SUPPLEMENTAL MATERIAL

Defining high bleeding risk in patients undergoing percutaneous coronary intervention – a consensus document from the Academic Research Consortium for High Bleeding Risk

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Supplementary table 1. Key patient-related characteristics and exclusion criteria in pivotal randomized trials of DES submitted for FDA review

Trial	**ENDEAVOR II** [1]	**RESOLUTE US** [2]	**SPIRIT III** [3]	**PLATINUM** [4]	**EVOLVE II** [5]	**BIONICS** [6]	**BIOFLOW-V** [7]
Investigational device	permanent polymer ZES	permanent polymer ZES	permanent polymer EES	permanent polymer EES	bioabsorbable polymer EES	permanent polymer RES	bioabsorbable polymer SES
Age, y (mean ± SD)	62±11	64±10	63±10	64±10	64±10	63±10	65±10
Upper age limit	not specified	not specified	not specified	not specified	not specified	not specified	not specified
Advanced renal impairment	Cr >2.0 mg/dl	Cr >2.5 mg/dl	Cr >2.5 mg/dl	CrCl <50 mL/min	Cr >2.0 mg/dl	CrCl <30 mL/min	CrCl <30 mL/min
Bleeding disorders or recent bleeding	X	not specified	X	X	X	X	X
Hematological disorders and/or coagulopathy	X	X	X	X	X	X	X
Stroke or TIA: exclusion time frame	<6 months	<6 months	<6 months	<6 months	<6 months	<6 months	<6 months
Contraindications or inability to comply with DAPT	X	X	X	not specified	X	X	X
OAC required	not specified	not specified	X	X	X	not specified	X
Likely unable to comply with	not specified	X	X	X	X	X	X

DAPT protocol							

Cr = creatinine; Cr Cl = creatinine clearance; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; EES = everolimus-eluting stents; OAC = oral anticoagulation; RES = ridaforolimus -eluting stents; SES = sirolimus-eluting stents; ZES = zotarolimus-eluting stents

X denotes excluded. Inclusion and exclusion criteria were abstracted from the published manuscript reporting the primary results or trial design, the trial registration entry or the trial protocol (according to availability)

Supplementary table 2. Inclusion criteria in completed and selected ongoing trials in patients at increased bleeding risk

	LEADERS FREE [8]	**ZEUS-HBR** [9]	**SENIOR** [10]	**MASTER DAPT** (NCT03023020)	**ONYX ONE** (NCT03344653)	**COBRA REDUCE** (NCT02594501)	**EVOLVE SHORT DAPT** (NCT02605447)	**XIENCE 28/ XIENCE 90** (NCT03355742 and NCT03218787)
Type of trial	RCT (published)	RCT (published)	RCT (published)	RCT (ongoing)	RCT (ongoing)	RCT (ongoing)	Single arm (ongoing)	Single arm (ongoing)
Age ≥75 (or >80*)		✔ *	✔	✔	✔		✔	✔
OAC	✔	✔		✔	✔	✔	✔	✔
Renal failure	✔				✔		✔	✔
Liver disease	✔			✔	✔			
Recent cancer	✔			✔	✔			
Anemia or transfusion	✔	✔		✔	✔			✔
Thrombocytopenia	✔	✔		✔	✔		✔	✔
Stroke or ICH	✔			✔	✔		✔	✔
Actionable bleed				✔			✔	✔
Hospitalization for bleeding	✔	✔		✔	✔			

NSAID	✔	✔		✔	✔			
Early planned surgery	✔				✔			
PRECISE-DAPT score >25				✔				

ICH = intracranial hemorrhage; NSAIDS = non-steroidal anti-inflammatory drugs; OAC = oral anticoagulation; RCT: randomized controlled trial

*The lower age cut-off for HBR is ≥75 years in all trials but ZEUS-HBR (age cut-off >80 years).

Supplementary table 3. One-year bleeding rates according to inclusion criteria in the LEADERS FREE trial

Inclusion criteria*	**Patients, n (%)**	**Patients with BARC 3-5 bleeding†, n (%)**
Age ≥75 years	1564 (64.3)	118 (7.6)
Planned oral anticoagulant after PCI	879 (36.1)	78 (8.9)
Renal insufficiency‡	464 (19.1)	49 (10.6)
Planned major surgery that would require interruption of DAPT	398 (16.4)	30 (7.5)
Hemoglobin < 11 g/dL or transfusion during the prior 4 weeks	377 (15.5)	61 (16.2)
Non-skin cancer diagnosed or treated during the prior 3 years	239 (9.8)	23 (9.6)
Expected poor compliance with DAPT for other medical reasons	88 (3.6)	4 (4.6)
Hospital admission for bleeding during the prior 12 months	79 (3.2)	10 (12.7)
Chronic glucocorticoid- or NSAID-use	72 (3.0)	6 (8.3)
Thrombocytopenia (< 100 x 10^9/L)	38 (1.6)	2 (5.3)

Any stroke during the prior 12 months	39 (1.6)	1 (2.6)
Any prior intra-cerebral bleed	33 (1.4)	2 (6.1)
Severe liver disease§	21 (0.9)	3 (14.3)

* Inclusion criteria are not mutually exclusive (on average, patients met 1.7 criteria).

† according to inclusion criterion

‡ defined as creatinine clearance <40 ml/min

§ history of variceal hemorrhage, presence of ascites, hepatic encephalopathy or jaundice

DAPT = dual antiplatelet therapy; NSAID = non-steroidal anti-inflammatory drug; PCI = percutaneous coronary intervention

Supplementary table 4. Variables in scores to assess long-term bleeding risk in patients taking antiplatelet therapy

	REACH [11]	**Dutch ASA and NSAIDS score** [12]	**DAPT*** [13]	**PARIS** [14]	**PRECISE-DAPT** [15]	**BleeMACS** [16]
Age	✔	✔	✔	✔	✔	✔
BMI		NA		✔	NA	NA
OAC	✔	✔	Excluded	✔	Excluded	Excluded
APT (*DAPT)	✔	✔	✔	NA	NA	NA
Anemia	NA	✔	NA	✔	✔	✔
White cell count	NA	NA	NA	NA	✔	NA
Renal insufficiency		NA	✔	✔	✔	✔
Prior bleed	NA	NA	NA	NA	✔	✔
Diabetes	✔	✔				
Current smoking	✔	NA		✔		
Hypertension	✔	NA	✔			✔
Hypercholesterolemia	✔	NA	NA			
Peripheral artery disease	✔	NA	✔		NA	✔
Chronic heart failure	✔	NA		NA	NA	

Prior malignancy	NA	NA		NA	NA	✔

✔ indicates that the variable is included in the multivariate model

ACS = acute coronary syndrome; ASA = aspirin; APT = antiplatelet treatment; AUC = area under the curve; BMI: body mass index; CAD = coronary artery disease; DAPT = dual antiplatelet treatment; HBR: high bleeding risk; NA = not assessed; OAC = oral anticoagulation

*The DAPT score is not purely a bleeding risk score, rather a score to predict benefit vs. harm of prolonged dual antiplatelet therapy (> one year) in patients after PCI. As such, it integrates covariates independently associated with bleeding (but not ischemic) risk and vice versa.

Supplementary table 5. Recent large non-randomized head-to-head comparisons of OAC therapies

Author	OAC evaluated	Patients, n	Statistical adjustment	Main outcome
Noseworthy P.A. et al.[17]	Dabigatran Rivaroxaban Apixaban	57,788	PSM	Similar efficacy Apixaban: ↓ major bleeding vs. rivaroxaban or dabigatran Rivaroxaban: ↑ major bleeding vs. dabigatran
Lip G.Y. et al.[18]	Dabigatran Rivaroxaban Apixaban Warfarin	45,361	PSM	Rivaroxaban: ↑ major bleeding vs. apixaban
Hernandez I. et al.[19]	Dabigatran Rivaroxaban	17,507	PSW	Similar efficacy for stroke Rivaroxaban: ↑ major bleeding vs. dabigatran
Hernandez I. et al.[20]	Apixaban Warfarin No OAC	42,952	MA	Similar efficacy Rivaroxaban: ↑ major bleeding vs. dabigatran or apixaban
Vinogradova Y. et al.[21]	Dabigatran Rivaroxaban Apixaban Warfarin	196,061	MA, PSW	Apixaban: ↓ major bleeding, intracranial bleeding, gastrointestinal bleeding vs. warfarin Rivaroxaban and low dose apixaban: ↑ all-cause mortality vs. warfarin
Deitelzweig S. et al.[22]	Dabigatran Rivaroxaban Apixaban	194,532	PSM	Apixaban ↓ stroke or systemic embolism and major bleeding than dabigatran or rivaroxaban Rivaroxaban ↑ major bleeding vs dabigatran

OAC = oral anticoagulation; MA = multivariable adjustment; PSM = propensity score matching; PSW = propensity score weighting

Supplementary table 6. Risk factors for bleeding specific to cancer patients

Actively bleeding solid tumors	Direct effect
Intracerebral metastases	
Acute myeloid leukemia	Systemic bleeding diathesis
Thrombocytopenia	
Platelet dysfunction	
Acquired von Willebrand syndrome, coagulation factor deficiencies or presence of inhibitors	
Disseminated intravascular coagulation	
Cancer Surgery	Effect of treatment
Myelosuppressive chemotherapy	
Mucositis	
Use of VEGF receptor tyrosine-kinase inhibitors	
Hyperfibrinolysis in hematological malignancies or tumor lysis syndrome	
Hematopoietic stem cell transplantation	

Data from Kamphuisen P.W. et al.[23]

Bleeding definitions referred to in the manuscript

1. **ACTION Registry-defined in-hospital major bleeding**[24]: absolute hemoglobin decrease ≥4 g/dl (baseline to nadir), intracranial hemorrhage, documented or suspected retroperitoneal bleed, any blood transfusion with baseline hemoglobin ≥9 g/dl, or any transfusion with hemoglobin <9 g/dl and a suspected bleeding event

2. **ACUITY-HORIZONS major bleeding**[25, 26]**:** intracranial, retroperitoneal, or intraocular bleeding, access site hemorrhage requiring intervention, hematoma ≥5 cm in diameter, reduction in hemoglobin of ≥4 g/dl without or ≥3 g/dl with an overt bleeding source, reoperation for bleeding, or blood product transfusion

3. **BARC 3 or 5 bleeding**[27]:

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

   a. Type 3a
      - Any transfusion with overt bleeding
      - Overt bleeding plus hemoglobin drop ≥3 to <5 g/dL (provided hemoglobin drop is related to bleeding). Hemoglobin drop should be corrected for intercurrent transfusion in which 1 U packed red blood cells or 1 U whole blood would be expected to increase hemoglobin by 1 g/dL.

   b. 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 drugs

c. Type 3c

- Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation; does include intraspinal); subcategories confirmed by autopsy, imaging, or lumbar puncture
- Intraocular bleed compromising vision

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

4. **BleeMACS serious spontaneous bleeding**[16]: any intracranial bleeding or any other bleeding leading to hospitalization and/or red blood transfusion (≥1 unit), occurring within the first year after hospital discharge. Bleeding and/or red blood transfusions related to procedures or surgeries were not considered spontaneous bleeding and were not included

5. **CONCERN-defined recurrent upper gastro-intestinal bleeding**[28]: hematemesis or melena or a hemoglobin decrease of ≥2 g/dL in the presence of endoscopy-proven ulcers or bleeding erosions

6. **GUSTO**[29]**:**

   Moderate bleeding

   - bleeding requiring blood transfusion but not resulting in hemodynamic compromise

   Severe or life-threatening bleeding

   - intracerebral hemorrhage
   - bleeding resulting in substantial hemodynamic compromise requiring treatment

7. **International Society on Thrombosis and Haemostasis (ISTH) bleeding definitions**[30, 31]:

   Major bleeding (in non-surgical patients): bleeding that result in death, are life-threatening, cause chronic sequelae or consume major health-care resources

   - Fatal bleeding, and/or
   - Symptomatic 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 fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells

8. **NCDR Cath PCI post-procedural bleeding after PCI**[32]**:** access site, retroperitoneal, gastrointestinal, or genitourinary bleeding, or other

9. **OPTIMIZE**[33]: protocol-defined major bleeding was based on a combination of 2 different bleeding criteria: modified major REPLACE-2 (Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events) and severe or life-threatening GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) criteria (intracranial, intraocular, or retroperitoneal hemorrhage; clinically overt blood loss resulting in a decrease in hemoglobin of more than 3 g/dL, any decrease in hemoglobin level of more than 4 g/dL, or transfusion of 1 or more units of packed red blood cells or whole blood; or either intracranial hemorrhage or bleeding that caused hemodynamic compromise and required intervention)

10. **POISE-2 major bleeding**[34]: hemoglobin ≤7g/dL or a hemoglobin drop of ≥5 g/dL plus transfusion of ≥2 units; transfusion of ≥4 units in 24 hours; retroperitoneal, intraspinal, or intraocular bleeding or embolization, superficial vascular repair, or nasal packing

11. **REACH**[11]**:** protocol-defined serious bleeding was defined as non-fatal hemorrhagic stroke or bleeding leading to hospitalization and transfusion

12. **STEEPLE**[35] (bleeding endpoint in ARCTIC)**:** major bleeding was defined as bleeding that met at least one of the following criteria: fatal bleeding, retroperitoneal, intracranial or intraocular bleeding, bleeding that causes hemodynamic compromise requiring specific treatment, bleeding requiring intervention (surgical or endoscopic), or decompression of

a closed space to stop or control the event, clinically overt bleeding requiring any transfusion of ≥ 1 unit of packed red cells or whole blood, clinically overt bleeding causing a decrease in hemoglobin of ≥ 3 g/dl (or if hemoglobin level not available, a decrease in hematocrit of ≥ 10%)

13. TIMI bleeding[36, 37]:

Non-CABG related bleeding

Major

- Any intracranial bleeding (excluding micro-hemorrhages <10 mm evident only on gradient-echo MRI)
- Clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dL
- Fatal bleeding (bleeding that directly results in death within 7 d)

Minor

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

14. **Chan et al.**[38]**:** recurrent ulcer bleeding was defined as hematemesis or melena documented by the admitting physician, with ulcers or bleeding erosions confirmed on endoscopy, or a decrease in the hemoglobin level of at least 2 g per deciliter in the presence of endoscopically documented ulcers or bleeding erosions

15. **Potts et al**.[39]: in-hospital bleeding was defined using ICD-9-CM codes for post-procedural complications and included gastrointestinal (578.9), retroperitoneal (568.81), intracranial

(432.9), intracerebral haemorrhage (431), unspecified haemorrhage (459.0), and whether a blood transfusion was required (V58.2, 99.0x [procedure]).

16. **Sung et al**.[40]: recurrent ulcer bleeding was defined as the presence of ≥1 or more of the following clinical features (recurrent hematemesis with vomiting of fresh blood; melena after a normal stool; a decrease in hemoglobin level greater than 2 g/dL within 24 hours, despite 2 or more units of blood transfused; or unstable hemodynamic status (systolic blood pressure ≤90 mm Hg or pulse ≥110 beats/min) after achieving stabilization) and confirmed by endoscopic evidence, which included arterial spurter, nonbleeding visible vessel, adherent clot, or fresh blood in the stomach.

17. **Villanueva et al.**[41]: in-hospital bleeding was defined as hematemesis or fresh melena associated with signs of hemodynamic instability (systolic blood pressure <100 mmHg and/or pulse rate >100 bpm) or a hemoglobin drop of ≥2 g/dl within a 6-hour period

Bleeding definitions in stroke trials (Table 6):

Life-threatening bleeding in **MATCH** was defined as any fatal bleeding event; a drop in hemoglobin of ≥5 g/dL; significant hypotension with need for inotropes (hemorrhagic shock); symptomatic intracranial hemorrhage, or transfusion of ≥4 units of red-blood cells or equivalent amount of whole blood.[42]

Major bleeding in **POINT** was defined as symptomatic ICH, intraocular bleeding causing vision loss, transfusion of ≥2 units of red cells or an equivalent amount of whole blood, hospitalization or prolongation of an existing hospitalization, or death due to hemorrhage.[43]

Major bleeding in **PRoFESS** was defined as a hemorrhagic event that resulted in clinically significant disability, symptomatic intracranial hemorrhage, intraocular bleeding causing loss of vision, the need for a transfusion of ≥2 units of red cells or the equivalent amount of whole blood, or the need for hospitalization.[44]

Major bleeding in **SPS3** was defined as intracranial hemorrhage (included those in intracerebral, subdural, epidural, and subarachnoid locations as documented on neuroimaging) and/or serious or life-threatening bleeding requiring transfusion of red cells or surgery or resulting in permanent functional sequelae or death.[45]

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