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# 1 INVESTIGATORS AND COMMITTEES

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# 2 SUPPLEMENTARY TABLE

**Supplementary Table** Post-hoc subgroup analyses by sex

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Colchicine | | Placebo | | Comparison | P interaction |
| Sex | Patients | Events (%) | Patients | Events (%) | HR (95% CI) |  |
| **Clinically important perioperative atrial fibrillation** | | | | | | |
| Male | 831 | 55 (6·6) | 825 | 69 (8·4) | 0·78 (0·55-1·11) | 0·50 |
| Female | 777 | 48 (6·2) | 776 | 51 (6·6) | 0·94 (0·63-1·39) |  |
| **Myocardial injury after noncardiac surgery** | | | | | | |
| Male | 831 | 153 (18·4) | 825 | 175 (21·2) | 0·84 (0·67-1·05) | 0·47 |
| Female | 777 | 142 (18·3) | 776 | 150 (19·3) | 0·95 (0·75-1·20) |  |

HR=hazard ratio; CI=confidence interval

# 3 EVENTS DEFINITIONS

**Atrial fibrillation/atrial flutter (AF):**

AF is defined as the replacement of the consistent P waves on 12-lead electrocardiogram (ECG), rhythm strip or documented telemetry tracing, by rapid oscillation or fibrillatory/flutter waves.

**Clinically important perioperative atrial fibrillation/atrial flutter (AF):**

Clinically important perioperative AF is defined as AF developing after randomization until the end of follow-up 14 days after randomization, that is documented on an ECG, rhythm strip or telemetry tracing, and that results in angina, heart failure, symptomatic hypotension, or that requires treatment with a rate controlling drug, antiarrhythmic drug, or electrical cardioversion.

**Sub-classification of death:**

Vascular death is defined as any death with a vascular cause and includes those deaths following a myocardial infarction (MI), 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 (e.g. trauma, infection, malignancy).

**Myocardial Injury after Noncardiac Surgery (MINS)**

MINS is defined as MI (as defined below) or an elevated postoperative troponin (higher than the local lab threshold) judged to be due to myocardial ischemia (i.e., without evidence of a non-ischemic etiology [e.g., chronic elevation, pulmonary embolism, sepsis, cardioversion]) that occurred within the first 14 days after the initiation of surgery. The only exceptions to the definition of an elevated troponin will be to use a higher threshold for troponin T (TnT) of ≥30 ng/L, and for high-sensitivity troponin T (hsTnT) of 20 to <65 ng/L with an absolute change of at least 5 ng/L or an hsTnT level ≥65 ng/L, based on data from the VISION study establishing these thresholds.1

**Myocardial Injury after Noncardiac Surgery not fulfilling the Fourth Universal Definition of Myocardial Infarction:**

Using the MINS definition above, MINS not fulfilling the Fourth Universal Definition of MI includes all MINS events that do not fulfil the definition of MI below (i.e., MINS without ischemic signs or symptoms, ischemic changes on the ECG and evidence of new loss of viable myocardium or new regional wall motion abnormality on non-invasive tests).

**Myocardial infarction (Fourth Universal Definition)**

The diagnosis of MI requires any one of the following criteria:

1. Detection of a rise or fall of a cardiac troponin value (cTn) with at least one value above the 99th percentile of the upper reference limit (URL) with at least one of the following:
   1. Ischemic signs or symptoms (i.e., chest, arm, neck, or jaw discomfort, shortness of breath, pulmonary edema);
   2. Development of pathologic Q waves present in any two contiguous leads that are >30 milliseconds;
   3. New, or presumed new, ECG changes indicative of ischemia (i.e., ST elevation [≥2mm in leads V1, V2, or V3 and ≥1mm in the other leads], ST segment depression [≥1mm], or symmetric inversion of T waves ≥1mm in at least two contiguous leads, or development of new left bundle branch block (LBBB);
   4. Imaging evidence of new loss of viable myocardium or new or presumed new, cardiac regional wall motion abnormality in a pattern consistent with an ischemic etiology; or
   5. Identification of a coronary thrombus by angiography or autopsy (i.e., post-mortem demonstration of an atherothrombus in the artery supplying the infarcted myocardium, or a macroscopically large, circumscribed area of necrosis with or without intramyocardial hemorrhage).
2. Cardiac death, with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cTn were obtained, or before cTn values would be increased.
3. PCI related MI is defined by elevation of a cTn value (>5 x 99th percentile URL) in patients with a normal baseline cTn value (≤99th percentile URL) or a rise of a cTn measurement >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 (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
4. Stent thrombosis or restenosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cTn values with at least one of value above the 99th percentile URL (as defined under 1).
5. CABG related MI is defined by elevation of cTn values (>10 x 99th percentile URL) in patients with a normal baseline cTn value (≤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.
6. Isolated development of new pathological Q waves with either revascularization procedure if cTn values are elevated and rising but less than the pre-specified thresholds for PCI and CABG.

**Myocardial infarction after Myocardial Injury after Noncardiac Surgery:**

MI after MINS requires the following criteria:

1. Detection of a rise or fall of a cardiac biomarker with at least one value above the 99th percentile of the upper reference limit (URL) and 20% higher than the last troponin measurement related to the preceding event together with evidence of myocardial ischemia with at least one of the following:
   1. Ischemic signs or symptoms (i.e., chest, arm, neck, or jaw discomfort; shortness of breath, pulmonary edema);
   2. Development of pathologic Q waves present in any two contiguous leads that are >30 milliseconds;
   3. New or presumed new ECG changes indicative of ischemia (i.e., ST segment elevation [>2 mm in leads V1, V2, or V3 OR >1 mm in the other leads], ST segment depression [>1mm], or symmetric inversion of T waves >1 mm) in at least two contiguous leads;
   4. New LBBB;
   5. New cardiac wall motion abnormality on echocardiography or new fixed defect on radionuclide imaging; or
   6. Identification of intracoronary thrombus on angiography or autopsy.

**Stroke:**

Stroke is defined as the rapid onset of a new persistent neurologic deficit attributed to focal ischemia of the brain, retina or spinal cord and/or cerebral hemorrhage with no apparent non-vascular cause (e.g., trauma, tumor, or infection). Signs or symptoms must last at least 24 hours, unless supported by clear evidence of infarction on neurologic imaging (magnetic resonance imaging [MRI] or computerized tomography [CT]). Available neuroimaging studies will be considered to support the clinical impression and to determine if there is a demonstrable lesion compatible with an acute stroke. Stroke will be sub-classified into hemorrhagic and non-hemorrhagic stroke, or uncertain (used when no imaging is available to exclude hemorrhage). Non-hemorrhagic stroke will sub-classified into ischemic, ischemic with secondary transformation, or stroke of uncertain classification. Hemorrhagic stroke will be sub-classified into primary intracerebral hemorrhage and primary subarachnoid hemorrhage.

1. Ischemic stroke: focal brain infarction caused by an arterial (or rarely venous) obstruction (see above, this excludes flow related infarcts distal to stenosis) and as documented by CT scan/MRI that is consistent with infarction.
2. Secondary hemorrhagic transformation of ischemic stroke: hemorrhagic transformation of ischemic stroke may be symptomatic or asymptomatic.
3. Symptomatic transformation of ischemic stroke is defined as a hematoma occupying 30% or more of the infarcted tissue associated with a significant neurologic deterioration (i.e., a decrease of at least 4 points in the NIHSS) compared to immediately before the worsening and an absence of an alternative explanation for deterioration.
4. Asymptomatic transformation of ischemic stroke is defined as a hemorrhagic transformation not meeting the criteria for symptomatic transformation.
5. Undetermined stroke: definite stroke that does not meet the criteria for ischemic or hemorrhagic stroke because CT scan or MRI are not done and there are no autopsy data. Rarely it cannot be determined with confidence whether the stroke was ischemic vs hemorrhagic, even after review of CT/MRI images (e.g., primary intracerebral hemorrhage vs severe hemorrhagic transformation); these stroke events will be classified as undetermined.
6. Hemorrhagic stroke: hemorrhagic stroke requires neuroimaging or autopsy confirmation and includes two subcategories: primary intracerebral hemorrhage (intraparenchymal or intraventricular) and primary subarachnoid hemorrhage. Intracranial bleeding caused by head trauma, bleeding associated with tumors, hemorrhagic transformation of ischemic stroke and subdural/epidural hematomas are not considered as hemorrhagic strokes (but these will be counted separately as major hemorrhages). Microbleeds are not considered intracranial hemorrhage.
7. Primary intracerebral hemorrhage: These are symptomatic hemorrhagic strokes with CT/MRI or autopsy evidence of bleeding into the substance of the brain or ventricular spaces. Large or superficial intracerebral hemorrhages often are associated with minor amounts of subarachnoid hemorrhage, but these should be classified as intracerebral hemorrhages. Does not include secondary hemorrhage into cerebral infarct (i.e., hemorrhagic transformation which is defined separately), or intracerebral bleeding (i.e., contusions) due to trauma, or microbleeds detected by MRI.
8. Primary subarachnoid hemorrhage: Typical clinical syndrome of sudden onset headache, with or without focal signs (subarachnoid hemorrhage may not have focal deficits), and CT or cerebrospinal fluid evidence of bleeding primarily into the subarachnoid space. Subarachnoid bleeding due to ruptured intracranial aneurysms and vascular malformation are counted as hemorrhagic strokes, but traumatic subarachnoid hemorrhage is not.

**Acute heart failure:**

Acute heart failure is defined as a clinical sign (i.e., at least one of the following: elevated jugular venous pressure, respiratory rales/crackles, crepitations, or presence of S3) and at least one of the following:

1. Radiographic findings (i.e., at least one of the following: vascular redistribution, interstitial pulmonary edema, frank alveolar pulmonary edema, or multiple and diffuse bilateral B lines on ultrasonography);
2. Elevated levels of natriuretic peptides; or
3. Heart failure treatment implemented with diuretics with documented clinical improvement.

**Pulmonary embolism:**

The diagnosis of pulmonary embolism requires any one of the following:

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; or
4. A positive diagnostic test for deep vein thrombosis and one of the following:
5. Non-diagnostic (i.e., indeterminate or intermediate probability) ventilation/perfusion lung scan; or
6. Non-diagnostic (i.e., subsegmental defect or technically inadequate study) helical CT scan.

**Deep venous thrombosis of leg or arm:**

The diagnosis of deep venous thrombosis requires any one of the following:

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

**Life-threatening bleeding:**

Life-threatening bleeding is bleeding that is fatal, or leads to: significant hypotension that requires inotrope therapy/vasopressor therapy, urgent (within 24 hours) surgery (other than superficial vascular repair), or intracranial hemorrhage.

**Major bleeding:**

Major bleeding is defined as bleeding that is not specified under “life-threatening bleeding” above, and

1. Results in a postoperative hemoglobin ≤70g/L and the patient receiving a transfusion of ≥2 units of red blood cells
2. Results in a hemoglobin drop of ≥50 g/L and the patient receiving a transfusion of ≥2 units of red blood cells
3. Results in the patient receiving a transfusion of ≥4 units of red blood cells within a 24-hour period
4. Leads to one of the following interventions: embolization, superficial vascular repair, nasal packing; or
5. Is retroperitoneal, intraspinal, or intraocular (confirmed clinically or on imaging).

**Sepsis/infection:**

Infection is defined as a pathologic process caused by the invasion of normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic organisms.

The Third International Consensus Definitions Task Force defines sepsis as a “life-threatening organ dysfunction due to a dysregulated host response to infection.” Based on the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) criteria, sepsis will require a quick Sequential Organ Failure Assessment (qSOFA) Score ≥2 points due to infection. The qSOFA includes the following items and scoring system:

1. Glasgow Coma Scale (GCS) score of 13 or less (1 point);
2. Systolic blood pressure of 100 mm Hg or less (1 point); and
3. Respiratory rate of 22 breaths/min or more (1 point).

**Noninfectious diarrhea:**

Noninfectious diarrhea is defined as a new onset of >3 loose bowel movements per day. The diarrhea should not be caused by an infectious organism.

# 3 REFERENCES

1. Devereaux PJ, Biccard BM, Sigamani A, et al. Association of Postoperative High-Sensitivity Troponin Levels With Myocardial Injury and 30-Day Mortality Among Patients Undergoing Noncardiac Surgery. *Jama* 2017; **317**: 1642-51.