SUPPLEMENTARY METHODS

All cardiovascular endpoint definitions are based on the draft standardized definitions for cardiovascular and stroke endpoints for clinical trials for Clinical Data Interchange Standard Consortium (CDISC) [14].

Cardiovascular endpoints

Death from any cause

1) Cardiovascular death

Cardiovascular death includes the following categories.

(1) Death due to acute myocardial infarction

Death occurring within 30 days after a myocardial infarction (MI), related to the consequences of the acute event such as progressive congestive heart failure (CHF), inadequate cardiac output, or refractory arrhythmias. If these events occur after a period of 'stability' (e.g., without CHF or arrhythmias), the immediate cause should be specified. Acute MI should be confirmed by diagnostic criteria (including post-mortem findings indicative of recent MI or coronary thrombosis) and should not have decisive evidence for another cause of death. Sudden and unexpected cardiac death with symptoms suggestive of myocardial ischemia, accompanied by new ST-segment elevation or new left bundle branch block (LBBB), and/or new thrombus evidence on angiography or autopsy, should be considered death due to acute MI if it occurs before blood samples for biomarkers could be obtained or before cardiac biomarkers appear in the blood. Death due to a procedure intended to treat myocardial ischemia or complications of MI is also considered death due to acute MI. If death occurs before biochemical confirmation of myocardial necrosis, clinical symptoms and electrocardiography (ECG) evidence should be used for diagnosis.

(2) Sudden cardiac death

Includes witnessed deaths that occur immediately and unexpectedly without new or worsening symptoms, within 60 minutes of the onset of cardiac symptoms, due to documented arrhythmia (recorded on ECG or witnessed by medical staff, emergency personnel, or found on review of implantable cardioverter-defibrillator data), following unsuccessful resuscitation from cardiac arrest, or following successful resuscitation with no identified non-cardiac cause within 24 hours.

(3) Death due to heart failure or cardiogenic shock

Death in the context of worsening clinical symptoms and/or signs of heart failure (HF), not following acute MI and with no evidence of another cause. Worsening symptoms or signs of CHF may include the need for new or increased HF treatment, continuous intravenous (IV) therapy or oxygen for HF symptoms, bed rest primarily due to HF symptoms, sufficient pulmonary edema to cause distress, or cardiogenic shock not resulting from acute MI or arrhythmias. Cardiogenic shock is defined by systolic blood pressure (SBP) <90 mm Hg for >1 hour despite fluid resuscitation or correction of arrhythmia, presumed due to cardiac dysfunction and associated with signs of hypoperfusion, such as cold, clammy skin, oliguria (<30 mL/hour), altered mental status, or cardiac index <2.2 L/min/m^2. Cardiogenic shock can also be defined as SBP ≥90 mm Hg achieved within 1 hour using inotropic/vasopressor agents and/or mechanical assist devices. This category includes sudden death during hospitalization for worsening HF.

(4) Death due to stroke

Death due to cerebrovascular disease resulting in deficits leading to death generally within 30 days. The cerebrovascular event must be confirmed by diagnostic criteria (including post-mortem findings) and without evidence of another cause of death.

(5) Death due to cardiovascular hemorrhage

Deaths related to non-stroke intracranial hemorrhage, non-procedural or non-traumatic vascular rupture (e.g., aortic aneurysm), or tamponade-producing bleeding.

(6) Other cardiovascular causes

Includes deaths not fitting the above categories but with a clear cardiovascular cause (e.g., pulmonary embolism or peripheral arterial disease).

2) Non-cardiovascular death

Non-cardiovascular death is defined as any death not fitting the cardiovascular death categories and includes:

- Respiratory failure
- Renal
- Gastrointestinal disease
- Hepatobiliary or pancreatic disease
- Infection (including sepsis)
- Inflammatory conditions (e.g., systemic inflammatory response syndrome)

- Immune conditions (including autoimmune and environmental anaphylaxis)
- Non-cardiovascular bleeding
- Non-cardiovascular surgical causes
- Trauma
- Suicide
- Overdose (prescription or non-prescription drugs)
- Neurological causes (non-cardiovascular)
- Malignancy
- Other specified causes

3) Undetermined cause of death

An undetermined cause of death applies when the death cannot be classified as cardiovascular or non-cardiovascular due to insufficient information (e.g., the only information available is 'patient died'). Most deaths should be classifiable as cardiovascular or non-cardiovascular, and the use of this category should be minimal and only in well-operated clinical trials.

Non-fatal myocardial infarction

1) Definition of MI

Clinical Event Adjudication (CEA) will use the third universal MI definition [13] as study specific MI criteria during adjudication.

2) Criteria for acute MI

Acute MI should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Diagnosis is made if one of the following criteria is met:

(1) Detection of cardiac biomarkers (preferably cardiac troponin [cTn]) with at least one value above the 99th percentile upper reference limit (URL) and at least one of the following:
- Symptoms of ischemia
- New or presumed new significant ST-T changes or new LBBB
- Development of pathological Q waves on ECG
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- Identification of an intracoronary thrombus by angiography or autopsy

(2) Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB but death before biomarkers were obtained or before they appear in the blood.

(3) Percutaneous coronary intervention (PCI)-related MI defined as cTn values >5 times the 99th percentile URL in patients with normal baseline values or a rise of cTn values >20% if the baseline is elevated and stable or falling, with additional evidence of myocardial ischemia.

(4) Stent thrombosis associated with MI as detected by coronary angiography or autopsy in the setting of myocardial ischemia with an increase and/or decrease of cardiac biomarkers above the 99th percentile URL.

(5) Coronary artery bypass graft (CABG)-related MI defined as cTn values >10 times the 99th percentile URL in patients with normal baseline values, with additional evidence of myocardial ischemia.

3) Prior MI criteria

Diagnosis of prior MI is made if any of the following criteria are met:

(1) Pathological Q waves with or without symptoms in the absence of a non-ischemic cause

(2) Imaging evidence of a region of myocardial loss in the absence of a non-ischemic cause

(3) Pathological findings of a prior MI

4) Universal classification of MI

The CEA will use the following classification for MI:

(1) Type 1: Spontaneous MI related to ischemic imbalance

(2) Type 2: MI secondary to ischemic imbalance

(3) Type 3: MI resulting in death when biomarker values are unavailable

(4) Type 4a: MI related to PCI

(5) Type 4b: MI related to stent thrombosis

(6) Type 5: MI related to CABG

Non-fatal stroke

1) Definition of stroke

Stroke is defined as an acute neurological dysfunction of vascular origin with evidence of infarction or hemorrhage on imaging (e.g., computed tomography or magnetic resonance imaging [MRI]) or confirmed by autopsy.

2) Criteria for stroke

A stroke diagnosis requires meeting the following four criteria:

(1) Rapid onset of focal/global neurological deficit with at least one of the following:
- Change in the level of consciousness
- Change in the modified Rankin Scale

- Hemiplegia
- Hemiparesis
- Sensory loss on one side of the body
- Aphasia
- Hemianopia
- Transient monocular blindness
- Other new neurological signs/symptoms consistent with stroke

(2) Neurological deficit lasting ≥24 or <24 hours if associated with one of the following therapeutic interventions:
- Pharmacologic (e.g., thrombolytic therapy)
- Non-pharmacologic (e.g., neurointervention)

(3) Imaging evidence of new hemorrhage or infarction
(4) No other clear, non-stroke cause (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion)

3) Stroke classification
Strokes should be classified as:
(1) Primary ischemic stroke
- Infarction due to thrombosis or embolism impairing central nervous system perfusion, with or without hemorrhagic transformation.

(2) Primary hemorrhagic stroke
- Intracranial hemorrhage into parenchymal tissue or subarachnoid space documented by imaging, lumbar puncture, surgery, or autopsy.

(3) Unspecified stroke
- When stroke type cannot be determined by imaging or other means but meets the diagnostic criteria for stroke, it is classified as ischemic for research purposes.

Hospitalization for unstable angina
Hospitalization for unstable angina 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:
(1) New or worsening ST or T wave changes on resting ECG (in the absence of confounders, such as LBBB or left ventricular hypertrophy)
- Transient ST elevation (duration <20 minutes)
- ST depression and T wave changes

(2) 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 metabolic equivalents, 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.

(3) Angiographic evidence of new or worse ≥70% lesion and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischemic symptoms/signs.
(4) 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

Hospitalization for heart failure
1) Hospitalization due to heart failure
A HF 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 the 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 upon presentation, including at least one of the following: ① Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal

dyspnea); ② Decreased exercise tolerance; ③ Fatigue; ④ Other symptoms of worsened end-organ perfusion or volume overload (as determined by the medical judgement of the investigator).

(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: ① Physical examination findings indicative of HF, including new or worsened (peripheral edema; increasing abdominal distention or ascites [in the absence of primary hepatic disease]; pulmonary rales/crackles/crepitations; increased jugular venous pressure and/or hepatojugular reflux; S3 gallop; clinically significant or rapid weight gain thought to be related to fluid retention); ② Laboratory evidence of new or worsening HF, obtained within 24 hours of presentation, including (increased B-type natriuretic peptide [BNP] or N-terminal pro-BNP [NT-proBNP] concentrations consistent with decompensation of HF [e.g., BNP >500 pg/mL or NT-proBNP >2,000 pg/mL]—In patients with chronically elevated natriuretic peptides, a significant increase above baseline should be noted; radiological evidence of pulmonary congestion; 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 minute stroke distance [time velocity integral]; or invasive diagnostic evidence with right heart catheterization showing a pulmonary capillary wedge pressure [pulmonary artery occlusion pressure] ≥18 mm Hg, central venous pressure ≥12 mm Hg, or a cardiac index <2.2 L/min/m^2).

(5) The patient receives initiation or intensification of treatment specifically for HF, including at least one of the following: ① Augmentation of oral diuretic therapy; ② IV diuretic or vasoactive agent (e.g., inotrope, vasopressor, or vasodilator); ③ Mechanical or surgical intervention, including mechanical circulatory support (e.g., intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation, total artificial heart) and mechanical fluid removal (e.g., ultrafiltration, hemofiltration, dialysis).

Coronary or peripheral revascularization

1) Percutaneous coronary intervention status

(1) Elective

The procedure can be performed on an outpatient basis or during a subsequent hospitalization without significant risk of MI or death. For stable inpatients, the procedure is performed during the current hospitalization for convenience and scheduling ease, not due to a clinical necessity prior to discharge.

(2) Urgent

The procedure should be performed on an inpatient basis before discharge due to significant concerns about the risk of myocardial ischemia, MI, and/or death. Outpatients or emergency department patients requiring cardiac catheterization should be admitted to the hospital based on their clinical presentation.

(3) Emergency

The procedure should be performed as soon as possible due to substantial concerns that ongoing myocardial ischemia and/or MI could lead to death. 'As soon as possible' refers to a patient with sufficient acuity that a scheduled case would be canceled to perform this procedure immediately in the next available room during business hours, or the on-call team would be activated if this occurs during off-hours.

(4) Salvage

The procedure is a last resort. The patient is in cardiogenic shock at the beginning of the PCI (i.e., when the first guide wire or intracoronary device is introduced into a coronary artery or bypass graft for mechanical revascularization) or within the last 10 minutes before the start of the case or during the diagnostic portion of the case, the patient has received chest compressions or has been on unanticipated circulatory support (e.g., intra-aortic balloon pump, extracorporeal mechanical oxygenation, or cardiopulmonary support).

2) Percutaneous coronary intervention

The placement of an angioplasty guide wire, balloon, or other device (e.g., stent, atherectomy catheter, brachytherapy delivery device, or thrombectomy catheter) into a native coronary artery or CABG for mechanical coronary revascularization. In the assessment of coronary lesion severity using intravascular ultrasound, coronary flow reserve, or fractional flow reserve, the insertion of a guide wire will not be considered PCI.

3) Peripheral (non-coronary) vascular intervention

(1) Peripheral vascular intervention

Peripheral vascular intervention is a catheter-based or open surgical procedure designed to improve peripheral arterial or venous blood flow or otherwise modify or revise vascular conduits. Procedures may include, but are not limited to, 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.

Generally, the intention to perform percutaneous peripheral vascular intervention is indicated by the insertion of a guide wire into a peripheral artery or vein. The target vessel(s) and type of revascularization procedure (e.g., surgical bypass, thrombectomy, endarterectomy, percutaneous angioplasty, stent placement, thromboembolectomy, and thrombolysis) should be specified and recorded. This definition applies to the extracranial carotid artery and other non-cardiac arteries and veins, excluding intracranial vessels and lymphatics.

(2) Procedural status: non-elective and elective

① Non-elective: Non-elective procedures include emergent and urgent procedures. A non-elective procedure is performed without delay due to clinical consensus that it should occur imminently, implying patient instability, urgency of the medical condition, or instability of the threatening lesion.

Emergent: A procedure performed immediately due to the acute nature of the medical condition (e.g., acute limb ischemia, acute aortic dissection), where a delay in treatment increases morbidity or mortality.

Urgent: A procedure that is not emergent but should be performed timely (≤24 hours) (e.g., a patient stabilized after initial treatment of acute limb ischemia, with clinical consensus that a definitive procedure should occur within the next 24 hours).

② Elective: An elective procedure is scheduled and performed on a patient with stable disease or when there is no urgency and/or increased morbidity or mortality associated with a planned procedure.

Renal endpoints

Sustained estimated glomerular filtration rate decline ≥40%

Sustained decline ≥40% from baseline estimated glomerular filtration rate (eGFR) must be confirmed by at least two consecutive laboratory measurements ≥28 days apart. Event start date is the first laboratory date after baseline. Repeat sampling ≥28 days later if initial eGFR decline exceeds 40% from baseline.

Onset of end-stage kidney disease

1) Sustained eGFR

Sustained eGFR <15 mL/min/1.73 m^2 confirmed by at least two consecutive measurements ≥28 days apart. Event start date is the first laboratory date after baseline.

2) Renal transplantation

Renal transplantation meets the criteria. Transplant date is used to determine endpoint achievement. Pre- and post-transplant deaths or transplant organ failures are still considered transplants.

3) Chronic dialysis

Meeting any of the following criteria qualifies as chronic dialysis:

- The treatment has been ongoing for at least 28 days.
- The dialysis treatment was stopped before day 28 due to death, futility or patient electing to stop dialysis and the renal deterioration is deemed irreversible.

Event start date is the first dialysis session date. The cause of renal failure must be determined as acute kidney injury or progression of underlying chronic kidney disease.

Renal death

Renal death is defined as death due to end-stage kidney disease (ESKD) but dialysis treatment was deliberately withheld (dialysis was not started or discontinued) for any reason (e.g., patient refuses dialysis, treating physician considers the dialysis futile, or dialysis is not available). If death is related to other causes than ESKD, the death will not be adjudicated as renal cause of death. Renal death will be classified as a non-cardiovascular death.

Progression of macroalbuminuria

Albuminuria status are assessed by urinary albumin-to-creatinine ratio. Moderate increase defined as ratio ≥30 mg/g (microalbuminuria) and severe increase as ratio ≥300 mg/g (macroalbuminuria) are confirmed by two different measurements ≥3 months apart.