Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials

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Introduction

The purpose of this document is to provide a framework of definitions for cardiovascular and stroke endpoints 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 and stroke endpoints may change over time, as new biomarkers or other diagnostic tests become available, or as standards evolve and perceptions of clinical importance become modified.

Endpoint 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 endpoints in clinical 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 trials with cardiovascular outcomes 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 ten chapters. Each chapter provides the definition for a particular cardiovascular event.

CHAPTER 1. Definition of Cardiovascular Death

Cardiovascular death includes death resulting from an acute myocardial infarction (MI), sudden cardiac death, death due to heart failure (HF), death due to stroke, death due to cardiovascular (CV) procedures, death due to CV hemorrhage, and death due to other CV causes.

Classifying CV mortality more specifically (MI, sudden death etc.) is usually not needed for outcome trials. However, such classification is difficult because the classifications refer both to underlying cause (e.g., acute MI) and to mode of death (sudden/arrhythmic, progression of HF), and they overlap substantially. The following definitions can, however, be used if desired.

1. **Death due to Acute Myocardial Infarction** refers to a death by any cardiovascular mechanism (e.g., arrhythmia, sudden death, heart failure, stroke, pulmonary embolus, peripheral arterial disease) ≤ 30 days[1] after a MI related to the immediate consequences of the MI, such as progressive heart failure or recalcitrant arrhythmia. We note that there may be assessable mechanisms of cardiovascular death during this time period, but for simplicity, if the cardiovascular death occurs ≤ 30 days of the myocardial infarction, it will be considered a death due to myocardial infarction.

   Acute MI should be verified to the extent possible by the diagnostic criteria outlined for acute MI (see Chapter 4) or by autopsy findings showing recent MI or recent coronary thrombosis.

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

   Death resulting from an elective coronary procedure to treat myocardial ischemia (i.e., chronic stable angina) or death due to a MI that occurs as a direct consequence of a CV investigation/procedure/operation should be considered as a death due to a CV procedure.

[1] **The 30 day cut-off is arbitrary.**

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

   a. Death witnessed and occurring without new or worsening symptoms

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

   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.g., implantable cardioverter defibrillator (ICD) unresponsive sudden cardiac death, pulseless electrical activity arrest)

   e. Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or non-cardiac etiology

   f. Unwitnessed death in a subject seen alive and clinically stable ≤ 24 hours prior to being found dead without any evidence supporting a specific non-cardiovascular cause of death (information regarding the patient's clinical status preceding death should be provided, if available)

General Considerations

- Unless additional information suggests an alternate specific cause of death (e.g., Death due to Other Cardiovascular Causes), if a patient is seen alive ≤ 24 hours of being found dead, sudden cardiac death (criterion 2f) should be recorded. For patients who were not observed alive within 24 hours of death, undetermined cause of death should be recorded (e.g., a subject found dead in bed, but who had not been seen by family for several days).

3. **Death due to Heart Failure** refers to a death in association with clinically worsening symptoms and/or signs of heart failure regardless of HF etiology (see Chapter 7). Deaths due to heart failure can have various etiologies, including single or recurrent myocardial infarctions, ischemic or non-ischemic cardiomyopathy, hypertension, or valvular disease.

4. **Death due to Stroke** refers to death after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke (see Chapter 6).

5. **Death due to Cardiovascular Procedures** refers to death caused by the immediate complications of a cardiac procedure.

6. **Death due to Cardiovascular Hemorrhage** refers to death related to hemorrhage such as a non-stroke intracranial hemorrhage (see Chapter 6), non-procedural or non-traumatic vascular rupture (e.g., aortic aneurysm), or hemorrhage causing cardiac tamponade.

7. **Death due to Other Cardiovascular Causes** refers to a CV death not included in the above categories but with a specific, known cause (e.g., pulmonary embolism or peripheral arterial disease).

CHAPTER 2. Definition of Non-Cardiovascular Death

Non-cardiovascular death is defined as any death with a specific cause that is not thought to be cardiovascular in nature, as listed in Chapter 1. Detailed recommendations on the classification of non-CV 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-CV deaths. Any specific anticipated safety concern should be included as a separate cause of death. The following is a suggested list of non-CV causes of death:

- Pulmonary
- Renal
- Gastrointestinal
- Hepatobiliary
- Pancreatic
- Infection (includes sepsis)
- Inflammatory (e.g., Systemic Inflammatory Response Syndrome (SIRS) / Immune (including autoimmune) (may include anaphylaxis from environmental (e.g., food) allergies)
- Hemorrhage that is neither cardiovascular bleeding or a stroke (see Chapter 1, Section 6, and Chapter 6)
- Non-CV procedure or surgery
- Trauma
- Suicide
- Non-prescription drug reaction or overdose
- Prescription drug reaction or overdose (may include anaphylaxis)
- Neurological (non-cardiovascular)
- Malignancy
- Other non-CV, specify: _____

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 CV death or to a non-CV 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, most deaths should be classifiable as CV or non-CV, and the use of this category of death, therefore, should be discouraged and should apply to few 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 CV category (e.g., presumed CV death, specifically "death due to other CV 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 endpoint adjudication procedures and/or the statistical analysis plan.

CHAPTER 4. Definition of Myocardial Infarction: Please also see 2012 Third Universal 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, 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. In general, troponins are preferred. CK-MB should be used if troponins are not available, and total 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.

- **ECG manifestations of 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 contiguous leads with the cut-points: ≥ 0.1 mV in all leads other than leads V2-V3 where the following cut-points apply: ≥ 0.2 mV in men ≥ 40 years (≥ 0.25 mV in men < 40 years) or ≥ 0.15 mV in women.

  - 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 with prominent R wave or R/S ratio > 1.

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; V1-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.

- **ECG changes associated with 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

- **Criteria for prior myocardial infarction**

  Any one of the following criteria meets the diagnosis for prior MI:
  - Pathological Q waves with or without symptoms in the absence of non-ischemic causes
  - 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
  - Pathological findings of a prior myocardial infarction

CHAPTER 5. Definition of Hospitalization for Unstable Angina

Unstable angina requiring hospitalization is defined as

1. Ischemic discomfort (angina, or symptoms thought to be equivalent) ≥ 10 minutes in duration occurring
   - at rest, or
   - in an accelerating pattern with frequent episodes associated with progressively decreased exercise capacity.

AND

2. Prompting an unscheduled hospitalization **within 24 hours** of the most recent symptoms. Hospitalization is 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 change in calendar date if the hospital admission or discharge times are not available).

AND

3. At least one of the following:

   a. New or worsening ST or T wave changes on resting ECG (in the absence of confounders, such as LBBB or LVH)

      - Transient ST elevation (duration < 20 minutes)
        New ST elevation at the J point in two contiguous leads with the cut-points: ≥ 0.1 mV in all leads other than leads V2-V3 where the following cut-points apply:
        ≥ 0.2 mV in men ≥ 40 years (≥ 0.25 mV in men < 40 years) or
        ≥ 0.15 mV in women.

      - 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 ≥ 0.3 mV in two contiguous leads with prominent R wave or R/S ratio > 1.

   b. Definite evidence of inducible myocardial ischemia as demonstrated by:
      - an early positive exercise stress test, defined as ST elevation or ≥ 2 mm ST depression prior to 5 mets

      OR
      - stress echocardiography (reversible wall motion abnormality) **OR**
      - myocardial scintigraphy (reversible perfusion defect), **OR**
      - MRI (myocardial perfusion deficit under pharmacologic stress).

and believed to be responsible for the myocardial ischemic symptoms/signs.

c. Angiographic evidence of new or worse ≥ 70% lesion (≥ 50% for left main 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) for the presumed culprit lesion(s). This criterion would be fulfilled if revascularization was undertaken during the unscheduled hospitalization, or subsequent to transfer to another institution without interceding home discharge.

AND

4. Negative cardiac biomarkers and no evidence of acute MI

General Considerations

1. Escalation of pharmacotherapy for ischemia, such as intravenous nitrates or increasing dosages of β-blockers, should be considered supportive but not diagnostic 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 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 hospitalization or rehospitalization for performance of an elective revascularization in patients who do not fulfill the criteria for unstable angina should not be considered a hospitalization for unstable angina. For example,

   - Hospitalization of a patient with stable exertional angina for coronary angiography and PCI that is prompted by a positive outpatient stress test should not be considered hospitalization for unstable angina.

   - Rehospitalization of a patient meeting the criteria for unstable angina who was stabilized, discharged, and subsequently readmitted for revascularization, does not constitute a second 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 endpoint.

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.

The distinction between a Transient Ischemic Attack and an Ischemic Stroke is the presence of infarction. Persistence of symptoms is an acceptable indicator of acute infarction. Thus, duration of symptom persistence that will be used to distinguish between transient ischemia and acute infarction should be defined for any clinical trial in which it is used.

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.

Subdural hematomas are intracranial hemorrhagic events and not strokes.

Transient Ischemic Attack

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

Stroke

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

Classification:

A. Ischemic Stroke

Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by 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 intraparenchymal, intraventricular, or subarachnoid hemorrhage.

C. Undetermined Stroke

Undetermined stroke is defined as an acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as A or B.

Stroke Disability

Disability should be measured by a reliable and valid scale in all cases, typically at each visit and 90 days after the event. 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

CHAPTER 7. Definition of Heart Failure Event

A **Heart Failure Event** includes hospitalization for heart failure and may include urgent outpatient visits. HF hospitalizations should remain delineated from urgent visits. If urgent visits are included in the HF event endpoint, the number of urgent visits needs to be explicitly presented separately from the hospitalizations.

A Heart Failure Hospitalization is defined as an event that meets **ALL** of the following criteria:

1) The patient is admitted to the hospital with a primary diagnosis of HF

2) The patient's length-of-stay in hospital extends for at least 24 hours (or a change in calendar date if the hospital admission and discharge times are unavailable)

3) The patient exhibits documented new or worsening symptoms due to HF on presentation, including **at least ONE** of the following:

    a. Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea)
    b. Decreased exercise tolerance
    c. Fatigue
    d. Other symptoms of worsened end-organ perfusion or volume overload (must be specified and described by the protocol)

4) The patient has objective evidence of new or worsening HF, consisting of **at least TWO** physical examination findings **OR** one physical examination finding and **at least ONE** laboratory criterion), including:

    a. Physical examination findings considered to be due to heart failure, including new or worsened:

        i. Peripheral edema
        ii. Increasing abdominal distention or ascites (in the absence of primary hepatic disease)
        iii. Pulmonary rales/crackles/crepitations
        iv. Increased jugular venous pressure and/or hepatojugular reflux
        v. S_3 gallop
        vi. Clinically significant or rapid weight gain thought to be related to fluid retention

b. Laboratory evidence of new or worsening HF, if obtained within 24 hours of presentation, including:

i. Increased B-type natriuretic peptide (BNP)/ N-terminal pro-BNP (NT-proBNP) concentrations consistent with decompensation of heart failure (such as BNP > 500 pg/mL or NT-proBNP > 2,000 pg/mL). In patients with chronically elevated natriuretic peptides, a significant increase should be noted above baseline.

ii. Radiological evidence of pulmonary congestion

iii. Non-invasive diagnostic evidence of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output. For example, echocardiographic criteria could include: E/e' > 15 or D-dominant pulmonary venous inflow pattern, plethoric inferior vena cava with minimal collapse on inspiration, or decreased left ventricular outflow tract (LVOT) minute stroke distance (time velocity integral (TVI))

OR

iv. Invasive diagnostic evidence with right heart catheterization showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥ 18 mmHg, central venous pressure ≥ 12 mmHg, or a cardiac index < 2.2 L/min/m^2

Note: All results from diagnostic tests should be reported, if available, even if they do not meet the above criteria, because they provide important information for the adjudication of these events.

5) The patient receives initiation or intensification of treatment specifically for HF, including **at least ONE** of the following:

a. Augmentation in oral diuretic therapy
b. Intravenous diuretic or vasoactive agent (e.g., inotrope, vasopressor, or vasodilator)
c. Mechanical or surgical intervention, including:
   i. Mechanical circulatory support (e.g., intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation, total artificial heart)
   ii. Mechanical fluid removal (e.g., ultrafiltration, hemofiltration, dialysis)

An **Urgent Heart Failure Visit** is defined as an event that meets all of the following:

1) The patient has an urgent, unscheduled office/practice or emergency department visit for a primary diagnosis of HF, but not meeting the criteria for a HF hospitalization
2) All signs and symptoms for HF hospitalization (i.e., 3) symptoms, 4) physical examination findings/laboratory evidence of new or worsening HF, as indicated above) must be met
3) The patient receives initiation or intensification of treatment specifically for HF, as detailed in the above section with the exception of oral diuretic therapy, which will not be sufficient

CHAPTER 8. Interventional Cardiology Definitions

A. Clinical Definitions

1. **Clinically-Driven Target Lesion Revascularization:** Revascularization is clinically-driven if the target lesion diameter stenosis is > 50% by quantitative coronary angiography (QCA) and the subject has 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 (electrocardiographic changes) or during exercise test (or equivalent), presumably related to the target vessel
   c. Abnormal results of any invasive functional diagnostic test [e.g., coronary flow reserve (CFR) or fractional flow reserve (FFR)]

   Comment: *Target lesion revascularization of a > 70% diameter stenosis by QCA in the absence of the above signs or symptoms may be considered clinically-driven.*

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

2. **Non-Target Lesion and Non-Target Lesion Revascularization:** A lesion for which revascularization is not attempted or one in which revascularization is performed using a non-study device, respectively.

3. **Non-Target Vessel and Non-Target Vessel Revascularization:** A vessel for which revascularization is not attempted or one in which revascularization is performed using a non-study device, respectively.

4. **Percutaneous Coronary Intervention (PCI) Status:**

   a. Elective: The procedure can be performed on an outpatient basis or during a subsequent hospitalization without significant risk of myocardial infarction (MI) or death. For stable in-patients, the procedure is being performed during this hospitalization for convenience and ease of scheduling and **NOT** because the patient's clinical situation demands the procedure prior to discharge.

   b. Urgent: The procedure should be performed on an inpatient basis and prior to discharge because of significant concerns that there is risk of myocardial ischemia, MI, and/or death. Patients who are outpatients or in the emergency department at the time that the cardiac catheterization is requested would warrant hospital admission based on their clinical presentation.

589 c. **Emergency:** The procedure should be performed as soon as possible because of
590 substantial concerns that ongoing myocardial ischemia and/or MI could lead to death.
591 "As soon as possible" refers to a patient who is of sufficient acuity that one would
592 cancel a scheduled case to perform this procedure immediately in the next available
593 room during business hours, or one would activate the on-call team were this to occur
594 during off-hours.
595
596 d. **Salvage:** The procedure is a last resort. The patient is in cardiogenic shock when the
597 PCI begins (i.e., the time at which the first guide wire or intracoronary device is
598 introduced into a coronary artery or bypass graft for the purpose of mechanical
599 revascularization) **OR** within the last ten minutes prior to the start of the case or
600 during the diagnostic portion of the case, the patient has also received chest
601 compressions or has been on unanticipated circulatory support (e.g., intra-aortic
602 balloon pump, extracorporeal membrane oxygenation, or cardiopulmonary support).
603
604 5. **Percutaneous Coronary Intervention (PCI):** Placement of an angioplasty guide wire,
605 balloon, or other device (e.g., stent, atherectomy catheter, brachytherapy delivery device,
606 or thrombectomy catheter) into a native coronary artery or coronary artery bypass graft
607 for the purpose of mechanical coronary revascularization. In the assessment of the
608 severity of coronary lesions with the use of intravascular ultrasound, coronary flow
609 reserve (CFR), or fractional flow reserve (FFR), insertion of a guide wire will **NOT** be
610 considered PCI.
611
612 6. **Procedural Success:** Achievement of < 30 % residual diameter stenosis of the target
613 lesion assessed by visual inspection or QCA and no in-hospital major adverse cardiac
614 events (MACE, a composite of death, MI, or repeat coronary revascularization of the
615 target lesion). Ideally, the assessment of the residual stenosis at the end of the procedure
616 should be performed by an angiographic core laboratory.
617
618 ***Comment:*** *For some device interventions (e.g., balloon angioplasty), achievement of*
619 *< 50% diameter stenosis by visual inspection or QCA is an acceptable definition for*
620 *procedural success.*
621
622 7. **Target Lesion:** Any lesion treated or attempted to be treated during the PCI with the
623 study device. The target lesion includes the arterial segment treated with the study device
624 (stent, in most cases) plus 5 mm proximal and 5 mm distal to the treatment site.
625
626 8. **Target Lesion Failure (TLF):** The composite of ischemia-driven revascularization of
627 the target lesion, MI related to the target vessel, or cardiac death related to the target
628 vessel. If it cannot be determined with certainty whether the MI or death was related to
629 the target vessel, it is considered a TLF.
630

9. **Target Lesion Revascularization (TLR):** Any repeat percutaneous intervention of the target lesion (including 5 mm proximal and 5 mm 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 CEC for review upon request.

10. **Target Vessel:** A major native coronary artery (e.g., left main coronary artery, left anterior descending coronary artery, left circumflex coronary artery, or right coronary artery) or bypass graft containing the target lesion. A native coronary artery target vessel includes the arterial segments upstream and downstream to the target lesion plus major side branches.

11. **Target Vessel Failure (TVF):** The composite of ischemia-driven revascularization of the target vessel, MI related to the target vessel, or cardiac death related to the target vessel. If it cannot be determined with certainty whether the MI or death was related to the target vessel, it is considered a TVF.

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

13. **Target Vessel Revascularization (TVR):** 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 upon request.

14. **Vascular Complications**:
    - **Access site hematoma**: Development of a new, localized collection of blood at a vascular access site sufficient to produce a palpable mass within 72 hours of a procedure.
    - **Arteriovenous fistula:** Development of a new, unintended communication between an artery and a vein occurring at a vascular access site within 72 hours of a procedure.
    - **Peripheral ischemia:** Development of new arterial insufficiency sufficient to produce clinical signs or symptoms of ischemia (pallor, pain, paresthesia) distal to a vascular access site within 72 hours of a procedure.
    - **Peripheral nerve injury:** Development of new sensory or motor loss of peripheral nerve function from external nerve compression (e.g., as a result of positioning during a procedure), or internal compression or direct nerve damage from the procedure, occurring within 72 hours of a procedure.
    - **Pseudoaneurysm:** Development of a new localized collection of blood with a persistent communication (neck) originating at a vascular access site and occurring within 72h of a procedure.
    - **Retroperitoneal hemorrhage:** Development of new bleeding into the retroperitoneal space originating at a vascular access site and occurring within 72 hours of a procedure.

678 **B. Angiographic Definitions**
679
680 **1. Abrupt Closure**: New intra-procedural severely reduced flow (TIMI grade 0-1) within
681 the target vessel that persists and requires intervention by stenting or other treatment, or
682 results in MI or death. Abrupt closure requires an association with a vascular dissection,
683 thrombus, or severe spasm at the treatment site or within the instrumented vessel.
684
685 **2. Coronary Lesions Treated**
686

Coronary Artery Segments	Definition
Right coronary artery ostium	Origin of the right coronary artery, including the first 3 mm of the artery
Proximal right coronary artery	Proximal portion of the right coronary artery, from the ostium of the right coronary artery to the origin of the first right ventricular branch (pRCA)
Mid right coronary artery	Middle portion of the right coronary artery, from the origin of the first right ventricular branch to the acute margin (mRCA)
Distal right coronary artery	Distal portion of the right coronary artery, from the acute margin to the origin of the posterior descending artery (dRCA)
Right posterior descending artery	In right dominant and mixed circulations, the vessel that runs in the posterior interventricular groove and supplies septal perforator branches (PDA)
Posterolateral segmental artery	In right dominant circulations, the distal continuation of the right coronary artery in the posterior atrioventricular groove after the origin of the right posterior descending artery (PLSA)
First right posterolateral branch	In right dominant circulations, the first posterolateral branch originating from the right posterior atrioventricular artery (RPL1)
Second right posterolateral branch	In right dominant circulations, the second posterolateral branch originating from the right posterior atrioventricular artery (RPL2)
Third right posterolateral branch	In right dominant circulations, the third posterolateral branch originating from the right posterior atrioventricular artery (RPL3)
Posterior descending septal perforator	Septal perforator vessel originating from the posterior descending artery
Right ventricular branch	Branch arising from the right coronary artery to supply the right ventricular wall (RV)
Left main coronary artery ostium	Origin of the left coronary artery, including the first 3 mm of the artery
Left main coronary artery body	Body of the left main coronary artery, from the

Coronary Artery Segments	Definition
	ostium to the bifucation (LM)
Left main coronary artery bifucation	Distal end of the left main, including the terminal 3 mm through the bifurcation of the left main into the left anterior descending and left circumflex arteries
Left anterior descending artery ostium	Origin of the left anterior descending coronary artery, including the first 3 mm of the artery
Proximal left anterior descending artery	Proximal portion of the left anterior descending coronary artery, from the ostium to the origin of the first septal (pLAD)
Mid left anterior descending artery	Middle portion of the left anterior descending coronary artery, from the origin of the first septal artery to the origin of the third septal artery (mLAD)
Distal left anterior descending artery	Distal portion of the left anterior descending coronary artery, from the origin of the third septal artery to the terminus (dLAD)
First diagonal branch	First of the three longest branches originating from the left anterior desending artery to supply the anterolateral wall of the left ventricle (D1)
First diagonal lateral branch	Branch of the first diagonal branch
Second diagonal branch	Second of the three longest branches originating from the left anterior desending artery to supply the anterolateral wall of the left ventricle (D2)
Second diagonal lateral branch	Branch of the second diagonal branch
Third diagonal branch	Third of the three longest branches originating from the left anterior desending artery to supply the anterolateral wall of the left ventricle (D3)
Third diagonal lateral branch	Branch of the third diagonal branch
Anterior descending septal perforator	Septal perforator vessel originating from the left anterior descending artery to supply the interventricular septum
Left circumflex artery ostium	Origin of the left circumflex coronary artery, including the first 3 mm of the artery
Proximal left circumflex artery	Proximal portion of the left circumflex coronary artery, from the ostium to the origin (or the nominal location of) the first marginal branch (pLCX)
Mid left circumflex artery	Middle portion of the left circumflex coronary artery, from the origins of (or nominal locations of) the first marginal to the second marginal (mLCX)
Distal left circumflex artery	Distal portion of the left circumflex coronary artery, from the origin of (or the nominal location of) the second marginal to the terminus

Coronary Artery Segments	Definition
	(in right dominant systems), or to the origin of the 1st left posterolateral in all other dominance systems (dLCX)
First obtuse marginal branch	First of the three longest branches originating from the left circumflex artery to supply the laterall wall of the left ventricle (OM1)
First obtuse marginal lateral branch	Branch of the first marginal branch
Second obtuse marginal branch	Second of the three longest branches originating from the left circumflex artery to supply the laterall wall of the left ventricle (OM2)
Second obtuse marginal lateral branch	Branch of the second marginal branch
Third obtuse marginal branch	Third of the three longest branches originating from the left circumflex artery to supply the laterall wall of the left ventricle (OM3)
Third obtuse marginal lateral branch	Branch of the third marginal branch
Left atrioventricular artery	In left dominant and mixed circulations, the distal continuation of the left circumflex coronary artery in the posterior atrioventricular groove
Left posterior descending artery	In left dominant circulations, the vessel that arises from the distal continuation of the left atrioventricular artery, travels in the posterior interventricular groove, and supplies septal perforator branches (LPDA)
First left posterolateral branch	In left dominant and mixed circulations, the first posterolateral branch originating from the posterior atrioventricular left circumflex artery (LPL1)
Second left posterolateral branch	In left dominant and mixed circulations, the second posterolateral branch originating from the posterior atrioventricular left circumflex artery (LPL2)
Third left posterolateral branch	In left dominant and mixed circulations, the third posterolateral branch originating from the posterior atrioventricular left circumflex artery (LPL3)
Ramus intermedius branch	Branch vessel whose origin bisects the origins of the left anterior descending and circumflex arteries (RI)
Ramus intermedius lateral branch	Branch of the ramus intermedius branch

3. **Dissection:**

   Based on the National Heart, Lung, and Blood Institute (NHLBI) Dissection Classification System:
   - **Grade A:** Minor radiolucencies within the lumen during contrast injection with no persistence after dye clearance
   - **Grade B:** Parallel tracts or double lumen separated by a radiolucent area during contrast injection with no persistence after dye clearance
   - **Grade C:** Extraluminal cap with persistence of contrast after dye clearance from the lumen
   - **Grade D:** Spiral luminal filling defect with delayed but complete distal flow
   - **Grade E:** New persistent filling defect with delayed antegrade flow
   - **Grade F:** Non-A-E types with total coronary occlusion and no distal antegrade flow

   Note: Grade E and F dissections may represent thrombus

4. **Late Loss:** Minimum lumen diameter (MLD) assessed at follow-up angiography minus the MLD assessed immediately after the index procedure. MLDs are measured by QCA.

5. **Minimum Lumen Diameter (MLD):** The mean minimum lumen diameter (typically measured in-lesion, in-stent, and in-segment) derived from two orthogonal views by QCA.

6. **No Reflow:** An acute reduction in coronary flow (TIMI grade 0-1) in the absence of dissection, thrombus, spasm, or high-grade residual stenosis at the original target lesion.

7. **Percent Diameter Stenosis (% DS):** The value calculated as 100 x (1 – MLD/RVD) using the mean values determined by QCA from two orthogonal views (when possible).

8. **Reference Vessel Diameter (RVD):** Defined as the average of normal segments within 10 mm proximal and 10 mm distal to the target lesion from two orthogonal views using QCA.

9. **Restenosis:** Re-narrowing of the vessel following the treatment of a prior stenosis

   - **Binary restenosis:** A diameter stenosis of > 50% at the previously treated lesion site, including the originally treated site plus the adjacent vascular segments 5 mm proximal and 5 mm distal to the site.

   - **In-stent restenosis (ISR):** A previously stented lesion with a > 50% diameter. stenosis.

10. **Thrombus (Angiographic):** A discrete, mobile, intraluminal filling defect with defined borders with or without associated contrast staining.

11. **TIMI (Thrombolysis in Myocardial Infarction) Flow Grades:**

    - **Grade 0 (no perfusion):** There is no antegrade flow beyond the point of occlusion.

    - **Grade 1 (penetration without perfusion):** The contrast material passes beyond the area of obstruction but "hangs up" and fails to opacify the entire coronary bed distal to the obstruction for the duration of the cineangiographic filming sequence.

    - **Grade 2 (partial perfusion):** The contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. However, the rate of entry of contrast material into the vessel distal to the obstruction or its rate of clearance from the distal bed (or both) is perceptibly slower than its entry into or clearance from comparable areas not perfused by the previously occluded vessel (e.g., the opposite coronary artery or the coronary bed proximal to the obstruction).

    - **Grade 3 (complete perfusion):** Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction and clearance of contrast material from the involved bed is as rapid as from an uninvolved bed in the same vessel or the opposite artery..

12. **Vessels**
    - Left main coronary artery (LMCA)
    - Left anterior descending artery (LAD) with septal and diagonal branches
    - Left circumflex artery (LCX) with obtuse marginal branches
    - Ramus intermedius artery
    - Right coronary artery (RCA) and any of its branches
    - Posterior descending artery
    - Saphenous vein bypass graft(s)
    - Arterial bypass graft(s): Right internal mammary graft, left internal mammary graft, radial artery graft, and gastroepiploic artery graft.

CHAPTER 9. Definition of Peripheral Vascular Intervention

1. **Peripheral Vascular Intervention (PVI):** Peripheral vascular intervention[2] is a catheter-based or open surgical procedure designed to improve arterial or venous blood flow or otherwise modify or revise vascular conduits. Procedures may include, but are not limited to, percutaneous transluminal balloon angioplasty, stent placement, thrombectomy, embolectomy, atherectomy, dissection repair, aneurysm exclusion, treatment of dialysis conduits, placement of various devices, intravascular thrombolysis or other pharmacotherapies, and open surgical bypass or revision.

   In general, the intention to perform *percutaneous* peripheral vascular intervention is denoted by the insertion of a guide wire into a peripheral artery or vein.

   The target vessel(s) and the type of revascularization procedure (e.g., surgical bypass, thrombectomy, endarterectomy, percutaneous transluminal angioplasty, stent placement, thromboembolectomy, and thrombolysis) should be specified and recorded. For the sake of simplicity, this definition applies to the extracranial carotid artery and other non-cardiac arteries and veins and excludes the intracranial vessels and lymphatics.

2. **Procedural Success:** In the case of percutaneous intervention for obstructive lesions, procedural success is defined as the achievement of a satisfactory final residual diameter stenosis by angiography at the end of the procedure (and without flow limiting dissection or hemodynamically significant translesional pressure gradient). The specific parameter for final percent residual stenosis is typically between < 30% and < 50%; selection of the appropriate percentage may vary depending upon the specific intervention applied, the vascular territory, and anticipated or desired therapeutic response. Procedural success also implies absence of in-hospital major adverse events (e.g., death, stroke, myocardial infarction, acute onset of limb ischemia, need for urgent/emergent vascular surgery, and other procedure-specific major adverse events). The balloon inflation, stent placement, or other therapeutic intervention may be preceded by use of adjunctive devices (e.g., percutaneous mechanical thrombectomy, directional or rotational atherectomy, laser, and chronic total occlusion crossing device), as predefined in the protocol.

3. **Procedural Status: Non-Elective and Elective:**

   a. **Non-Elective:** Non-elective procedures include emergent and urgent procedures. A non-elective procedure is a procedure that is performed without delay, because there is clinical consensus that the procedure should occur imminently. Non-elective procedures imply a degree of instability of the patient, urgency of the medical condition, or instability of the threatening lesion.

[2] **We note that peripheral vascular disease includes veins, arteries, and lymphatics. However, for simplicity, this definition will focus on peripheral artery and venous interventions.**

- **Emergent:** A procedure that is performed immediately because of the acute nature of the medical condition (e.g., acute limb ischemia, acute aortic dissection), and the increased morbidity or mortality associated with a temporal delay in treatment.

- **Urgent:** An urgent procedure is one that is not an emergency but is required to be performed on a timely basis (≤ 24 hrs) (e.g., a patient who has been stabilized following initial treatment of acute limb ischemia, and there is clinical consensus that a definitive procedure should occur within the next 24 hours).

b. Elective: An elective procedure is one that is scheduled and is performed on a patient with stable disease, or in whom there is no urgency and/or increased morbidity or mortality associated with a planned procedure.

4. Target Lesion: A target lesion is any vascular segment treated or attempted to be treated during the trial procedure with the index device. The target lesion is the treated segment starting 10 mm proximal and ending 10 mm distal to the index device or therapy (stent, balloon, atherectomy catheter, or aortic stent-graft).

5. Target Vessel: A target vessel is any vessel (e.g., non-cardiac or non-intracranial) that contains the target lesion treated with the study device. The target vessel includes the target lesion as well as the entire length of native vessel upstream and downstream from the target lesion, including side branches. For the arteries of the leg, the vasculature is divided into 3 vessel "levels:" aorto-iliac, femoral-popliteal, and tibial-crural.

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

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

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

9. Target Lesion Revascularization (TLR): Target lesion revascularization is any repeat intervention of the target lesion (including 10 mm proximal and 10 mm distal to the index device, as target lesion is defined above) or surgical intervention/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). Angiograms (and core laboratory assessment thereof) and other source documentation should be made available to the CEC for review upon request.

10. **Target Vessel Revascularization (TVR):** Target vessel revascularization is any repeat 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). Angiograms (and core laboratory assessment thereof) and other source documentation should be made available to the CEC for review upon request.

11. **Clinically-Driven Target Lesion Revascularization:** Clinically-driven target lesion revascularization is defined as target lesion revascularization performed due to target lesion diameter stenosis > 50% **AND** either evidence of clinical or functional ischemia (e.g. recurrent/progressive intermittent claudication, critical limb ischemia) **OR** recurrence of the clinical syndrome for which the initial procedure was performed. Clinically-driven target lesion revascularization occurs in the absence of protocol-directed surveillance ultrasound or angiography.

12. **Vessel Patency:** Vessel patency at a given time point will be determined by the absence of clinically-driven target lesion revascularization and/or absence of recurrent target lesion diameter stenosis > 50% by imaging (e.g., invasive angiography or most commonly, duplex ultrasonography). If patency data are incorporated within the primary endpoint of a clinical trial, the angiographic images or duplex ultrasonographic images should be assessed by appropriate core laboratories and made available to the CEC for review upon request.

13. **Restenosis:** Re-narrowing of the artery following the treatment of a prior stenosis

    - **Binary restenosis:** A diameter stenosis of > 50% at the previously treated lesion site, including the originally treated site plus the adjacent vascular segments 10 mm proximal and 10 mm distal to the site (or as otherwise defined by the protocol, as noted above).

    - **In-stent restenosis (ISR):** A previously stented lesion that has > 50% diameter stenosis.

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 pathological confirmation:

a. Angiographic confirmation of stent thrombosis[3]

- The presence of a thrombus[4] that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48-hour time window:
  - Acute onset of ischemic symptoms at rest
  - New ischemic ECG changes that suggest acute ischemia
  - Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI)

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

[4]**Intracoronary thrombus**

- Nonocclusive thrombus
  Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 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

- Occlusive thrombus
  TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch).

b. Pathological 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

Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:

a. Any unexplained death within the first 30 days[5]

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

3. Possible Stent Thrombosis

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

[5]For studies with ST-elevation MI population, one may consider the exclusion of unexplained death within 30 days as evidence of probable stent thrombosis

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