BLEEDING, THROMBOSIS AND VASCULAR BIOLOGY
Editor-in-Chief: Giovanni de Gaetano, Italy | eISSN: 2785-5309
The Official Journal of the Italian Society for the Study of Hemostasis and Thrombosis
SISET
Società Italiana per lo Studio dell'Emostasi e Trombosi

SUPPLEMENTARY MATERIAL

Impact of CYP2C19 loss-of-function variants on outcomes in atrial fibrillation patients undergoing percutaneous coronary intervention: rationale and study design of the WOEST-3 genetic substudy

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Bleeding, Thrombosis and Vascular Biology 2026; 5:421
doi:10.4081/btvb.2026.421

Appendix

Outcomes definition

1. Bleeding

1.1. ISTH definition [1, 2]

- **Major bleeding**

  Having a symptomatic presentation and:

  - Fatal bleeding, and/or
  - Bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or
  - Bleeding causing a fal in haemoglobin level of 20 g L^{-1} (1.24 mmol L^{-1}) or more, or leading to transfusion of two or more units of whole blood or red cells.

- **Clinically relevant non-major bleeding**

  Any sign or symptom 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 the ISTH definition of major bleeding but does meet at least one of the following criteria:

  - Requiring medical intervention by a healthcare professional
  - Leading to hospitalization or increased level of care
  - Prompting a face to face (i.e., not just a telephone or electronic communication) evaluation

  Examples include:

  - *Epistaxis if it lasts for more than 5 minutes, if it is repetitive (i.e., 2 or more episodes of true bleeding [i.e., no spots on a handkerchief] within 24 hours), or leads to an intervention (packing, electrocautery, etc.)*
  - *Gingival bleeding if it occurs spontaneously (i.e., unrelated to toothbrushing or eating), or if it lasts for more than 5 minutes*
  - *Haematuria if it is macroscopic, and either spontaneous or lasts for more than 24 hours after instrumentation (e.g., catheter placement or surgery) of the urogenital tract*
  - *Macroscopic gastrointestinal haemorrhage: At least 1 episode of melena or haematemesis, if clinically apparent*
  - *Rectal blood loss, if more than a few spots*
  - *Haemoptysis, if more than a few speckles in the sputum*

- *Intramuscular haematoma*
- *Subcutaneous haematoma if the size is larger than 25 cm2 or larger than 100 cm2 if provoked*
- *Multiple source bleeding events*

- **Minor**

  Bleeding episodes not requiring any medical attention and therefore not meeting the criteria for major of clinically relevant non-major bleeding

1.2. BARC definition [3]

- **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 healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare 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 type 3, 4, or 5 but does meet at least one of the following criteria:
  - requiring nonsurgical, medical intervention by a healthcare professional,
  - leading to hospitalization or increased level of care, or
  - prompting evaluation

- **Type 3**
  - **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 micro bleeds or haemorrhagic 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 h
  - 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-h period *Cell saver products are not counted.*
  - Chest tube output ≥2L within a 24-h 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

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

CABG indicates coronary artery bypass graft. 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-h time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.

- **TIMI definition [3]**
  - **Major bleedling**
    - Any intracranial bleeding (excluding micro haemorrhages <10 mm evident only on gradient-echo MRI)
    - Clinically overt signs of haemorrhage associated with a drop in haemoglobin of ≥5 g/dL or a ≥15% absolute decrease in haematocrit
    - Fatal bleeding (bleeding that directly results in death within 7 days)
  - **Minor bleeding**
    - Clinically overt (including imaging), resulting in haemoglobin drop of 3 to <5 g/dL

- Requiring medical attention
  - Any overt sign of haemorrhage that meets one of the following criteria and does not meet criteria for a major or minor bleeding event, as defined above
  - Requiring intervention (medical practitioner-guided medical or surgical treatment to stop or treat bleeding, including temporarily or permanently discontinuing or changing the dose of a medication or study drug)
  - Leading to or prolonging hospitalization
  - Prompting evaluation (leading to an unscheduled visit to a healthcare professional and diagnostic testing, either laboratory or imaging)

- **Minimal bleeding**
  - Any overt bleeding event that does not meet the criteria above
- **CABG related bleeding**
  - 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

2. Death (after ARC-2 and SCTI definitions [4, 5])

All-cause death: death of any cause, which is further categorised in:

- **Cardiovascular Death**

  Death resulting from an acute myocardial infarction, sudden cardiac death, death due to heart failure, death due to stroke, death due to cardiovascular (CV) procedures, death due to CV haemorrhage, and death due to other CV causes. Deaths related to the procedure or concomitant treatment are always classified as cardiovascular.
- **Non-Cardiovascular Death**

  Any death with a specific cause that is not thought to be CV in nature, as defined above. This may be one of, but not limited to, the following: pulmonary, renal, gastrointestinal, hepatobiliary, pancreatic, infection, inflammatory, haemorrhage that is neither CV bleeding or a stroke, non-CV procedure or surgery, trauma, suicide, (non-)prescription drug reaction or overdose, neurological (excluding CV death from ischemic or haemorrhagic stroke or undetermined cause of stroke or CV haemorrhage of central nervous system), malignancy.
- **Undetermined Cause of Death**

  Death not attributable to one of the above categories of CV death or to a non-CV cause. Inability to classify the cause of death may be due to lack of information or when there is

insufficient supporting information or detail to assign the cause of death. In general, most death should be classifiable as CV or non-CV, and the use of this category of death, therefore, should be avoided and should apply to few patients. Such deaths will be classified as cardiovascular for end point determination.

3. Myocardial infarction (according to the 4th Universal Definition of Myocardial Infarction [6])

Universal definitions of myocardial injury and myocardial infarction

Criteria for myocardial injury

The term myocardial injury should be used when there is evidence of elevated cardiac troponin values (cTn) with at least one value above the 99th percentile upper reference limit (URL). The myocardial injury is considered acute if there is a rise and/or fall of cTn values.

Criteria for acute myocardial infarction (types 1, 2 and 3 MI)

The term acute myocardial infarction should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischaemia and with detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and at least one of the following:

- Symptoms of myocardial ischaemia;
- New ischaemic ECG changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology;
- Identification of a coronary thrombus by angiography or autopsy (not for types 2 or 3 MIs).

Post-mortem demonstration of acute athero-thrombosis in the artery supplying the infarcted myocardium meets criteria for *type 1 MI*.

Evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute athero-thrombosis meets criteria for *type 2 MI*.

Cardiac death in patients with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes before cTn values become available or abnormal meets criteria for *type 3 MI*.

Criteria for coronary procedure-related myocardial infarction (types 4 and 5 MI)

Percutaneous coronary intervention (PCI) related MI is termed *type 4a MI.*

Coronary artery bypass grafting (CABG) related MI is termed *type 5 MI.*

Coronary procedure-related MI ≤ 48 hours after the index procedure is arbitrarily defined by an elevation of cTn values > 5 times for *type 4a MI* and > 10 times for *type 5 MI* of the 99th percentile URL in patients with normal baseline values. Patients with elevatedpre-procedural cTn values,

in whom the pre-procedural cTn level are stable (≤ 20% variation) or falling, must meet the criteria fora > 5 or > 10 fold increase and manifest a change from the baseline value of > 20%. In addition with at least one of the following:

- New ischaemic ECG changes (this criterion is related to *type 4a MI* only);
- Development of new pathological Q waves;
- Imaging evidence of loss of viable myocardium that is presumed to be new and in a pattern consistent with an ischaemic aetiology;
- Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or graft, side-branch occlusion-thrombus, disruption of collateral flow or distal embolization.

Isolated development of new pathological Q waves meets the *type 4a MI* or *type 5 MI* criteria with either revascularization procedure if cTn values are elevated and rising but less than the pre-specified thresholds for PCI and CABG.

Other types of 4 MI include *type 4b MI* stent thrombosis and *type 4c MI* restenosis that both meet type 1 MI criteria.

Post-mortem demonstration of a procedure-related thrombus meets the *type 4a MI* criteria or *type 4b MI* criteria if associated with a stent.

Criteria for prior or silent/unrecognized myocardial infarction

Any one of the following criteria meets the diagnosis for prior or silent/unrecognized MI:

- Abnormal Q waves with or without symptoms in the absence of non-ischaemic causes.
- Imaging evidence of loss of viable myocardium in a pattern consistent with ischaemic aetiology.
- Patho-anatomical findings of a prior MI.

4. Stent thrombosis (according to the ARC-2 definitions [4])

Further categorized in:

- Definite stent/scaffold thrombosis

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

  - Angiographic confirmation of stent/scaffold thrombosis
    - The presence of a thrombus that originates in the stent/scaffold or in the segment 5 mm proximal or distal to the stent/scaffold or in a side branch originating from the stented/scaffolded segment and the presence of at least one of the following criteria:
      - Acute onset of ischemic symptoms at rest
      - New electrocardiographic changes suggestive of acute ischemia

- Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous myocardial infarction)

Occlusive thrombus: Thrombolysis in Myocardial Infarction grade 0 or 1 flow within or proximal to a stent/scaffold segment. Nonocclusive thrombus: intracoronary thrombus is defined as a (spherical, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, persistence of contrast material within the lumen, or visible embolization of intraluminal material downstream.

Or

- Pathological confirmation of stent/scaffold thrombosis
  - Evidence of recent thrombus within the stent/scaffold determined at autopsy
  - Examination of tissue retrieved following thrombectomy (visual/histology)

- Probable stent/scaffold thrombosis
  - Regardless of the time after the index procedure, any myocardial infarction that is related to documented acute ischemia in the territory of the implanted stent/scaffold without angiographic confirmation of stent/scaffold thrombosis and in the absence of any other obvious cause.

    When the stented/scaffolded segment is in the left circumflex coronary artery or in the presence of pre-existing electrocardiographic abnormalities (eg, left bundle branch block, paced rhythms), definitive evidence of localization may be absent and Clinical Events Committee Adjudication is based on review of all available evidence
- Silent stent/scaffold occlusion
  - The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered stent thrombosis.

<u>Timing of stent thrombosis (duration after stent implantation)</u>

- Acute 0–24 h
- Subacute >24 h–30 d
- Late >30 d–1 y
- Very late >1

0h defined as the moment the patients is undraped and taken off the catheterization table
Early stent thrombosis is 0-30 days (acute plus subacute stent thrombosis)

5. Stroke and TIA (after VARC-2 definitions [7])

Diagnostic criteria

- Acute episode of a focal or global neurological deficit with at least one of the following: change in the level of consciousness, hemiplegia, hemiparesis, numbness, or sensory loss

affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke

- **Stroke:** duration of a focal or global neurological deficit≥24 h; OR<24 h if available neuroimaging documents a new haemorrhage or infarct; OR the neurological deficit results in death
- **TIA:** duration of a focal or global neurological deficit <24 h, any variable neuroimaging does not demonstrate a new haemorrhage or infarct
- No other readily identifiable non-stroke cause for the clinical presentation, to be determined by or in conjunction with the designated neurologist
- Confirmation of the diagnosis by at least one of the following
    - Neurologist or neurosurgical specialist
    - Neuroimaging procedure (CT scan or brain MRI), but stroke maybe diagnosed on clinical grounds alone

Stroke classification

Ischaemic without haemorrhagic transformation: an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue

Ischaemic with haemorrhagic transformation: haemorrhage may be consequence of a ischaemic stroke. In this situation, the stroke is an ischaemic stroke with haemorrhagic transformation and not a haemorrhagic stroke

Haemorrhagic: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid haemorrhage

Undetermined: a stroke may be classified as undetermined if there is insufficient information to allow categorization as ischaemic or haemorrhagic

Stroke definitions

Disabling stroke: an mRS score of 2 or more at 90 days and an increase in at least one mRS category from an individual's pre-stroke baseline

Non-disabling stroke: an mRS score of <2 at 90 days or one that does not result in an increase in at least one mRS category from an individual's pre-stroke baseline

6. Systemic embolism (according to ENTRUST-AF PCI definition [8])

A SEE is defined as an abrupt episode of arterial insufficiency associated with clinical or radiologic evidence of arterial occlusion in the absence of other likely mechanisms (e.g., atherosclerosis, instrumentation). Arterial embolic events involving the CNS (including the eye), coronary, and pulmonary arterial circulation are not considered SEEs, but correspond respectively to stroke/TIA, myocardial infarction, and pulmonary embolism. In the presence of

atherosclerotic peripheral vascular disease, diagnosis of embolism to the lower extremities requires arteriographic demonstration of abrupt arterial occlusion.

SEE will be further classified according to the affected location:
- upper extremity
- lower extremity
- abdominal excluding renal
- renal

Fatal SEEs are defined as those that lead to death within 7 days.

7. Coronary revascularization (according to the ARC-2 definitions [4])

Target lesion revascularization

- The target lesion is defined as the treated segment including the 5-mm margin proximal and distal to the stent/scaffold.
- Target lesion revascularization is defined as a repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion.

Target vessel revascularization

- The target vessel is defined as the entire major intervened coronary vessel, including side branches.
- Target vessel revascularization is defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel including the target lesion.

Target vessel non-target lesion revascularization

- Target vessel non-target lesion revascularization is defined as any repeat percutaneous intervention or surgical bypass of the target vessel for pre-existing disease, disease progression or other reasons unrelated to the target lesion as defined above.

8. PCI/revascularization status (according to SCTI definitions [5])

Elective:

The procedure can be performed on an outpatient basis or during a subsequent hospitalization without significant risk of myocardial infarction (MI) or death. For stable in-patients, the procedure is being performed during this hospitalization for convenience and ease of scheduling and **NOT** because the patient's clinical situation demands the procedure prior to discharge.

Urgent:

The procedure should be performed on an inpatient basis and prior to discharge because of significant concerns that there is risk of myocardial ischemia, MI, and/or death. Patients who are

outpatients or in the emergency department at the time that the cardiac revascularization is requested would warrant hospital admission based on their clinical presentation.

Emergency:

The procedure should be performed as soon as possible because of substantial concerns that ongoing myocardial ischemia and/or MI could lead to death. "As soon as possible" refers to a patient who is of sufficient acuity that one would cancel a scheduled case to perform this procedure immediately in the next available room during business hours, or one would activate the on-call team were this to occur during off-hours.

Salvage:

The procedure is a last resort. The patient is in cardiogenic shock when the PCI begins (i.e., the time at which the first guide wire or intracoronary device is introduced into a coronary artery or bypass graft for the purpose of mechanical revascularization) **OR** within the last ten minutes prior to the start of the case or during the diagnostic portion of the case, the patient has also received chest compressions or has been on unanticipated circulatory support (e.g., intra-aortic balloon pump, extracorporeal membrane oxygenation, or cardiopulmonary support).

9. NYHA functional classification

Symptoms include fatigue, palpitation, dyspnea (shortness of breath), angina etc. attributed to the patient's cardiac disease.

Ordinary physical activity comprises walking, climbing the stairs etc.

Class I - No limitation in ordinary physical activity. Ordinary activity does not cause undue symptoms.

Class II - Mild symptoms and slight limitation during ordinary activity. Comfortable at rest. Ordinary physical activity results in symptoms.

Class III - Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20-100 m). Comfortable only at rest.

Class IV - Severe limitations. Unable to carry on any physical activity without discomfort. Experiences symptoms even while at rest. If any physical activity is undertaken, discomfort increases. Mostly bedbound patients.

10. Canadian Cardiovascular Society (CCS) Angina grade

Grade I - Angina with strenuous/rapid/prolonged exertion at work or recreation only; no angina with ordinary physical activity, e.g. walking, climbing stairs.

Grade II - Ordinary activity slightly limited: angina with walking/climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold/wind, under emotional stress, during few hours

after awakening, walking >2 blocks on level ground, or climbing >1 flight of stairs at normal pace and normal conditions.

Grade III - Marked limitation of ordinary physical activity: angina with walking 1-2 blocks on level ground or climbing 1 flight of stairs at normal pace and normal conditions.

Grade IV - Inability to carry on any physical activity without discomfort; anginal syndrome may be present at rest.

SUPPLEMENTARY APPENDIX – REFERENCES

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