Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Table of Contents

Supplemental Methods – Endpoint Definitions

I. DEATH

A. 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.

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 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 Definition of Myocardial Infarction) 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

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. 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)

   <u>General Considerations</u>

- 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 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 Definition of Heart Failure Event). 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 Definition of Transient Ischemic Attack and Stroke).

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 Definition of Transient Ischemic Attack and Stroke), 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).

B. 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 Definition of Cardiovascular Death. 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)
- Hemorrhage that is neither cardiovascular bleeding or a stroke (See Definition of Cardiovascular Death and Definition of Transient Ischemic Attack and Stroke)
- Non-CV procedure or surgery
- Trauma

• Suicide
• Non-prescription drug reaction or overdose
• Prescription drug reaction or overdose
• Neurological (non-cardiovascular)
• Malignancy
• Other non-CV, in which case specify:

C. 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.

II. CARDIAC ISCHEMIC EVENTS ACUTE CORONARY SYNDROMES

A. 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: $\geq$ 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 causes
- Pathological findings of a prior myocardial infarction

d. ST-Segment Elevation MI versus Non-ST-segment Elevation MI

All events meeting criteria for MI* will also be classified as either ST-segment elevation MI (STEMI), non-ST-segment elevation MI (NSTEMI), or unknown.

- **STEMI** – To be classified as a STEMI the event must meet all of the above criteria for myocardial infarction and one of the four criteria below.

  - New ST segment elevation at the J point in ≥2 contiguous leads, defined as: ≥ 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. Subjects must have an interpretable ECG (i.e., without evidence of left ventricular hypertrophy or pre-existing left bundle branch block), *or*

  - New left bundle branch block

- **NSTEMI** – To be classified as a NSTEMI the event must meet all of the above criteria for myocardial infarction and not meet criteria for classification as STEMI. In order to be classified as NSTEMI there must be adequate interpretable ECG documentation associated with the event.

- **Unknown** – Events which meet criteria as specified above for MI but do not meet criteria for STEMI or NSTEMI. All cases where ECG documentation of the acute event is missing, inadequate, or uninterpretable should be classified as Unknown.

e. Criteria for universal classification of myocardial infarction

Type 1: Spontaneous myocardial infarction

Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion non-obstructive or no CAD.

Type 2: Myocardial infarction secondary to an ischemic imbalance
In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anaemia, respiratory failure, hypotension, and hypertension with or without LVH.

Type 3: Myocardial infarction resulting in death when biomarker values are unavailable
Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarkers could rise, or in rare cases cardiac biomarkers were not collected.

Type 4a: Myocardial infarction related to percutaneous coronary intervention (PCI)
Myocardial infarction associated with PCI is arbitrarily defined by elevation of cTn values >5 x 99th percentile URL in patients with normal baseline values ($\leq 99^{th}$ percentile URL) or a rise of cTn values $\geq$20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia, or (ii) new ischemic ECG changes or new LBBB, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow or no-flow or embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

Type 4b: Myocardial infarction related to stent thrombosis
Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarkers values with at least one value above the 99th percentile URL.

Type 4c: Myocardial infarction related to restenosis
Restenosis is defined as $\geq$50% stenosis at coronary angiography or a complex lesion associated with a rise and/or fall of cTn values >99th percentile URL and no other significant obstructive CAD of greater severity following: (i) initially successful stent deployment or (ii) dilatation of a coronary artery stenosis with balloon angioplasty (<50%).

Type 5: Myocardial infarction related to coronary artery bypass grafting (CABG)
Myocardial infarction associated with CABG is arbitrarily defined by elevation of cardiac biomarker values >10 x 99th percentile URL in patients with normal baseline cTn values ($\leq$99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Note: As noted in criterion 2b, although language states troponin, CKMB can be used with similar cut points.

B. Coronary Revascularization

1. **Percutaneous Coronary Intervention (PCI):** 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 coronary artery bypass graft for the purpose of mechanical coronary revascularization. In the assessment of the severity of coronary lesions with the use of intravascular ultrasound, CFR, or FFR, insertion of a guide wire will NOT be considered PCI.

   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.

   c. Emergency: The procedure should be performed as soon as possible because of substantial concerns that ongoing myocardial ischemia and/or MI could lead to death. "As soon as possible" refers to a patient who is of sufficient acuity that one would cancel a scheduled case to perform this procedure immediately in the next available room during business hours, or one would activate the on-call team were this to occur during off-hours.

   d. Salvage: The procedure is a last resort. The patient is in cardiogenic shock when the PCI begins (i.e., the time at which the first guide wire or intracoronary device is introduced into a coronary artery or bypass graft for the purpose of mechanical revascularization) **OR** within the last ten minutes prior to the start of the case or during the diagnostic portion of the case, the patient has also received chest compressions or has been on unanticipated circulatory support (e.g., intra-aortic balloon pump, extracorporeal mechanical oxygenation, or cardiopulmonary support).

C. 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 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 that 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 end point.

III. HEART FAILURE

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

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

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

        1) Peripheral edema
        2) Increasing abdominal distention or ascites (in the absence of primary hepatic disease)
        3) Pulmonary rales/crackles/crepitations
        4) Increased jugular venous pressure and/or hepatojugular reflux
        5) S_3 gallop
        6) 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:

        1) 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.

        2) Radiological evidence of pulmonary congestion

        3) Non-invasive or 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

        4) 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/m2

        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, inotrope, or vasodilator therapy
c) Mechanical or surgical intervention, including

1) Mechanical circulatory support (e.g., intra-aortic balloon pump, ventricular assist device)
2) 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, and 5) 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

IV. CEREBROVASCULAR EVENTS

A. Definition of Transient Ischemic Attack and Stroke

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.

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 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:

1. **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.

2. **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

3. **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 1 or 2.

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:

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:

TABLE 1

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
7	Unable to Determine

General Considerations

- Evidence of vascular central nervous system injury without recognized neurological dysfunction including microhemorrhage, silent infarction, and silent hemorrhage, if appropriate, will not be adjudicated as cerebrovascular events for this trial.
- Subdural hematomas are intracranial hemorrhagic events and not strokes
- Epidural hemorrhages are intracranial bleeds and not strokes

References:

Hicks KA, Hung HMJ, Mahaffey KW, et al. Standardized definitions for cardiovascular and stroke end point events in clinical trials. November 9, 2012.

Supplemental Results

A total of 136 (4.6%) patients allocated to evolocumab and 28 (1.9%) patients allocated to standard of care alone either discontinued a statin or switched from an intensive to a less-intensive statin regimen during OSLER. Conversely, 56 (1.9%) patients allocated to evolocumab and 106 (7.1%) patients allocated to standard of care alone initiated a statin or switched from a less-intensive to an intensive statin during OSLER; for initiating ezetimibe, the analogous numbers were 10 (0.3%) and 34 (2.3%), respectively.

Supplemental Figure S1 – Consort Diagram

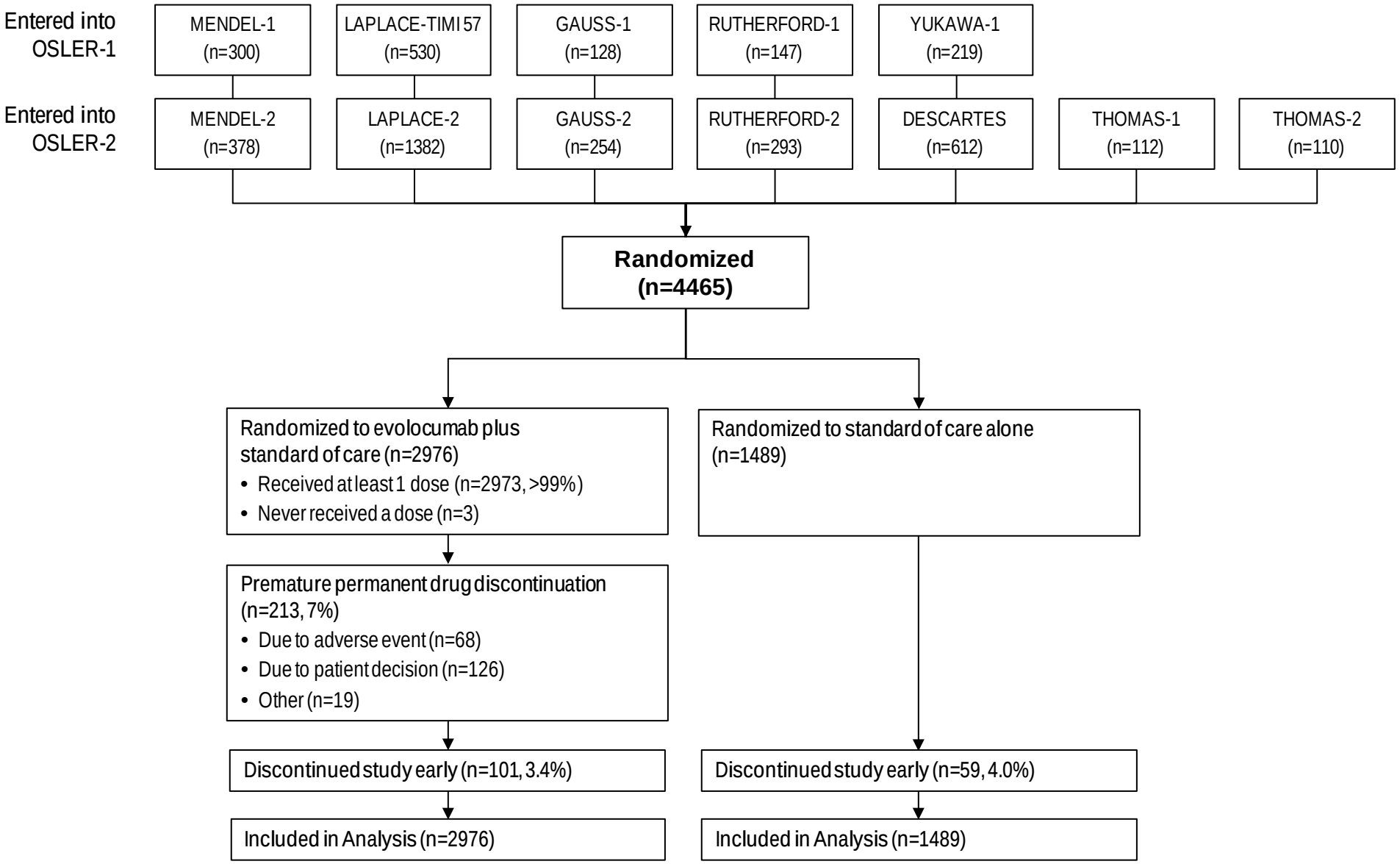
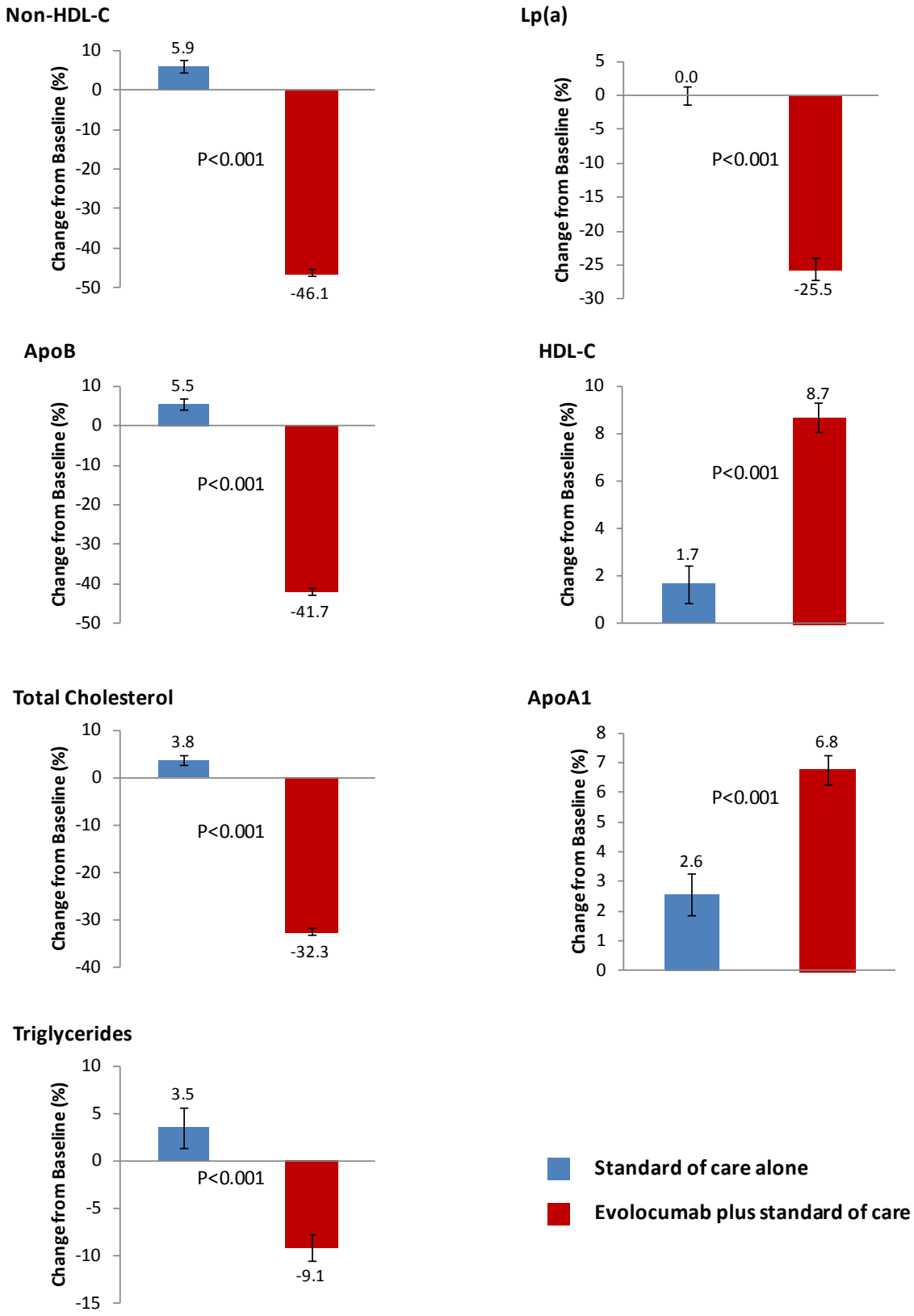


Diagram of parent trials that contributed to OSLER-1 and OSLER-2 and disposition of patients in OSLER-1 and OSLER-2.

Supplemental Figure S2 - Effect of evolocumab on other lipids



Data are for changes from baseline in lipoproteins by 12 weeks in OSLER. Changes are means for all lipids except triglycerides and Lp(a), which are displayed using medians. Error bars represent 95% confidence intervals.

Supplemental Table S1 – Effect of Evolocumab on LDL Cholesterol by OSLER Trial

Trial	Number of subjects	Baseline (Parent Trial), mg/dL (Q1, Q3)	Absolute Reduction, with Evolocumab*, mg/dL (95% CI)	Percent Reduction with Evolocumab* (95% CI)	Achieved in Evolocumab Arm, mg/dL (Q1, Q3)
OSLER-1	1324	133 (114, 156)	74 (70, 77)	55% (52%, 57%)	51 (35, 72)
OSLER-2	3141	114 (91, 145)	73 (70, 76)	64% (61%, 67%)	48 (30, 71)
Combined	4465	120 (97, 150)	73 (71, 76)	61% (59%, 63%)	48 (32, 71)

*Relative to standard of care alone. Reductions and achieved data are at 12 weeks. Baseline and achieved LDL cholesterol are medians; reductions are means.

Supplemental Table S2 – Adverse Events and Laboratory Results by Achieved LDL Cholesterol

	Evolocumab subjects stratified by minimum post-baseline (achieved) LDL cholesterol				All evolocumab subjects (N =2976)
Subject incidence, n (%)	**<25 mg/dL (N =773)**	**25 to <40 mg/dL (N = 759)**	**<40 mg/dL (N = 1532)**	**≥40 mg/dL (N= 1426)**	
Adverse event	541 (70.0)	517 (68.1)	1058 (69.1)	1000 (70.1)	2060 (69.2)
Serious adverse event	59 (7.6)	52 (6.9)	111 (7.2)	111 (7.8)	222 (7.5)
Muscle-related adverse event	38 (4.9)	54 (7.1)	92 (6.0)	98 (6.9)	190 (6.4)
CK >5× ULN	3 (0.4)	7 (0.9)	10 (0.7)	7 (0.5)	17 (0.6)
ALT/AST >3× ULN	7 (0.9)	6 (0.8)	13 (0.8)	18 (1.3)	31 (1.0)
Neurocognitive adverse event	4 (0.5)	9 (1.2)	13 (0.8)	14 (1.0)	27 (0.9)

Supplemental Table S3 – Adverse Events

Adverse event*	Evolocumab plus standard of care (N=2976) n (%)	Standard of care alone (N=1489) n (%)
Nasopharyngitis	280 (9.4)	140 (9.4)
Upper Respiratory Tract Infection	160 (5.4)	71 (4.8)
Arthralgia	137 (4.6)	48 (3.2)
Back Pain	124 (4.2)	55 (3.7)
Headache	106 (3.6)	32 (2.1)
Influenza	106 (3.6)	45 (3.0)
Cough	105 (3.5)	48 (3.2)
Pain In Extremity	99 (3.3)	32 (2.1)
Myalgia	89 (3.0)	43 (2.9)
Fatigue	83 (2.8)	15 (1.0)
Urinary Tract Infection	83 (2.8)	34 (2.3)
Diarrhoea	81 (2.7)	27 (1.8)
Muscle Spasms	73 (2.5)	29 (1.9)
Osteoarthritis	72 (2.4)	24 (1.6)
Musculoskeletal Pain	62 (2.1)	30 (2.0)
Dizziness	56 (1.9)	26 (1.7)
Nausea	53 (1.8)	15 (1.0)
Oropharyngeal Pain	47 (1.6)	20 (1.3)
Vomiting	46 (1.5)	10 (0.7)
Gastroenteritis	44 (1.5)	12 (0.8)
Insomnia	44 (1.5)	16 (1.1)
Rash	43 (1.4)	12 (0.8)
Constipation	40 (1.3)	11 (0.7)
Gastrooesophageal Reflux Disease	40 (1.3)	19 (1.3)
Injection Site Bruising	38 (1.3)	0 (0.0)
Non-Cardiac Chest Pain	36 (1.2)	15 (1.0)
Injection Site Erythema	35 (1.2)	0 (0.0)
Contusion	34 (1.1)	14 (0.9)
Diabetes Mellitus	34 (1.1)	11 (0.7)
Injection Site Pain	33 (1.1)	0 (0.0)
Muscle Strain	33 (1.1)	12 (0.8)
Abdominal Pain	32 (1.1)	12 (0.8)
Anxiety	32 (1.1)	11 (0.7)
Abdominal Pain Upper	31 (1.0)	11 (0.7)
Dyspepsia	31 (1.0)	14 (0.9)
Dyspnoea	31 (1.0)	11 (0.7)
Oedema Peripheral	31 (1.0)	10 (0.7)
Vertigo	31 (1.0)	10 (0.7)
Neck Pain	30 (1.0)	6 (0.4)
Influenza Like Illness	29 (1.0)	13 (0.9)

* AEs that had a frequency ≥1% in the evolocumab arm and that were more frequent with evolocumab

Supplemental Table 4 – Patient Incidence of Cardiovascular Clinical Events

Endpoint	Evolocumab plus standard of care (N=2976) n (%)	Standard of care alone (N=1489) n (%)	Hazard Ratio (95% CI)
All cardiovascular events	29 (0.95)	31 (2.18)	0.47 (0.28-0.78)
MACE	28 (0.95)	30 (2.11)	0.47 (0.28, 0.78)
Death	4 (0.14)	6 (0.41)	
Cardiovascular or unknown	4 (0.1)	3 (0.2)	
Non-cardiovascular	0 (0.0)	3 (0.2)	
Coronary events	22 (0.75)	18 (1.30)	
Myocardial infarction	9 (0.3)	5 (0.3)	
Hospitalization for unstable angina	3 (0.1)	3 (0.2)	
Coronary revascularization	15 (0.5)	17 (1.1)	
Cerebrovascular events	4 (0.14)	7 (0.47)	
Stroke	3 (0.1)	2 (0.1)	
Transient ischemic attack	1 (0.0)	5 (0.3)	
Heart failure requiring hospitalization	1 (0.03)	1 (0.07)	

Patients could have more than one type of event. Rates for composite endpoints are 1-year Kaplan-Meier estimates, rates for individual endpoints are proportions.

MACE is a post hoc composite that includes death, major coronary events, and major cerebrovascular events.