

Appendix 2 (as supplied by the authors): Definitions of clinical outcome events.

Outcome	Definition
Death sub-classification	Deaths were classified as vascular or non-vascular. Vascular death is defined as any death with a vascular cause and includes those deaths following a myocardial infarction, myocardial injury after noncardiac surgery (MINS), cardiac arrest, stroke, cardiac revascularization procedure (i.e., percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG] surgery), pulmonary embolus, hemorrhage, or deaths due to an unknown cause. Non-vascular death is defined as any death due to a clearly documented non-vascular cause (i.e., trauma, infection, malignancy, etc.).
Preoperative myocardial infarction	Any one of the following criterion: 1. A typical rise of troponin or a typical fall of an elevated troponin detected post randomization and before surgery, in a patient without a documented alternative explanation for an elevated troponin (e.g., pulmonary embolism). This criterion also requires that 1 of the following must also exist: a. ischemic signs or symptoms (i.e., chest, arm, or jaw discomfort; shortness of breath, pulmonary edema) within 24 hours of Troponin T elevation

- b. development of pathologic Q waves present in any two contiguous leads that are ≥ 30 milliseconds
- c. Electrocardiography (ECG) changes indicative of ischemia (i.e., ST segment elevation [≥ 2 mm in leads V_1 , V_2 , or V_3 and ≥ 1 mm in the other leads], ST segment depression [≥ 1 mm], or symmetric inversion of T waves ≥ 1 mm in at least two contiguous leads), or development of left bundle branch block (LBBB). ST-depression/elevation and LBBB development must occur within 3 days of Troponin T elevation or ischemic symptoms. T-wave inversion must occur within 5 days of Troponin T elevation or ischemic symptoms.
- d. coronary artery intervention (i.e., PCI or CABG surgery) within 2 weeks of Troponin T elevation or ischemic symptoms.
- e. new or presumed new cardiac wall motion abnormality on echocardiography or new or presumed new fixed defect on radionuclide imaging

- 2. Pathologic findings of an acute or healing myocardial infarction
- 3. Development of new pathological Q waves on an ECG if troponin levels were not obtained or were obtained at times that could have missed the clinical event

Myocardial injury after noncardiac surgery (MINS)	<p>Myocardial cell injury caused by ischemia, which occurs during or within 30 days after noncardiac surgery and has short-term prognostic relevance.</p> <p>The diagnostic criteria for MINS is during or within the first 30-days after noncardiac surgery a troponin T value ≥ 0.03 ng/mL that is felt due to ischemia. MINS does not include perioperative myocardial injury that is due to pulmonary embolism, sepsis, cardioversion, a known troponin antibody or known chronically elevated troponin measurements, or another known non-ischemic etiology.</p>
Coronary revascularization	PCI or CABG surgery.
Stroke	New focal neurological deficit thought to be vascular in origin with signs and symptoms lasting more than 24 hours.
Pneumonia	<p>Any one of the following:</p> <ol style="list-style-type: none"> 1. Rales or crackles or dullness to percussion on physical examinations of chest AND any of the following: <ol style="list-style-type: none"> a. New onset of purulent sputum or change in character of sputum b. Isolation of organism from blood culture c. Isolation of pathogen from specimen obtained by transtracheal aspirate, bronchial brushing, or biopsy d. Isolation of virus or detection of viral antigen in respiratory

secretions or immunological pathogen identification (IgM titer)

e. Histopathologic evidence of pneumonia

2. Chest radiography showing new or progressive infiltrate, consolidation, cavitation, or pleural effusion AND any of the following:

a. New onset of purulent sputum or change in character of sputum

b. Isolation of organism from blood culture

c. Isolation of pathogen from specimen obtained by transtracheal aspirate, bronchial brushing, or biopsy

d. Isolation of virus or detection of viral antigen in respiratory secretions or immunological pathogen identification (IgM titer)

e. Histopathologic evidence of pneumonia

Pulmonary

Any one of the following:

embolism

1. A high probability ventilation/perfusion lung scan

2. An intraluminal filling defect of segmental or larger artery on a helical CT scan

3. An intraluminal filling defect on pulmonary angiography

4. A positive diagnostic test for a deep venous thrombosis (i.e., positive compression ultrasound or venogram) and one of the following:
- a. non-diagnostic (i.e., intermediate probability)
ventilation/perfusion lung scan
 - b. non-diagnostic (i.e., subsegmental defects) helical CT scan

Nonfatal cardiac arrest Nonfatal cardiac arrest is defined as the successful resuscitation from either documented or presumed ventricular fibrillation, sustained ventricular tachycardia, asystole, or pulseless electrical activity requiring cardiopulmonary resuscitation, pharmacological therapy, or cardiac defibrillation.

New congestive heart failure The diagnosis of congestive heart failure requires at least ONE of the following clinical signs (i.e., any of elevated jugular venous pressure, respiratory rales/crackles, crepitations, or presence of S3)

AND

At least ONE of the following radiographic findings: vascular redistribution, interstitial pulmonary edema, or frank alveolar pulmonary edema.

Sepsis Sepsis diagnosis requires two or more signs of systemic inflammatory response syndrome present along with infection.

- a. Core temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$
- b. Heart rate >90 beats/min

- c. Respiratory rate >20 breaths/min
- d. White blood cell count >12x10⁹/L or , 4x10⁹/L

Diagnosis of sepsis with organ dysfunction requires ONE of the following:

- a. Respiratory failure
- b. Arterial pH <7.3
- c. Urine output <180mL over 6 hours
- d. Systolic blood pressure <90mmHg or fall in systolic blood pressure >40 mmHg and remaining >40mmHg for 2 hours despite fluid challenge of >500mL bolus or blood pressure requiring inotropic support
- e. Systemic vascular resistance <800 dyn·s/cm⁵
- f. Prothrombin time or partial thromboplastin time greater than normal or platelets <100 x10⁹/L or platelets decreased to <50% of most recent measurement before the current day
- g. Delirium

Bleeding sub classification

Bleeding events will be classified as Life-threatening and Major. Diagnosis of life threatening bleeding is bleeding that is fatal, or leads to: significant hypotension that requires inotrope therapy, urgent (within 24 hours) surgery (other than superficial vascular

repair), or intracranial hemorrhage. A Major bleeding event is bleeding that does not satisfy the “Life-threatening bleeding” criteria, AND satisfies any ONE of the following:

- a. Results in hemoglobin ≤ 70 g/L AND that requires a transfusion of ≥ 2 units of red blood cells
- b. Results in hemoglobin **drop** of ≥ 50 g/L AND that requires a transfusion of ≥ 2 units of red blood cells
- c. Requires a transfusion of >4 units of red blood cells within a 24 hour period
- d. Leads to any other intervention (i.e., embolization, superficial vascular repair, nasal packing)
- e. Is retroperitoneal, intraspinal, or intraocular (confirmed clinically or on imaging)

Deep venous

DVT diagnosis requires any ONE of the following:

thrombosis (DVT)

1. A persistent intraluminal filling defect on contrast venography
2. Noncompressibility of one or more venous segments on B mode compression ultrasonography
3. A clearly defined intraluminal filling defect on contrast enhanced computed tomography

New clinically important atrial fibrillation New atrial fibrillation that results in angina, congestive heart failure, symptomatic hypotension, or that requires treatment with a rate controlling drug, antiarrhythmic drug, or electrical cardioversion.

New acute renal failure New requirement for dialysis (i.e., use of dialysis machine or peritoneal dialysis apparatus in patients without dialysis prior to randomization).