APPENDIX

Clinical Events Committee

CEC project leader: Anna Franzone.

Clinical Events Committee Composition

Chair: Eugene Mc Fadden, Co-chair: Sergio Leonardi, Member: Raffaele Piccolo.

Endpoints Definitions

BLEEDING

All potential bleeding events will be primarily adjudicated according to Bleeding Academic Research Consortium (BARC) classification as well as according to the TIMI and the GUSTO classification as follows:

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: Any overt, actionable sign of haemorrhage (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 Types 3, 4, or 5 but does meet at least one of the following criteria:

Requiring non-surgical, medical intervention by a health care professional

Leading to hospitalization of increased level of care

Prompting evaluation

Type 3a:

- Overt bleeding plus haemoglobin drop of 3 to <5** g/dL (provided haemoglobin drop is related to bleed)
- Any transfusion with overt bleeding

Type 3b:

- Overt bleeding plus haemoglobin drop ≥5** g/dL (provided haemoglobin drop is related to bleed)
- Cardiac tamponade
- Bleeding requiring surgical intervention for control (excluding dental / nasal / skin / haemorrhoid)
- Bleeding requiring intravenous vasoactive agents

Type 3c:

- Intracranial haemorrhage (does not include microbleeds or haemorrhagic transformation; does include intraspinal)

Subcategories: confirmed by autopsy or imaging or LP

Intra-ocular bleed compromising vision

Type 4: CABG-related bleeding

- Perioperative intracranial bleeding within 48 hours
- Reoperation following closure of sternotomy for the purpose of controlling bleeding
- Transfusion of ≥ 5 units of whole blood or packed red blood cells within 48 hour period*
- Chest tube output ≥ 2 L within a 24 hour period

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

Obs: Platelet transfusions should be recorded and reported, but are not included in these definitions until further information is obtained about the relationship to outcomes. * Corrected for transfusion (1 U packed red blood cells or 1 U whole blood_1g/dL haemoglobin). † Cell saver products will not be counted.

TIMI Bleeding Criteria

Non-CABG related bleeding

- Major
  - Any intracranial bleeding (excluding microhaemorrhages < 10mm evident only on gradient-echo MRI)

- Clinically overt signs of haemorrhage associated with a drop in haemoglobin of ≥5g/dL
- Fatal bleeding (bleeding that directly results in death within 7 days

• Minor

- Clinically overt (including imaging), resulting in haemoglobin drop of 3 to < 5g/dL

• Other non-major or minor

- Any overt bleeding event that does not meet the criteria above

Bleeding in the setting of CABG

• Fatal bleeding (bleeding that directly results in death)

• Perioperative intracranial bleeding

• Reoperation after closure of the sternotomy incision for the purpose of controlling bleeding

• Transfusion of ≥5 U PRBCs or whole blood within a 48-h period; cell saver transfusion will not be counted in calculations of blood products.

• Chest tube output >2 L within a 24-h period

GUSTO Bleeding Criteria

Severe or life-threatening

- Intracerebral haemorrhage
- Resulting in substantial hemodynamic compromise requiring treatment

Moderate

- Requiring blood transfusion but not resulting in hemodynamic compromise

Mild

- Bleeding that does not meet above criteria

DEATH

All deaths will be categorized as cardiovascular, non-cardiovascular or undetermined based on the definitions below.

Cardiovascular death

Cardiovascular Death is defined as death resulting from an acute myocardial infarction,

sudden cardiac death, death due to heart failure, death due to stroke, death (immediate) due to cardiovascular (CV) procedures, death due to CV haemorrhage, and death due to other
cardiovascular causes.

Death due to Acute Myocardial Infarction:

- Death by any mechanism (arrhythmia, heart failure, mechanical complication, low output) within 30 days after a myocardial infarction (MI) related to the immediate consequences of the myocardial infarction, such as progressive congestive heart failure (CHF), inadequate cardiac output, or refractory arrhythmia. If these events occur after a "break" (e.g., a CHF and arrhythmia free period of at least a week), they should be designated by the immediate cause, even though the MI may have increased the risk of that event (e.g., late arrhythmic death becomes more likely after an acute myocardial infarction (AMI)). The acute myocardial infarction should be verified to the extent possible by the diagnostic criteria outlined for acute myocardial infarction or by autopsy findings showing recent myocardial infarction or recent coronary thrombus. Sudden cardiac death, if accompanied by symptoms suggestive of myocardial ischemia, new ST elevation, new LBBB, or evidence of fresh thrombus by coronary angiography and/or at autopsy should be considered death resulting from an acute myocardial infarction, even if death occurs before blood samples or 12-lead electrocardiogram (ECG) could be obtained, or at a time before the appearance of cardiac biomarkers in the blood. Death resulting from a procedure to treat a myocardial infarction percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG), or to treat a complication resulting from myocardial infarction, 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.

Sudden Cardiac Death:

- Death that occurs unexpectedly, not following an acute AMI, and includes the following deaths:
  - Death witnessed and occurring without new or worsening symptoms.

o Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless documented (i.e. by ECG or other objective) to be due to acute myocardial infarction.

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).Death after unsuccessful resuscitation from cardiac arrest.

o Death after successful resuscitation from cardiac arrest and without identification of a non-cardiac aetiology.

o Unwitnessed death without other cause of death (information regarding the patient's clinical status preceding death should be provided, if available).

General Considerations: A subject seen alive and clinically stable 24 hours prior to being found dead without any evidence or information of a specific cause of death should be classified as "sudden cardiac death." Typical scenarios include:

- Subject well the previous day but found dead in bed the next day.
- Subject found dead at home on the couch with the television on.
- Deaths for which there is no information beyond "Patient found dead at home" may be classified as "death due to other cardiovascular causes".

Death due to Heart Failure or Cardiogenic Shock:

• Death due to Congestive Heart Failure refers to a death in association with clinically worsening symptoms and/or signs of heart failure not following an acute MI (see section ***). Deaths due to heart failure can have various etiologies, including single or recurrent myocardial infarctions, ischemic or non-ischemic cardiomyopathy, hypertension, or valvular disease. Cardiogenic shock not occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure is defined as systolic blood pressure (SBP) < 90 mm Hg for greater than 1 hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypoperfusion:-

o Cool, clammy skin or

o Oliguria (urine output < 30 mL/hour) or

o Altered sensorium or

o Cardiac index < 2.2 L/min/m²

o Cardiogenic shock can also be defined if SBP < 90 mm Hg and increases to ≥ 90 mm Hg in less than 1 hour with positive inotropic or vasopressor agents alone and/or with mechanical support.

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.

Death due to Cardiovascular procedures refers to death caused by the immediate complications of a cardiac procedure and excludes death resulting from procedures to treat an acute MI or the complications resulting from an acute MI.

Death due to Cardiovascular Haemorrhage refers to death related to haemorrhage such as a non-stroke intracranial haemorrhage, non-procedural or non-traumatic vascular rupture (e.g., aortic aneurysm), or haemorrhage causing cardiac tamponade.

Death due to Other Cardiovascular Causes: Death due to Other Cardiovascular Causes refers to a cardiovascular death not included in the above categories (e.g., pulmonary embolism or peripheral arterial disease).

Non-cardiovascular death:

Non-cardiovascular death is defined as any death that is not thought to be due to a cardiovascular cause. The following categories may be collected

- Non-Malignant Causes
- Pulmonary
- Renal
- Gastrointestinal
- Hepatobiliary
- Pancreatic
- Infection (includes sepsis)
- Non-infectious (e.g., systemic inflammatory response syndrome (SIRS))
- Haemorrhage*, excluding haemorrhagic strokes and bleeding in the setting of coronary revascularization
- Non-cardiovascular procedure or surgery
- Accidental (e.g., physical accidents or drug overdose) or trauma
- Suicide

- Prescription Drug Error (e.g., prescribed drug overdose, use of inappropriate drug, or drug drug
- interaction)
- Neurological process that is not a stroke or haemorrhage
- Other non-cardiovascular, specify: _____

*Examples: Death due to GI bleeding is not considered a CV death. Death due to retroperitoneal haematoma following PCI is considered CV death. Death due to intracerebral haemorrhage is considered CV death.

Malignant Causes

Death results directly from the cancer;

OR

Death results from a complication of the cancer (e.g. infection, complication of surgery /
chemotherapy / radiotherapy);

OR

Death results from withdrawal of other therapies because of concerns relating to the poor
prognosis associated with the cancer

Cancer deaths may arise from cancers that were present prior to randomization or which
developed subsequently should be further classified (worsening prior malignancy; new
malignancy).

Undetermined cause of death:

Undetermined cause of death refers to a death not attributable to one of the above categories of cardiovascular death or to a non-cardiovascular cause, due to absence of any information (e.g., the only available information is “patient died”). The use of this category of death is discouraged and should apply to a minimal number of cases when no information at all on the circumstances of death are available (i.e. found on obituary of local newspaper). In all circumstances the reviewer will use all available information to attribute to one of the categories based on best clinical judgment.

For each death event an assessment will be made as to whether the event was caused, on the basis of the totality of the evidence, by a bleeding (ie a a fatal bleeding occurred) or not.

MYOCARDIAL INFARCTION

For the primary analysis, MI endpoint will be defined based on the third universal definition of myocardial infarction with the exception of peri-procedural MI after PCI, which will be defined according to the SCAI definition. 34,35

For secondary analyses, PCI-related MI according to the Third Universal MI definition (type 4a) will be also adjudicated.

1. Spontaneous MI (>48 hours after intervention, MI type 1)

Symptoms suggestive of ischemia/infarction in association with ECG, cardiac biomarker or pathologic evidence of infarction as follows:34:

- Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin T or I) with at least one value above the 99th percentile upper reference limit 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 LBBB.
- Development of new Q waves in the ECG

Evidence of new loss of viable myocardium or new regional wall motion abnormality

- Identification of an intracoronary thrombus by angiography or autopsy

Spontaneous MI typically occurs after the periprocedural period and may be secondary to late stent complications or progression of native disease (e.g., non-culprit lesion plaque rupture). Performance of ECG and angiography supports adjudication to either a target or non-target vessel or lesion in most cases.

Type 2 MI

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 LVH.

The distinction between type 1 and type 2 MI will be based by consensus on the preponderance of clinical evidence. The diagnosis of type 2 MI requires a predisposing condition as well as an acute Trigger of supply/demand imbalance, including acute anemia, respiratory failure, hypotension, sustained hypertension (with or without left ventricular hypertrophy), prolonged tachy- and brady-arrhythmias, coronary embolism, coronary artery spasm. If the evidence is conflicting or unclear, the MI will be classified as type 1.

Type 3 MI

Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.

Type 4a MI (NOT USED for primary analysis; see definition below)

Type 4 MI is defined by elevation of cTn values (>5 x URL) occurring within 48h of the procedure in patients with normal baseline values (≤URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling.

In addition, at least one of the following is required:

- symptoms suggestive of myocardial ischaemia
- new ischaemic ECG changes
- angiographic findings consistent with a procedural complication
- imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality

Type 4b MI

Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of evidence of myocardial ischaemia and with a rise and/or fall of cardiac biomarker values with at least one value above the URL.

Type 4c MI

A spontaneous MI where a restenosis is the only angiographic explanation

Type 5 MI
Coronary artery bypass grafting (CABG) related MI is defined by elevation of troponin
values (>10 x URL) occurring within 48h of the procedure in patients with normal baseline
cTn values (≤URL).

In addition, at least one of the following is required:
- o new pathological Q waves or new LBBB
- o angiographic documented new graft or new native coronary artery occlusion
- o imaging evidence of new loss of viable myocardium or new regional wall motion
abnormality.

2. Periprocedural MI after PCI (within 48 hours after PCI)
Periprocedural MI is defined based on the SCAI definitions as follows:
1) In patients with normal baseline CK-MB: The peak CK-MB measured within 48 hours of the procedure rises to ≥10x the local laboratory ULN, or to ≥5x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB, OR in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 hours of the PCI rises to ≥70x the local laboratory ULN, or ≥35x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB. .
2) In patients with elevated baseline CK-MB (or cTn) in whom the biomarker levels are stable or falling: The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level.
3) In patients with elevated CK-MB (or cTn) in whom the biomarker levels have not been shown to be stable or falling: The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.

STENT THROMBOSIS

Stent Thrombosis is defined by the Academic Research Consortium as follows:

Definite stent thrombosis is considered to have occurred by either angiographic or pathological confirmation:

a. Angiographic confirmation of stent thrombosis†

The presence of a thrombus‡ that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48-hour time window:

- Acute onset of ischemic symptoms at rest
- New ischemic ECG changes that suggest acute ischemia
- Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI: Troponin or CK-MB > 99th percentile of URL)
- Nonocclusive thrombus. Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolisation of intraluminal material downstream
- Occlusive thrombus TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch)

b. Pathological confirmation of stent thrombosis

Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy

†The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion)

‡Intracoronary thrombus

Probable stent thrombosis:

Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:

- Any unexplained death within the first 30 days.

- Irrespective of the time after the index procedure, any myocardial infarction (MI) which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause.

Possible stent thrombosis:
Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days following intracoronary stenting until end of trial follow up.

STROKE

Stroke is defined as an acute episode of focal or global neurological dysfunction caused by
central nervous system (CNS) vascular injury as a result of hemorrhage or infarction. CNS includes brain, spinal cord and retina.
Classification:
Ischemic Stroke
Ischaemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by CNS infarction. Evidence of infarction is defined as ”Pathological, imaging, or other objective evidence of acute cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; or in absence of the above (i.e. imaging or autopsy unavailable), clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury is based on symptoms persisting ≥24 hours or until death, and other etiologies excluded.
Note, Haemorrhagic infarction, defined as a parenchymal hemorrhage after CNS infarction, is considered an ischaemic stroke
Cerebral Haemorrhage
Hemorrhages in the CNS are classified as stroke if they are non-traumatic, caused by a vascular event, and result in injury to the CNS. In contrast, traumatic hemorrhages will not be characterized as stroke. Subdural hematoma will not be classified as a stroke. The diagnoses included in this section are intracerebral hemorrhage (intra-parenchymal and intraventricular) and subarachnoid hemorrhage (both aneurysmal and non-aneurysmal).
Stroke caused by intracerebral haemorrhage

Rapidly developing clinical signs of neurological dysfunction (focal or global) attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma.

Stroke caused by subarachnoid haemorrhage

Rapidly developing signs of neurological dysfunction (focal or global) and/or headache because of bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord), which is not caused by trauma.

Haemorrhages may be further classified according to location (example, supratentorial,
subtentorial, etc.)

Stroke not otherwise specified

An episode of acute neurological dysfunction presumed to be caused by ischemia or haemorrhage, persisting ≥24 hours or until death, but without sufficient evidence to be
classified as one of the above.

URGENT TARGET VESSEL REVASCULARIZATION

A urgent target vessel revascularization (TVR) is a urgent coronary revascularization in a target coronary vessel (ie a vessel treated during the index PCI). Urgent coronary revascularization is defined as follows:

One or more episodes of rest pain, presumed to be ischemic in origin, which results in either urgent repeat PCI or urgent CABG. In the absence of pain, new ST segment changes (a new ST segment shift > 0.05 mV (0.5 mm) on a 12-lead ECG), indicative of ischemia, acute pulmonary oedema, ventricular arrhythmias, or hemodynamic instability presumed to be ischemic in origin, will constitute sufficient evidence of ischemia. To be considered urgent, the repeat PCI or CABG will be initiated within 24 hours of the last episode of ischemia and not be identified as planned/staged. The episode of ischemia leading to urgent repeat PCI must occur following completion of the index PCI and guide wire removal. CABG initiated within 24 hours of PCI (index or repeat) due to an unsatisfactory result, even in the absence of documented ischemia, will also be considered a urgent coronary revascularization endpoint.

Approval Details of GLASSY Ethics Committee

Country	Sites	Central Ethic Committee	Protocol Number	Approval Date
Austria	4301	Ethikkommision der Stadt Wien	13-064-0413	03-Jul-2017
Belgium	3204-3202-3205-3203	Comité d'Etique LS.P.P.C OM 008	A17/31_23/08	27-Sep-2017
Germany	4902-4903	Ethikkommission des Fachbereichs Medizin-Bfarm	78/13 4038963	21-Jun-2017 15-Aug-2017
Netherlands	3101-3104	Medisch Etische Toetsings Commissie Erasmus MC	NL-43637.678.13	31-May-2017
Italy	3902-3905-3909-3903	Comitato Etico Area Pavia AIFA	20170018252 88004	03-Jul-2017 30-Jul-2018
UK	4404	North-West Liverpool Central Research Ethics Committee	13/NW/0283	26-Jun-2017
Switzerland	4106	Kantonale Ethikkommision Bern	039/13	18-Apr-2017
Poland	4802-4805-4801-4807	PRZEWODNICZACY Komisji Bioetycznej	2013/07/18/02	7-may-2018
Bulgaria	9901	MECTHA ETHYJA KOMHCHR	109-3-010	7-May-2018

GLASSY participating sites

Country	*Site*	*PI*
Belgium	JESSAZIEKENHUIS	Edouard Benit
Germany	Kerckhoff Heart Center	Christoph Liebetrau
Belgium	Imelda Ziekenhuis	Luc Janssens
Italy	Policlinico San Matteo	Maurizio Ferrario
Switzerland	Uni. Hospital Bern	Stephan Windecker
Poland	PAKS Chrzanów	Zurakowski Aleksander
Netherlands	Erasmus MC R'dam	Robert Jan van Geuns
Italy	Ospedaliera S. Maria	Marcello Dominici
Austria	Wilhelminenspital	Kurt Huber
Netherlands	OLVG A'dam	Ton Slagboom
Poland	PAKS Dabrowa	Paweł Buszman
Italy	Ospedale S. Donato	Leonardo Bolognese
Italy	Azienda Ospedaliero di Ferrara	Carlo Tumscitz
Poland	JP2 Krakov	Krzysztof Żmudka
Belgium	CHU de Charleroi	Adel Aminian
Belgium	ZOL St.Jan	Mathias Vrolix
Bulgaria	City Clinic Sofia	Ivo Petrov
UK	Royal Blackburn	Scot Garg
Germany	Rhein Ruhr Center	Christoph Naber
Poland	PAKS Kozle	Janusz Prokopczuk