Supplementary Material

Appendix A: Endpoint Definitions

1. Death
Classifications of death:
- Cardiac death:
  Any death due to proximate cardiac cause (e.g., myocardial infarction, low-output failure, fatal arrhythmia), witnessed death, and death of unknown cause, and all procedure-related deaths, including those related to concomitant treatment, will be classified as cardiac death.
- Vascular death:
  Death caused by noncoronary vascular causes, such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular diseases.
- Noncardiovascular death:
  Any death not covered by the above definitions, such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide, or trauma.

All deaths are considered cardiac unless an unequivocal noncardiac cause can be established. Specifically, any unexpected death even in patients with coexisting potentially fatal noncardiac disease (e.g., cancer, infection) is classified as cardiac.

2. Myocardial Infarction
Criteria for acute myocardial infarction include:
- Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin [cTn]) with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:
  - Symptoms of ischemia.
  - New or presumed new significant ST-segment-T wave (ST-T) changes or new left bundle branch block (LBBB).
  - Development of pathological Q waves in the electrocardiogram (ECG).
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
  - Identification of an intracoronary thrombus by angiography or autopsy.
  - Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.

Based on the third universal definition, myocardial infarction will be classified into various types:

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 nonobstructive 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-/bradyarrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without left ventricular hypertrophy (LVH).

Type 3: Myocardial infarction resulting in death when biomarker values are unavailable
Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker 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 (< 99th percentile URL) or a rise of cTn values < 20% if the baseline values are elevated and are stable or falling. In addition, either (1) symptoms suggestive of myocardial ischemia, or (2) new ischemic ECG changes or new LBBB, or (3) angiographic loss of patency of a major coronary artery or a side branch or persistent slow- or no-flow or embolization, or (4) 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 with at least one value above the 99th percentile URL.

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 (< 99th percentile URL). In addition, either (1) new pathological Q waves or new LBBB, or (2) angiographic documented new graft or new native coronary artery occlusion, or (3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Q-wave versus non-Q-wave myocardial infarction
Q-wave MI will be diagnosed if new pathologic Q-waves (> 25% of the height of the partner R wave and/or ≥ 0.04 seconds in duration) in ≥ 2 contiguous ECG leads
occur. All other MIs not fulfilling the above-mentioned criteria will be considered non-Q-wave MI.

3. Stroke
Stroke is defined as an acute episode of focal or global neurological dysfunction of at least 24 hours caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction. Diagnosis of stroke should be confirmed by cardiac computerized tomography (cCT), magnetic resonance imaging (MRI), or pathology.

Classification:
- 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.
- 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.
- 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 either ischemic or hemorrhagic.

Modified Rankin Scale – Stroke severity assessment scale
Scale 0
No symptoms at all.
Scale 1
No significant disability despite symptoms: able to carry out all usual duties and activities.
Scale 2
Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance.
Scale 3
Moderate disability: requiring some help, but able to walk without assistance.
Scale 4
Moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance.
Scale 5
Severe disability: bedridden incontinent and requiring constant nursing care and attention.
Scale 6
Dead.

4. Urgent Revascularization
Any PCI or bypass surgery performed for recurrent ischemia that in the investigators opinion cannot be delayed for more than 24 hours and is defined by the investigator as a non-selective procedure.

5. Stent Thrombosis
According to Academic Research Consortium (ARC):
- Definite stent thrombosis: Presence of an acute coronary syndrome with angiographic or autopsy evidence of thrombus or occlusion.
- Probable stent thrombosis: Unexplained death within 30 days after the procedure or acute myocardial infarction involving the target-vessel territory without angiographic confirmation.
- Possible stent thrombosis: All unexplained death occurring at least 30 days after the procedure.
- Acute stent thrombosis: Occurring within 24 hours following the index PCI.
- Subacute stent thrombosis: 24 hours to 30 days following the index PCI.
- Late stent thrombosis: 31 to 360 days following the index PCI.
- Very late stent thrombosis: after 360 days following the index PCI.

Type 0: No bleeding.
Type 1: Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a health care professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a health care professional.
Type 2: Overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a health care professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation.
Type 3:
Type 3a: Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL (provided hemoglobin drop is related to bleed). Any transfusion with overt bleeding.
Type 3b: Overt bleeding plus hemoglobin drop ≥ 5 g/dL (provided hemoglobin drop is related to bleed), cardiac tamponade, bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid), bleeding requiring intravenous vasoactive agents.

Type 3c: Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal). Subcategories confirmed by autopsy or imaging or lumbar puncture intraocular bleed compromising vision.

Type 4: CABG-related bleeding:
- Perioperative intracranial bleeding within 48 hours.
- Reoperation after closure of sternotomy for the purpose of controlling bleeding.
- Transfusion of ≥ 5 U whole blood or packed red blood cells within a 48 hour-period.**
- Chest tube output ≥ 2 L within 24 hour-period.

Type 5: Fatal bleeding.
Type 5a: Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious.
Type 5b: Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation.

Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes.

If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event.

If a bleeding event occurs with a clear temporal relationship to CABG (i.e., within a 48-hour time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.

Corrected for transfusion (1 U packed red blood cells or 1 U whole blood = 1 g/dL hemoglobin).

Exclusion criteria:
- Women of childbearing potential (WOCBP) who are unwilling or unable to use an acceptable method to avoid pregnancy for up to 4 weeks after receiving investigational product.
- Women who are pregnant or breastfeeding or are planning pregnancy during course of trial.
- Women with a positive pregnancy test on enrolment or prior to investigational product administration.
- Patients with elevated high-sensitivity cardiac troponin T levels at screening.
- Patients receiving antithrombotic therapy with prasugrel or ticagrelor within 7 days prior to randomization.
- History of hypersensitivity, contraindication, or serious adverse reaction to any component of the study drug (GPVI-Fc, sucrose, mannitol), acetylsalicylic acid, or clopidogrel.
- History of bleeding diathesis or active bleeding within the last 30 days.
- Recent intracerebral hemorrhage or trauma within the last 3 months.
- Thrombocytopenia (platelet count < 30 000/mm³) at screening.
- Sustained hypertension (systolic blood pressure [BP] > 179 mm Hg or diastolic BP > 109 mm Hg) at screening.
- Renal failure (estimated glomerular filtration rate < 30 mL/min and/or dialysis).
- Severe systemic disease, such as known malignancies or other comorbid conditions with life expectancy less than 1 year that may result in protocol noncompliance.
- Unable to provide informed consent (e.g., severe dementia, or psychosis).
- Current severe liver dysfunction (transaminase levels > 5-fold the upper normal range limit).
- Patients with an indication for anticoagulant therapy.
- Participation in any other clinical interventional trial (drug/device) within less than 30 days prior to screening.
- Any other contraindication to perform PCI.
- Any planned additional PCI or surgery within 30 days after randomization.
- Suspected poor capability to follow instructions and cooperate.
- Prisoners or subjects who are involuntarily incarcerated.
- Subjects who are compulsorily detained for treatment of either a psychiatric or physical illness (e.g., infectious disease).

Stable coronary artery disease is generally characterized by episodes of reversible myocardial demand/supply mismatch, related to ischemia or hypoxia, which are usually inducible by exercise, emotion, or other stress and reproducible—but, which may also be occurring spontaneously. Such episodes of ischemia/hypoxia are commonly associated with transient chest discomfort (angina pectoris). The diagnosis of...
stable coronary artery disease implies the exclusion of acute coronary syndromes as defined in current guidelines.\textsuperscript{28}

**Appendix D: Study Organizational Structure**

**Steering Committee:**
Adnan Kastrati (Chair, Coordinating Investigator), Steffen Massberg (Co-Coordinating Investigator), Karl-Ludwig Laugwitz, Stefanie Schüpke, Dirk Sibbing, and Andreas Zeiher.

**Data and Safety Monitoring Board:**
Marco Valgimigli (Chair), Peter Jüni, and Michael Maeng.

**Trial Statistician:**
Kurt Ulm.

**Event Adjudication Committee:**
Julia Ellert (Chair), Georg Fröhlich, and Fadil Ademaj.

**Coordinating Research Center**
ISAREsearch Center, Deutsches Herzzentrum München, Klinik an der Technischen Universität München, Lazarettstraße 36, 80636 Munich, Germany, Marion Janisch (Project Management).

**Core Laboratory:**
advanceCOR GmbH, Fraunhoferstraße 9a, 82152 Martinsried, Germany.