

Supplement 1

The primary endpoint is the first major adverse cardiovascular event (MACE), that is a composite of myocardial infarction, stroke, hospitalization for heart failure or vascular death as defined in *supplemental table 1*. The definitions are largely following the recommendations of the SCTI and US-FDA [1] Secondary endpoints reported in this publication encompass fist myocardial infarction, first stroke and first hospitalization for heart failure after study inclusion.

Suppl. Table 1 Endpoint definitions for myocardial infarction, stroke, hospitalization for heart failure, vascular death.

Clinical Event	Endpoint Definition
Myocardial infarction (MI)	Acute myocardial infarction is a clinical acute coronary syndrome with evidence for myocardial necrosis in ECG <i>and/or</i> blood sample analysis meeting the following criteria: - Acute MI type 1 or type 4b <i>with</i> cardiac catherization/ open heart surgery and <i>with</i> revascularization/ coronary surgery performed (STEMI or NSTEMI or undetermined) OR -Acute MI type 1 <i>with</i> cardiac catherization <i>without</i> revascularization/ coronary surgery performed (STEMI or NSTEMI or undetermined) OR - Acute peri-interventional MI type 4a or type 5 (STEMI or NSTEMI or undetermined) OR -Acute MI type 2 with <i>exclusion</i> of an obstructive coronary process
Stroke	<u>Ischemic stroke:</u> Documented diagnosis of acute ischemic stroke with -typical clinical neurological symptoms presenting for ≥ 24 hrs OR -typical clinical neurological symptoms presenting for < 24 hrs with evidence for acute ischemia in an according terroitory on CT- or MR (DWI) imaging OR - sudden monocular visulal impairment with evidence of retinal artery occlusion <u>Non-traumatic intracerebral hemorrhage</u> acute clinical neurological symptoms AND imaging evidence for a brain parenchyma hemorrhage
Hospitalization for heart failure	<u>Heart failure requiring hospitalization</u> defined as inpatient admission <i>or</i> at least 12hr stay at an ER or at a chest pain unit AND <u>at least one sign:</u> -dyspnea, orthopnea, paroxysmal nocturnal dyspnea, edema, pulmonary basilar crackles, jugular venous distension requiring at least 12 hrs of hospitalization, third heart sound or gallop rhythm, radiological evidence of worsening heart failure AND <u>additional/increased therapy:</u> -at least one: initiation of oral diuretic or IV diuretic or inotrope therapy or vasodilator therapy OR uptitration of oral or intravenous therapy if already under therapy OR initiation of mechanical or surgical intervention or the use of ultrafiltration,

	hemofiltration, or dialysis that is specifically directed at the treatment of alteration of biomarkers subsequent to heart failure
Vascular death	Fatal myocardial Infarction - acute MI as documented cause of death in autopsy results <i>OR</i> - acute MI as documented cause of death in hospital <i>OR</i> - sudden death outside of a hospital within 30 days after a documented acute MI without another clear cause <i>OR</i> Sudden cardiac death - witnessed (without new/worsening symptoms <i>or</i> within 60 minutes after new/ worsening symptoms <i>or</i> due to documented definite arrhythmia) <i>OR</i> - after cardiac resuscitation (cardiac arrest with unsuccessful resuscitation <i>or</i> death after successful resuscitation without identification of a non-cardial cause of death) - unwitnessed (sudden unexpected death without witnesses in a participant, that was seen alive and stable within ≤ 24hrs before death without a plausible evidence for a non-cardial cause of death) <i>OR</i> Death due to heart failure or cardiogenic shock =death in the context of the following new or worsening signs and/or symptoms of heart failure without evidence for another cause: - new of worsening signs of heart failure with the necessity to initiate or escalate therapy for heart failure or in a patient with already escalated therapy <i>OR</i> - new of worsening signs of heart failure with the necessity for continuous intravenous therapy of oxygen supply <i>OR</i> - bedriddenness due to symptoms of heart failure <i>OR</i> - pulmonary edema causing tachypnoea and unrest, which is not occurring in the context of myocardial infarction or following arrhythmia without worsening heart failure <i>OR</i> - cardiogenic shock which is not occurring in the context of myocardial infarction or following arrhythmia without worsening heart failure <i>OR</i> - cardiac index $< 2,2 \text{ L7min}$ <i>OR</i> - cardiac index < 2 shock <i>OR</i> Death by a cerebrovascular cause that is - an ischemic stroke <i>OR</i> - a non-traumatic intracerebral hemorrhage <i>OR</i> - a subarachnoid hemorrhage <i>OR</i> - a cerebral vein thrombosis any of which is mentioned as cause of death in discharge letters or if death is occurring due critical brain damage or secondary complications such as infection, pulmonary artery embolism or arrhythmia within 30 days after one of these events without evidence for another, non-vascular cause <i>OR</i> Death caused by cardiac arrhythmia, that was not definitely caused by acute myocardial infarction <i>OR</i> Death caused cardiac valve disease <i>OR</i>

	Death caused by direct complications of invasive diagnostic or therapeutic procedures of the coronary or cerebral arteries: -diagnostic or interventional cardiac catheterism <i>OR</i> - aorto-coronary bypass surgery <i>OR</i> - mechanical recanalization of brain supplying arteries <i>OR</i> - carotid artery -TEA or stenting <i>OR</i> - basal brain artery aneurysm surgery or clipping <i>OR</i> Death due to peripheral-vascular causes: - due to complications of aortic aneurysms <i>OR</i> - due to internal organ ischemia (mesenteric ischemia ect.) - due to peripheral (extremity) artery ischemia (including infectious complications of ulcers caused by peripheral artery disease) <i>OR</i> - due to pulmonary artery embolism
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References

Hicks KA, Mahaffey KW, Mehran R, Nissen SE, Wiviott SD, Dunn B, et al.; Standardized Data Collection for Cardiovascular Trials Initiative (SCTI). 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. *Circulation*. 2018;137(9):961-972.