgan failure, and death 10 days after the onset of bleeding. If bleeding has contributed to death (but the bleeding was not categorized as "fatal"), then the cause of death must be recorded as something other than intracranial / non-intracranial bleeding.

c. Bleeding in the Setting of Coronary Artery Bypass Graft Surgery (CABG)

Minor and minimal bleeding are not adjudicated in the setting of CABG.

As a drop in hemoglobin and transfusions are commonplace in routine CABG cases, one of the following criteria must be met to qualify for major bleeding in any of the preceding definitions:

1. Fatal bleeding (i.e., bleeding that directly results in death)
2. Perioperative intracranial bleeding
3. Reoperation following closure of the sternotomy incision for the purpose of controlling bleeding
4. Transfusion of ≥ 5 units of packed red blood cells (PRBCs) or whole blood within a 48 hour period. Cell saver transfusion will not be counted in calculations of blood products
5. Chest tube output > 2 L within a 24 hour period

3. CURE

a. Major Bleeding episodes are those which are:

1. Substantially disabling
2. Intraocular bleeds leading to loss of vision
3. Require at least 2 units of blood transfusion

b. Major bleeds are to be classified as life-threatening if they meet one or more of the following criteria:

1. Fatal, symptomatic intracranial bleed
2. Reduction in hemoglobin of at least 5 g/dL
3. Transfusion of at least 4 units of blood or packed cells, associated with substantial hypotension requiring the use of intravenous inotropic agents
4. Necessitated surgical intervention

c. Minor Bleeding

1. Other hemorrhages that led to interruption of the study medication

4. ACUITY

a. Major Bleeding is defined as

1. Intracranial bleeding
2. Intraocular bleeding
3. Access site hemorrhage requiring intervention
4. ≥ 5 cm diameter hematoma
5. Reduction in hemoglobin concentration of ≥ 4 g/dL without an overt source of bleeding
6. Reduction in hemoglobin concentration of ≥ 3 g/dL with an overt source of bleeding
7. Reoperation for bleeding
8. Use of any blood product transfusion

b. Minor bleeding

Clinically overt bleeding that did not meet criteria for major bleeding.

5. PLATO

a. Major Bleed—Fatal/life-threatening bleeding is defined as any one of the following:

1. Fatal
2. Intracranial
3. Intrapericardial bleed with cardiac tamponade
4. Hypovolemic shock or severe hypotension due to bleeding requiring pressors or surgery
5. Clinically overt or apparent bleeding associated with a decrease in Hgb of more than 50 g/L
6. Transfusion of 4 or more units (whole blood or packed red blood cells (PRBCs)) for bleeding

b. Major Bleed—Other is defined as any one of the following:

1. Significantly disabling (e.g., intraocular with permanent vision loss)
2. Clinically overt or apparent bleeding associated with a decrease in hemoglobin of 30 g/L (tetramer: 1.9 mmol/L, monomer: 0.465 mmol/L) to 50 g/L (3.1 mmol/L; 0.775 mmol/L)
3. Transfusion of 2-3 units (whole blood or PRBCs) for bleeding

c. Minor Bleed

Requires medical intervention to stop or treat bleeding (e.g., epistaxis requiring visit to medical facility for packing)

d. Minimal Bleed

All others (e.g., bruising, bleeding gums, oozing from injection sites, etc.) not requiring intervention or treatment.

6. RELY

a. Major bleeding is defined by ≥ 1 of the following criteria:

1. Bleeding associated with reduction in hemoglobin level of at least 2.0 g/L
2. Leading to transfusion of at least 2 units of blood or packed cells; or
3. Symptomatic bleeding in a critical area or organ such as intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding, or pericardial bleeding

Furthermore, major bleed is classified as life-threatening if they met ≥ 1 of the following criteria:

1. Fatal, symptomatic intracranial bleed;
2. Reduction in hemoglobin level of at least 5.0 g/L;
3. Transfusion of at least 4 U of blood or packed cells;
4. Associated with hypotension requiring the use of intravenous inotropic agents; or
5. Necessitated surgical intervention

b. Minor bleeds

Clinical bleeds that do not fulfill the criteria for major bleeds

7. ISTH

a. Major Bleed

- Fatal bleed

and/or

- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome

and/or

- Bleeding causing a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) or leading to transfusion of two or more units of whole blood or red cells

b. Minor Bleed

All non major bleeds will be considered minor bleeds. Minor bleeds will be further divided to those that are clinically relevant and those that are not

c. Clinically Relevant Minor Bleed

A clinically relevant minor bleed is an acute or subacute clinically overt bleed that does not meet the criteria for a major bleed but prompts a clinical response, in that it leads to at least one of the following:

- A hospital admission for bleeding
- **OR** a physician guided medical or surgical treatment for bleeding
- **OR** a change in antithrombotic therapy (including interruption or discontinuation of study drug)

8. ESTEEM

a. Major Bleeding must satisfy one or more of the following criteria:

- Fatal
- Clinically overt bleeding associated with a reduction in hemoglobin of at least 2 g/dL or leading to a transfusion of at least 2 units of blood or packed red blood cells
- Bleeding in areas of special concern such as: intraocular, intracranial, intraspinal, retroperitoneal, pericardial or atraumatic intra-articular bleeding

b. Minor bleeds must satisfy either

- Minor bleeds causing permanent stop of medication

or

- Other minor bleeds such as epistaxis, gingival bleeds, and microscopic hematuria

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