

Online Supplementary Appendices

Appendix 1: Definition of major and clinically relevant non-major bleeding events.

Major bleeding was defined based on the criteria of the International Society on Thrombosis and Hemostasis (ISTH): 1) fatal bleeding, and/or 2) symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome, and/or 3) bleeding causing a drop of hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of red blood cells [17].

Clinically relevant non-major bleeding was defined by the presence of at least one of the following criteria: (i) spontaneous skin hematoma of at least 2.5 cm in diameter; (ii) spontaneous nose bleed of more than 5 minutes duration; (iii) macroscopic hematuria (either spontaneous or, if associated with an intervention, lasting more than 24 hours); (iv) spontaneous rectal bleeds (more than spotting on toilet paper); (v) gingival bleeding for more than five minutes; (vi) bleeds leading to hospitalisation and/or requiring surgical treatment; (vii) bleeds leading to a transfusion of less than two units; or (viii) any other bleeding event considered clinically relevant by the investigator.

Appendix 2: Overview of variables (with definitions) included in analysis

- Age (years)
- Sex (male versus female)
- Male patients with age ≥ 70 years
- Uncontrolled Arterial hypertension at baseline (systolic blood pressure ≥ 140 mm Hg)
- Male patients with uncontrolled arterial hypertension at baseline (systolic blood pressure ≥ 140 mm Hg)
- BMI
- Age ≥ 70 years, BMI ≥ 30 kg/m²
- Race (Asian, black, white)
- Region (per continent)
- Previous VTE
- Pulmonary embolism (versus DVT)
- Known thrombophilia
- History of bleeding: Major or non-major clinically relevant bleeding event” or “Rectal bleeding” or “Frequent nose bleeding” or “Hematuria”
- Self-reported smoking history (never smoked, ever smoked)
- Active cancer
- History of non-hemorrhagic stroke or transient ischaemic attack
- Known coronary artery disease
- Known heart failure
- Known liver disease or elevated liver enzymes at baseline ($>$ normal value)
- History of gastric or duodenal ulcer
- Known gastro-esophageal reflux disease, gastritis, hiatal hernia
- Diabetes mellitus
- Renal dysfunction (estimated glomerular filtration rate 30-60 ml/min)
- Anaemia (Hb < 12 g/dL in men or < 11 g/dL in women)
- Platelet count $< 100 \times 10^9$ /L
- Platelet aggregation inhibitors (e.g. acetylsalicylic acid, clopidogrel, ticagrelor, or prasugrel)
- Baseline use of non-steroidal anti-inflammatory drugs
- Baseline application of thrombolytic drugs
- Active depression
- Use of selective serotonin re-uptake inhibitors or selective serotonin norepinephrine re-uptake inhibitors
- Baseline use of verapamil, amiodarone, dronedarone, or quinidine
- Baseline use of ritonavir or saquinavir
- Baseline use of clarithromycin
- Baseline use of systemic glucocorticoids

Appendix 3: Overview of existing bleeding prediction scores that were compared to the newly derived prediction score (Table adapted from reference 9).

Score	Kuijer score [5]		RIETE score [7]		HEMORR ₂ HAGES [12]		HAS-BLED [10]		ATRIA [11]		OBRI [6]	
Score items (points)	Age >60 years	1.6	Recent bleeding	2	Hepatic or renal disease ²	1	Hypertension ⁶	1	Anaemia ¹	3	Age ≥ 65 years	1
	Female sex	1.3	Abnormal renal function	1.5	Ethanol abuse ²	1	Abnormal liver function ⁷	1	Severe renal disease ¹³	3	History of GI tract bleeding	1
	Active malignancy	2.2	Anaemia ¹	1.5	Malignancy	1	Abnormal renal function ⁸	1	Age ≥75 years	2	History of stroke	1
			Age >75 years	1	Age ≥75 years	1	Stroke	1	Previous hemorrhage	1	≥1 comorbid conditions ¹⁵	1
			Active malignancy	1	Reduced platelet count or function ³	1	Bleeding history or predisposition ⁹	1	Diagnosed hypertension ¹⁴	1		
			PE diagnosis	1	Prior bleeding	2	Labile INR ¹⁰	1				
					Hypertension ²	1	Age ≥65 years	1				
					Anaemia ¹	1	Drug abuse ¹¹	1				
					Genetic factors ⁴	1	Alcohol abuse ¹²	1				
					Excessive fall risk ⁵	1						
				Prior stroke	1							
Original risk categories												
Low risk	0 points		0 points		0-1 points		0 points		0-3 points		0 points	
Intermediate risk	1-3 points		1-4 points		2-3 points		1-2 points		4 points		1-2 points	
Elevated risk	>3 points		>4 points		>3 points		>2 points		>4 points		3-4 points	

GI=gastrointestinal; PE= pulmonary embolism

¹Anaemia was defined as hemoglobin level <13 g/L in men (8.1 mmol/L) and <12 g/L in woman (7.4 mmol/L), renal insufficiency as creatinine levels >1.2 mg/dL (106 mmol/L).

²Hepatic or renal disease, ethanol abuse and hypertension were not further defined and, for the purpose of this analysis, scored according to identical criteria as for the HAS-BLED score.

³Reduced platelet count or function was defined as use of platelet-aggregation inhibitors or thrombocytopenia.

⁴Genetic factors was defined as CYP 2C9 single-nucleotide polymorphisms; since CYP 2C9 single-nucleotide polymorphisms were not assessed as part of this study, all patients were scored 0 points.

⁵Excessive fall risk included neuropsychiatric disease.

⁶Hypertension was defined as “uncontrolled”, or systolic blood pressure >160 mm Hg.

⁷Abnormal liver function was defined as chronic hepatic disease (e.g., cirrhosis) or biochemical evidence of significant hepatic derangement (liver enzymes >2-3x the upper limit of normal).

⁸Abnormal kidney function was defined as the need for chronic dialysis, renal transplantation or serum creatinine >200 mmol/L.

⁹Bleeding predisposition was defined as “anaemia” without further details. For the current analysis, we defined anaemia as hemoglobin level <13 g/L in men (8.1 mmol/L) and <12 g/L in women (7.4 mmol/L).

¹⁰Labile INR was defined as therapeutic time in range <60%; all patients were scored with 0 points for “labile INR” since therapeutic anticoagulation with VKA was not initiated yet at baseline, or patients were treated with dabigatran.

¹¹Alcohol abuse was defined as consumption of >8 units of alcoholic drinks per week.

¹²Drugs refers to any medications that increase bleeding risk during anticoagulation, such as aspirin, non-steroidal anti-inflammatory drugs or steroids.

¹³Severe renal disease was defined as an estimated glomerular filtration rate <30 ml/min.

¹⁴Diagnosed hypertension was not further defined; we awarded points when the criteria for hypertension according to HAS-BLED were met.

¹⁵Recent myocardial infarction, anaemia (hematocrit <30%), renal impairment (creatinine level >1.5 mg/dL), or diabetes mellitus.