Supplementary Appendix

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SUPPLEMENTAL TABLE

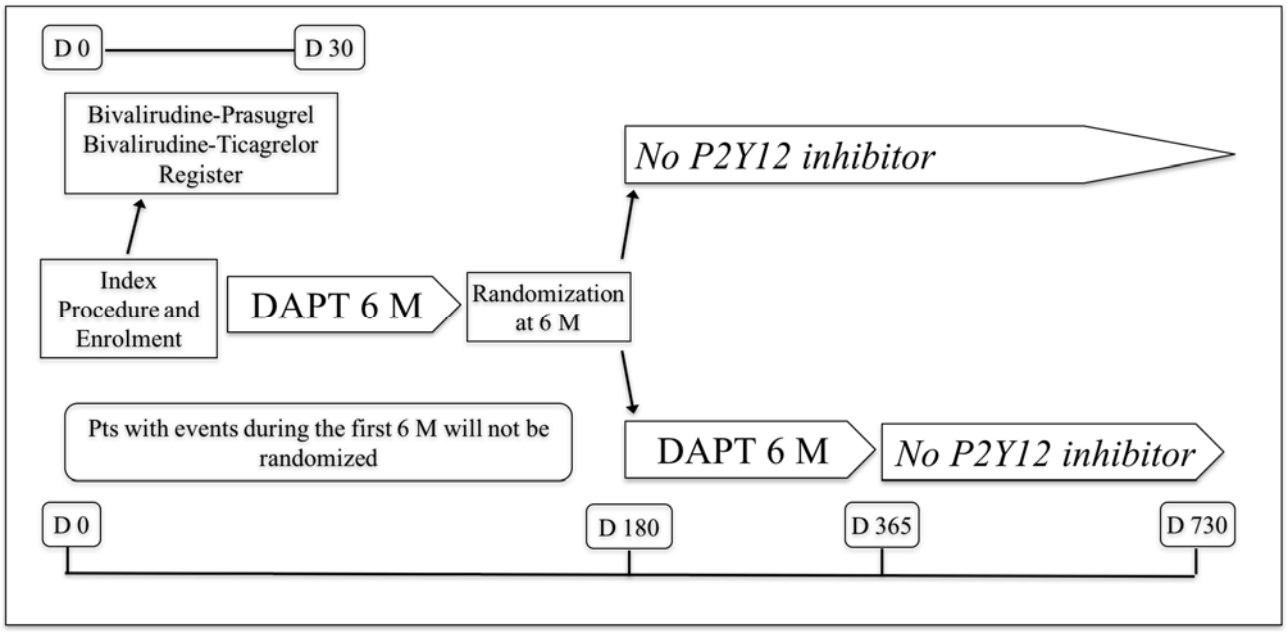
Table e1 Inclusion and Exclusion criteria

INCLUSION CRITERIA ENROLMENT
STEMI patients between 18-85 years, who underwent primary PCI with a second generation drug eluting stent implantation
EXCLUSION CRITERIA ENROLMENT
Intolerance to Aspirin, Prasugrel, Ticagrelor, Clopidogrel, Heparin, Bivaluridin, Zotarolimus or Everolimus
Known bleeding diathesis or known coagulopathy
Planned elective surgical procedure necessitating interruption of dual antiplatelet therapy during the first 6 months after randomization.
History of stent thrombosis
Drug eluting stent in main left coronary artery
Active bleeding, known bleeding diathesis or known coagulopathy.
Oral anticoagulant therapy with Coumadin derivates
Malignancies or other comorbidity with a life expectancy of less than one year or that may result in protocol noncompliance
Pregnancy (present, suspected or planned) or positive pregnancy test (in women with childbearing potential a negative pregnancy test is mandatory)
INCLUSION CRITERIA RANDOMIZATION
Patients that **are event-free and on** DAPT **at 6 months.**
EXCLUSION CRITERIA RANDOMIZATION
Occurrence of death, myocardial infarction, stent thrombosis and target vessel or any unscheduled revascularization during the first 6 months after inclusion, with the exception of (scheduled) revascularizations in non-culprit lesions, performed within 45 days from the primary PCI
Stroke or bleeding or surgical procedure requiring discontinuation of DAPT during the first 6 months after inclusion
Oral anticoagulant therapy

STEMI= ST elevation myocardial infarction; DAPT= dual antiplatelet therapy; PCI= percutaneous coronary intervention

SUPPLEMENTAL FIGUREs

Figure e1 Study Flow chart

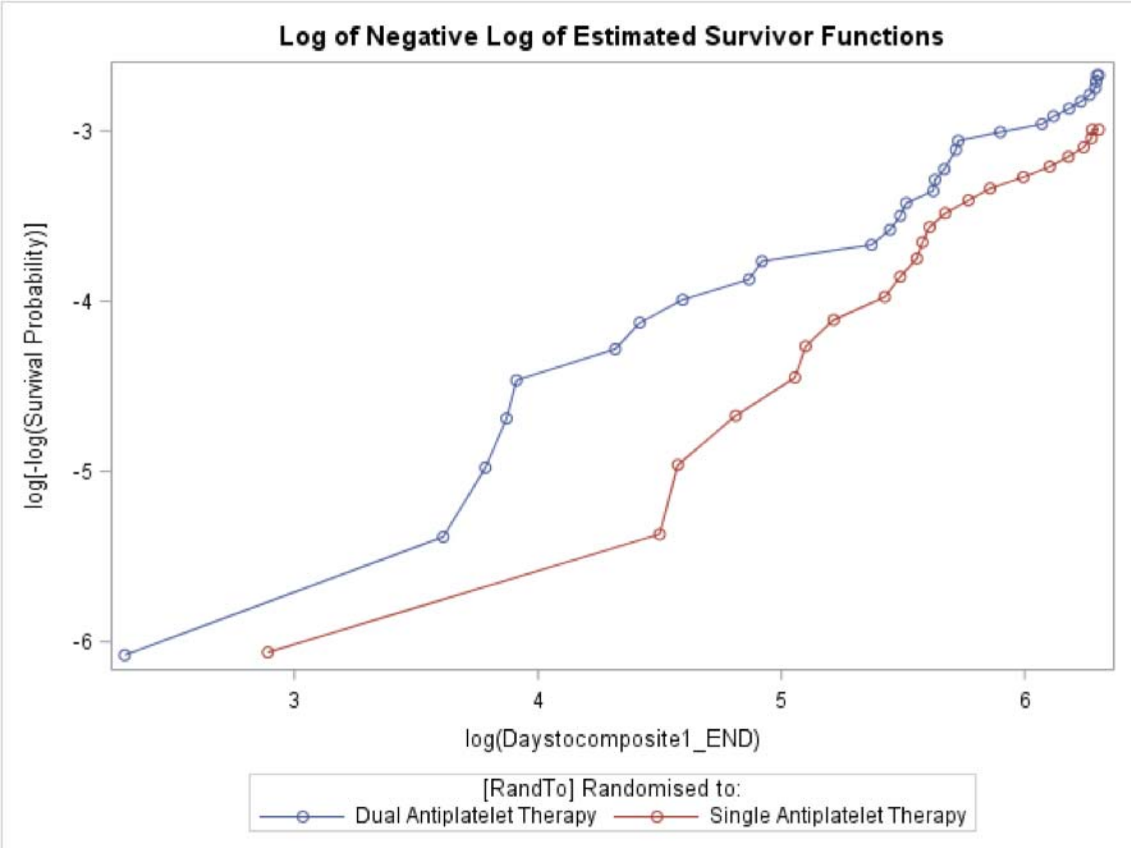


DAPT= dual antiplatelet therapy, M= months

E- figure 2.

Graphical checks examining HR proportionality assumption

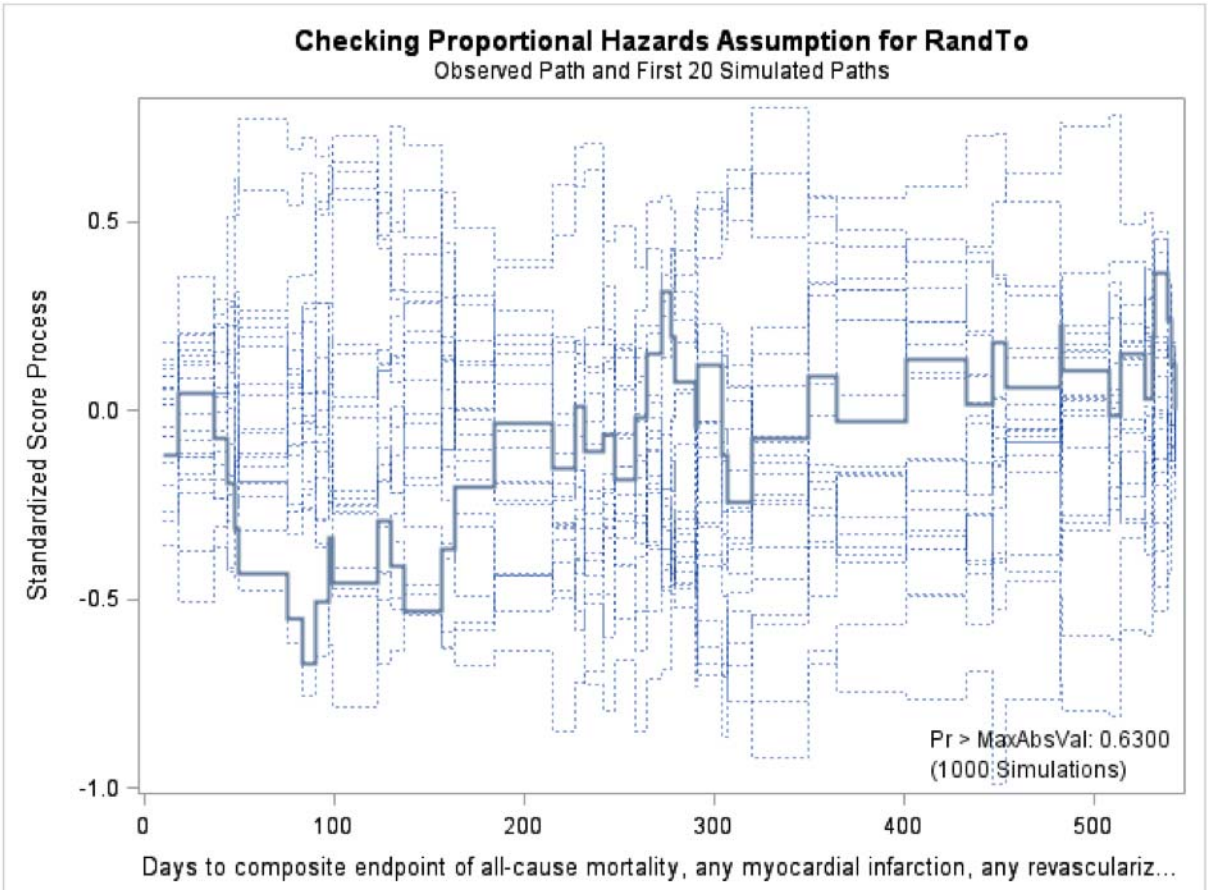
Graphical checks: If the two lines are parallel, then the hazards can be considered proportional



E-figure 3.

Supremum test examining HR proportionality assumption

The supremum test p-value of 0.63 indicates that the proportional hazards assumption does hold when comparing SAPT vs. DAPT.



Supremum Test for Proportionals Hazards Assumption				
Variable	**Maximum Absolute Value**	**Replications**	**Seed**	**Pr > MaxAbsVal**
RandTo	0.6715	1000	1963961059	0.6300

END POINT DEFINITIONS

1) Death

The primary end point includes death from any cause. All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established.

- **Cardiac death**: any death due to immediate cardiac cause (e.g. myocardial infarction, low-output failure, fatal arrhythmia). Unwitnessed death and death of unknown cause will be classified as cardiac death. This includes all procedure related cardio-vascular deaths including those related to concomitant treatment.
- **Non-cardiac death**: any death not covered by the above definitions, including death due to infection, sepsis, pulmonary causes, accident, malignancy, suicide or trauma.

2) Myocardial infarction (MI) definitions

All myocardial infarction data are analysed according the ARC definitions[1]

- Peri-procedural MI. Peri-procedural during percutaneous coronary intervention (PCI) (within 48 hours after PCI**):** a rise of CKMB >3 times ULN is considered evidence of peri-procedural MI.

- **Periprocedural MI during coronary artery by pass (CABG) (within 7 days after CABG):** in patients undergoing CABG during the study follow-up period, a periprocedural MI is diagnosed by a rise in the CK-MB level of five times the upper limit of normal
- **Peri-procedural Myocardial Infarction in the setting of evolving MI:**

  1) If the peak total CK (or CK-MB) from the index infarction has not yet been reached:
  recurrent chest pain lasting >20 minutes (or new ECG changes consistent with MI) and
  the peak CK (or CK-MB in absence of CK) level measured within 24 hours after the event
  is elevated by at least 50% above the previous level.

  2) If the elevated CK (or CK-MB) levels from the index infarction are falling or have returned to normal within 24 hours post index PCI: either a new elevation of CK >2 x ULN within 24 hours post index PCI if the CK level has returned to <ULN OR a rise by >50% above the previous nadir level if the CK level has not returned to <ULN.

Spontaneous MI. Either one of the following criteria satisfies the diagnosis for an acute, evolving or recent MI:

1) Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:

a) Ischemic symptoms; b) development of pathologic Q waves on the ECG c) ECG changes indicative of ischemia (ST segment elevation or depression);

2) Pathologic findings of an acute MI.

Q-wave MI: Development of new pathological Q waves in 2 or more contiguous leads with or without postprocedure CK or CK-MB levels elevated above normal.

Non-Q wave MI: Confirmed MIs (see above) without the development of Q-Wave

3) Revascularization

Any revascularisation: any clinically indicated revascularisation procedure (PCI or CABG) not foreseen at randomization will be considered as a revascularisation event.

The following definitions will be followed in the adjudication of secondary endpoints in the trial or registers.

- **Urgent revascularization**: any PCI or bypass surgery 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-elective procedure.

- **Target lesion revascularisation (TLR):** TLR is defined as any ischemia-driven repeat PCI of the target lesion or bypass surgery of the target vessel. Target lesion is defined as the vessel segment composed by the treated segment including the adjacent 5mm distal and proximal to the treated segment.

- Target vessel revascularisation (TVR): TVR as any ischemia-driven repeat PCI or bypass surgery in any lesion of the target vessel. The target vessel is one.

- Target lesion failure (TLF): TLF defined as cardiac death, target-vessel myocardial infarction, or any target lesion revascularization.

- Target vessel failure (TVF): TVF defined as cardiac death, target-vessel myocardial infarction, or

any target vessel revascularization.

4) Stent Thrombosis

We follow the ARC definitions[1]. Stent Thrombosis is reported as a cumulative value at the different time points and with the different separate time points. Time 0 is defined as the time point after the guiding catheter has been removed and the patient left the Cathlab.

Timing:

Acute stent thrombosis(*): 0 – 24 hours post stent implantation

Subacute stent thrombosis(*): >24 hours – 30 days post stent implantation

Late stent thrombosis: >30 days – 1 year post stent implantation

Very late stent thrombosis: >1 year post stent implantation

(*) acute/subacute can also be replaced by early stent thrombosis.
Early stent thrombosis (0 –30 days) – this definition is currently used in the community.

Category:

We recognize three categories of evidence in defining stent thrombosis:

1. Definite; 2. Probable; 3. Possible

Ad 1. Definite* stent thrombosis:

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)

* Definite stent thrombosis is considered to have occurred by either angiographic or pathological confirmation.
†The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion)

Degree of occlusion

A. 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 embolization of intraluminal material downstream.

B. Occlusive thrombus

TIMI 0 or TIMI 1 intra stent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch).

Pathologic confirmation of stent thrombosis: Evidence of recent thrombus within the stent determined at autopsy

Ad 2. Probable:

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

1. Any unexplained death within the first 30 days.
2. 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.

Ad 3. Possible:

Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death following intracoronary stenting until the end of the follow-up period

5) Stroke

Acute neurological event of at least 24 hours of duration, with focal signs and symptoms and without evidence supporting any alternative explanation. Diagnosis of stroke requires confirmation by computed tomography (CT) or magnetic resonance imaging (MRI) or pathological confirmation.

Aetiology:

- Hemorrhagic stroke: including intraparenchymal, subarachnoid hemorrhage and subdural hematomas)
- Ischemic stroke
- Unknown cause: in which case there was no brain imaging or autopsy

6) Bleeding

For the DAPT-STEMI, bleeding as a primary endpoint will be defined using the TIMI (major and minor) criteria[2], however the data will also be registered following the Bleeding Academic Research Consortium (BARC) classification[3].

TIMI: Types of TIMI Bleeding (DAPT-STEMI primary endpoint composite)

1. Major:

Any intracranial bleeding

OR

Clinically overt signs of hemorrhage associated with a drop in hemoglobin (Hb) of ≥ 5 g/dL or an absolute drop in hematocrit of at least 15% (when HB not available).

2. Minor:

Any clinically overt signs of hemorrhage (including imaging) that is associated with a fall in Hb of 3 to < 5 g/dL (when a Hb value was not available, a fall in the hematocrit of 9 % to <15% points) if no bleeding site was identifiable, or drop of ≥40 g/L in hemoglobin (or ≥12% in hematocrit)

3**. Medical Attention:**

Any overt sign of hemorrhage that requires medical evaluation, medical treatment (including discontinuation of medications), or surgical treatment, and that does not meet criteria for a major or minor bleeding event, as defined above.

4. Minimal

Any overt bleeding event that does not meet the criteria above

Relationship of Bleeding to Death

1. Fatal Bleeding:

Death in which a bleeding event directly led to death within 7 days. Examples of fatal bleeding events are an intracranial hemorrhage that led to herniation of the brain and death within 24 hours, and a massive gastrointestinal hemorrhage that results in shock, hemodynamic collapse, and death. If a bleeding event is considered fatal, then the cause of death must be either intracranial or non-intracranial bleeding.

2. Bleeding Contributed to Death:

Death in which a bleeding event was part of a causal chain of medical events that ultimately led to death within 30 days of the bleed, but bleeding was not directly and/or immediately related to the subject's death. An example of bleeding contributing to death is a large retroperitoneal bleed that leads to surgical evacuation, development of a subsequent abscess in the area of bleeding that leads to sepsis, multiorgan failure, and death 10 days after the onset of bleeding. If bleeding has contributed to death (but the bleeding was not categorized as "fatal"), then the cause of death must be recorded as something other than intracranial / non-intracranial bleeding.

Bleeding in the Setting of Coronary Artery Bypass Graft Surgery (CABG)

Minor and minimal bleeding are not adjudicated in the setting of CABG. As a drop in hemoglobin and transfusions are commonplace in routine CABG cases, one of the following criteria must be met to qualify for major bleeding in any of the preceding definitions:

1. Fatal bleeding (i.e., bleeding that directly results in death)
2. Perioperative intracranial bleeding
3. Reoperation following closure of the sternotomy incision for the purpose of controlling bleeding
4. Transfusion of ≥ 5 units of packed red blood cells (PRBCs) or whole blood within a 48 hour period. Cell saver transfusion will not be counted in calculations of blood products
5. Chest tube output > 2 L within a 24 hour period

BARC bleeding definitions

Type 0: No evidence of 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. Examples include, but are not limited to, bruising, hematoma, nosebleeds, or hemorrhoidal bleeding for which the patient does not seek medical attention. Type I bleeding may include episodes that lead to discontinuation of medications by the patient because of bleeding without visiting a health care provider.

Type 2: Any clinically overt sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance; including bleeding found by imaging alone) that is actionable, but does not meet criteria for Type 3 BARC bleeding, Type 4 BARC bleeding (CABG-related), or Type 5 BARC bleeding (fatal bleeding). The bleeding must require diagnostic studies, hospitalization or treatment by a health care professional. In particular, the bleeding mustmeet at least one of the following criteria: 1) Requiring intervention: defined as a health care professional-guided medical treatment or percutaneous intervention to stop or treat bleeding, including temporarily or permanently discontinuing a medication or study drug. Examples include, but are not limited to, coiling, compression, use of reversal agents (e.g. vitamin K, protamine), local injections to reduce oozing, or a temporary/permanent cessation of antiplatelet, antithrombin, or fibrinolytic therapy; 2) Leading to hospitalization or an increased level of care: defined as leading to or prolonging hospitalization or transfer to a hospital unit capable of providing a higher level of care; or 3) Prompting evaluation: defined as leading to an unscheduled visit to a healthcare professional resulting in diagnostic testing (laboratory or imaging). Examples include, but are not limited to, hematocrit testing, hemoccult testing, endoscopy, colonoscopy, computed tomography scanning, or urinalysis. A visit or phone call to a healthcare professional where neither testing nor treatment is undertaken does not constitute Type 2 bleeding.

Type 3: Clinical, laboratory, and/or imaging evidence of bleeding with specific healthcare provider responses, as listed below.

a. BARC Type 3a Bleeding

- Any transfusion with overt bleeding
- Overt bleeding plus hemoglobin drop ≥3 to <5 g/dL* (provided hemoglobin drop is related to

bleeding)

b. BARC Type 3b Bleeding

- 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 drugs

c. BARC Type 3c Bleeding

- Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation; does include intraspinal).
    - Subcategories; Confirmed by autopsy or imaging or lumbarpuncture
- Intra-ocular bleed compromising vision

*Hb drop should be corrected for intracurrent transfusion, where 1 unit of packed red blood cells or 1 unit of whole blood would be expected to increase Hb by 1g/dl

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 a 48 hour period*
- Chest tube output ≥ 2L within a 24 hour period.

Note: 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

* only allogenic transfusions are considered as transfusions for CABG-related bleeds

Type 5: Fatal Bleeding. Fatal bleeding is bleeding that directly causes death with no other explainable cause. BARC Fatal Bleeding is categorized as either definite or probable as follows:

a) Probable fatal bleeding (Type 5a) is bleeding that is clinically suspicious as the cause of death, but the bleeding is not directly observed and there is no autopsy or confirmatory imaging.

b) Definite fatal bleeding (Type 5b) is bleeding that is directly observed (either by clinical specimen – blood, emesis, stool, etc.- or by imaging) or confirmed on autopsy.

The site of fatal bleeding is specified as intracranial, gastrointestinal, retroperitoneal, pulmonary, pericardial, gastrourinary, or other.

BARC fatal bleeding is meant to capture deaths that are directly due to bleeding with no other cause. The time interval from the bleeding event to the death should be considered with respect to likely causality, but there is no specific time limit proposed. Bleeding that is contributory but not directly causal to death is not classified as fatal bleeding, but may be categorized as other forms of bleeding. Bleeding that leads to cessation of antithrombotic or other therapies may be contributory, but again, would not be classified as fatal bleeding.

Bleeding associated with trauma or with surgery may be fatal, depending on whether it was determined to be directly causal or not.

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2. Chesebro JH, Knatterud G, Roberts R, Borer J, Cohen LS, Dalen J, Dodge HT, Francis CK, Hillis D, Ludbrook P and et al. Thrombolysis in Myocardial Infarction (TIMI) Trial, Phase I: A comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. *Circulation*. 1987;76:142-54.

3. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, Serebruany V, Valgimigli M, Vranckx P, Taggart D, Sabik JF, Cutlip DE, Krucoff MW, Ohman EM, Steg PG and White H. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation*. 2011;123:2736-47.

DAPT STEMI TRIAL ORGANIZATION

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