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POSITION PAPER

Assessment and mitigation of bleeding risk in atrial fibrillation and venous thromboembolism: A Position Paper from the ESC Working Group on Thrombosis, in collaboration with the European Heart Rhythm Association, the Association for Acute CardioVascular Care and the Asia-Pacific Heart Rhythm Society

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Abstract

Whilst there is a clear clinical benefit of oral anticoagulation (OAC) in patients with atrial fibrillation (AF) and venous thromboembolism (VTE) in reducing the risks of thromboembolism, major bleeding events (especially intracranial bleeds) may still occur and be devastating. The decision to initiate and continue anticoagulation is often based on a careful assessment of both the thromboembolism and bleeding risk. The more common and validated bleeding risk factors have been used to formulate bleeding risk stratification scores, but thromboembolism and bleeding risk factors often overlap. Also, many factors that increase bleeding risk are transient and modifiable, such as variable international normalized ratio values, surgical procedures, vascular procedures, or drug–drug and food–drug interactions. Bleeding risk is also not a static 'one off' assessment based on baseline factors but is dynamic,

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being influenced by ageing, incident comorbidities, and drug therapies. In this Consensus Document, we comprehensively review the published evidence and propose a consensus on bleeding risk assessments in patients with AF and VTE, with the view to summarizing 'best practice' when approaching antithrombotic therapy in these patients. We address the epidemiology and size of the problem of bleeding risk in AF and VTE, review established bleeding risk factors, and summarize definitions of bleeding. Patient values and preferences, balancing the risk of bleeding against thromboembolism are reviewed, and the prognostic implications of bleeding are discussed. We propose consensus statements that may help to define evidence gaps and assist in everyday clinical practice.

Keywords Bleeding • Oral anticoagulation • Atrial fibrillation • Venous thromboembolism • Risk assessment

Introduction and scope

Whilst there is a clear clinical benefit of oral anticoagulation (OAC) in patients with atrial fibrillation (AF) and venous thromboembolism (VTE) in preventing future thromboembolic events, major bleeding events [especially intracranial haemorrhage (ICH)] may still occur and be devastating.[1] The decision to initiate and continue anticoagulation is often based on a careful assessment of the risks of both thromboembolism and bleeding. It is well recognized that the net clinical benefit of OAC generally outweigh the risks of bleeding, especially in AF patients at high ischaemic risk.[2]

The more common and validated bleeding risk factors have been used to formulate bleeding risk stratification scores, but many of these are also risk factors for thromboembolism. Many factors that increase bleeding are transient and modifiable. Bleeding risk is not static, with a 'one off' assessment based on baseline factors, but dynamic, influenced by ageing, incident comorbidities, and drug therapies. Another factor is ethnicity, where East Asians appear more sensitive to antithrombotic therapy-related bleeding.[3]

In 2011, the European Heart Rhythm Association (EHRA) and European Society of Cardiology (ESC) Working Group on Thrombosis published a position document on Bleeding Risk Assessment and Management in AF Patients.[4] Over the last decade, there have been advances in our understanding of the epidemiology, risks, and clinical prediction of bleeding, in patients with AF as well as VTE. We also have seen a major growth in the efforts to improve thromboprophylaxis, with increasing use of the non-vitamin K antagonist oral anticoagulants (NOACs) for AF and VTE,[5,6] comprising of direct thrombin inhibitors (dabigatran) and direct factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban).

Non-vitamin K antagonist oral anticoagulants offer improved effectiveness, safety, and convenience compared with vitamin K antagonists (VKA, e.g. warfarin, acenocoumarol, or phenprocoumon). The risks of thromboembolism and bleeding from VKAs are highly dependent on the quality of anticoagulation control, as reflected by the average time in therapeutic range (TTR), with the target international normalized ratio (INR) being 2.0–3.0.[7] Whilst a lower INR range may reduce bleeding risk, especially in East Asian populations, it greatly increases the risk of thromboembolism.[8] However, when using warfarin as part of triple antithrombotic therapy, a lower INR of 2.0–2.5 was associated with reduced bleeding risk compared with higher INRs.[9]

Furthermore, AF management has evolved towards a more integrated and holistic approach, summed up as the ABC (Atrial fibrillation Better Care) pathway: 'A' Avoid stroke (with Anticoagulants); 'B' Better symptom management; 'C' Cardiovascular and Comorbidity management[10] and is recommended in several guidelines, including the recent ESC Guidelines for the diagnosis and management of AF,[11] and the 2021 Asia Pacific Heart Rhythm Society guidelines.[12] In a systematic review, AF patients who were managed adherent to the ABC pathway had a lower risk of all-cause death [odds ratio (OR): 0.42, 95% confidence interval (CI) 0.31–0.56], cardiovascular death (OR: 0.37, 95% CI 0.23–0.58), stroke (OR: 0.55, 95% CI 0.37–0.82), and major bleeding (OR: 0.69, 95% CI 0.51–0.94)[13] (*Figure 1*).

Given the advances over the last decade, including the development and approval of reversal agents for NOACs, the ESC Working Group on Thrombosis, in collaboration with the EHRA, Acute CardioVascular Care Association, and Asia-Pacific Heart Rhythm Society convened a Task Force, with the remit to review the published evidence and to propose a consensus on bleeding risk assessment in patients with AF and VTE, with a view to facilitating 'best practice'. This position paper summarizes the available evidence and puts forwards consensus statements that may help to define evidence gaps and simple practical approaches to assist in everyday clinical practice.

The ultimate judgement regarding the care of each individual patient must be made by the healthcare provider and the patient together, considering all the circumstances presented by that patient.

Literature searches were performed on the following databases: PubMed/MEDLINE and the Cochrane Library (including the Cochrane Database of Systematic Reviews and the Cochrane Controlled Trials Registry), restricted to human subjects and English language sources. Articles related to animal experimentation were only cited when the information was important to understanding pathophysiological concepts pertinent to patient management and comparable data were not available from human studies.

Systematic review

Epidemiology of bleeding with oral anticoagulant in atrial fibrillation

Current guidelines suggest that most patients with AF will require OAC to reduce the risk of stroke,[11,12,14] although OAC increases the risk of bleeding. Randomized controlled trials (RCTs) in AF patients treated with VKA reported annual rates of major bleeding of

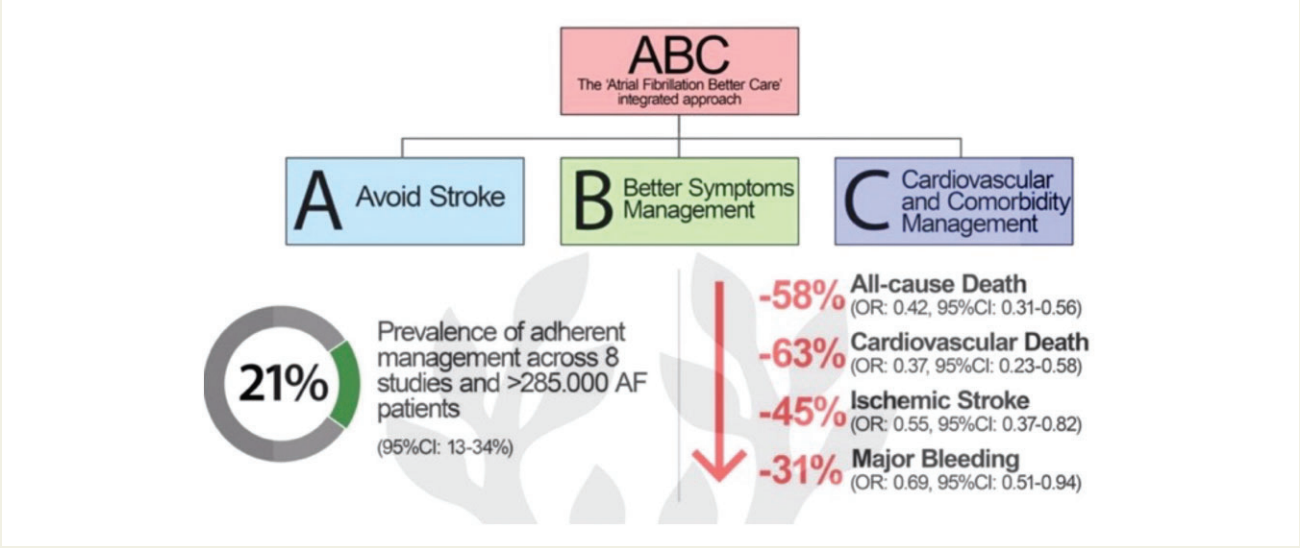

Figure 1 ABC pathway and improved outcomes in patients with AF. ABC, Atrial fibrillation Better Care; AF, atrial fibrillation.

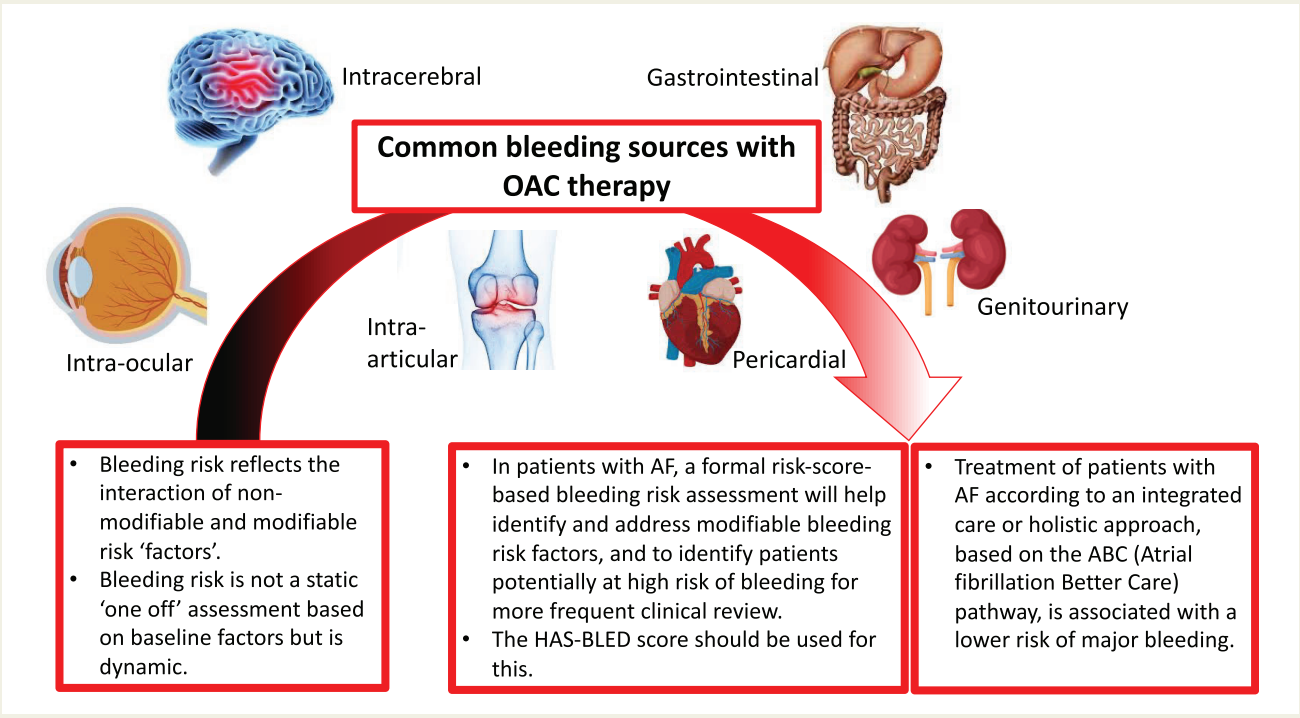

Figure 2 Common bleeding sources with oral anticoagulant therapy.

1.4–3.4%,[15] with much lower rates with NOACs.[2] The most serious bleed, ICH, is rare, occurring in 0.1–2.5% patients per year,[16] with more recent studies reporting a lower rate of 0.7–0.8%.[2] Importantly, OAC-related ICH leads to poorer clinical outcomes, greater disability, and higher mortality than ICH that is non-OAC related[17] (*Figure 2*). The risk of bleeding (and stroke) is highest when AF is newly diagnosed and during the initiation of OAC.[18]

Different variables have been observed to predict the risk of anticoagulation-related bleeding in patients with AF (*Figure 3*). Individual TTR and INR variability were associated with bleeding

	Risk Factors
Clinical variables	History of bleeding Concomitant antiplatelets or NSAID use Excessive alcohol intake Uncontrolled hypertension Increasing age Cancer Prior stroke, small vessel disease, amyloid angiopathy Diabetes Vascular disease
Biological markers	Poor anticoagulation quality (reduced TTR) Liver dysfunction Renal dysfunction Anaemia Reduced platelet count or function

Figure 3 Risk factors for anticoagulation-related bleeding.

complications, in particular ICH.[19] Non-vitamin K antagonist oral anticoagulants showed a lower incidence of major bleeding (−14%) and ICH (−52%) compared to warfarin.[2,20] However, the risk of gastrointestinal bleeding is not reduced with higher dose NOACs compared to warfarin.[2]

Epidemiology of bleeding with oral anticoagulant in venous thromboembolism

Venous thromboembolism, whether deep vein thrombosis (DVT) or pulmonary embolism (PE), requires anticoagulation to prevent complications or disease progression. Current guidelines recommend a minimum of 3 months' treatment for patients with a transient or reversible risk factor, whereas longer term treatment is needed for patients with an unprovoked event or due to a persistent risk factor.[21,22] Prediction of bleeding risk is crucial for patients at high risk of recurrent thrombosis.

A systematic review and meta-analysis comprising of 33 studies reported a 2.06% rate of VKA-related major bleeding (95% CI 2.04–2.08%) during the initial 3 months of anticoagulation, and a fatal bleeding rate of 0.37% (95% CI 0.36–0.38%),[23] similar to the 2.2% major and 0.55% fatal bleeding reported in the RIETE registry.[24] During the extended phase beyond the first 3 months, the rate of major bleeding associated with VKA treatment was 2.74% (95% CI 2.71–2.77).[23,25]

In general, NOACs are at least as effective as LMWH/VKA but are associated with less bleeding. A systematic review and meta-analysis of 10 trials showed that in patients with VTE, NOACs were associated with a lower risk of major bleeding [1.08% vs. 1.73%, risk ratio (RR) 0.63, 95% CI 0.51–0.77],[26] as well as fatal bleeding (RR 0.36%, 95% CI 0.15–0.87), compared to VKA. During the extended phase, there was a non-significant increase in major bleeding in patients receiving NOACs against placebo. Reduced-dose apixaban[27] and rivaroxaban[28] have been compared against standard-dose, aspirin, or placebo. Data from a meta-analysis showed that major or clinically relevant non-major bleeding events were similar with reduced-dose NOACs as with aspirin or placebo (RR 1.19, 95% CI 0.81–1.77), whereas there was no significant difference compared to full-dose NOAC, with a trend towards less bleeding with the reduced dose (RR 0.74, 95% CI 0.52–1.05).[29]

Definitions of bleeding

Defining bleeding events during OAC therapy is important to both quantify its prognostic impact and address the related diagnostic and therapeutic measures, and several definitions are in use (*Table 1*), including either qualitative definitions or objective quantitative data, such as drop in haemoglobin, or frequently both. The most widely used are the Thrombolysis in Myocardial Infarction (TIMI),[30] Global Use of Strategies To Open occluded arteries (GUSTO),[31] International Society of Thrombosis and Haemostasis (ISTH),[32,33] and the Bleeding Academic Research Consortium (BARC)[34] classifications, and all have been shown to predict mortality.[35,36] Heterogeneity in bleeding definitions may, at least partly, account for the variability in the reported rate of haemorrhagic complications with OAC.[16]

Clinical bleeding risk factors with oral anticoagulant for atrial fibrillation or venous thromboembolism

Studies reporting risk factors associated with bleeding are similar whether OAC is taken for VTE or AF[21,22,37] and are summarized in *Tables* 2–9, including age (*Table 2*), hypertension (*Table 3*), renal impairment (*Table 4*), abnormal liver function (*Table 5*), prior stroke (*Table 6*), prior bleeding (*Table 7*), anaemia (*Table 8*), and malignancy (*Table 9*).

Dynamic and modifiable nature of bleeding risk

Some bleeding risk factors are non-modifiable, such as age, sex, prior bleeding, or stroke, whereas other risks may be correctable, such as uncontrolled blood pressure (BP), transient renal or liver impairment, labile INR, excessive alcohol intake, or concomitant use of aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) in an anticoagulated patient.

It is crucial to recognize that bleeding risk is not a static 'one-off' assessment based on baseline factors but dynamic, being influenced by ageing, incident comorbidities, and drug therapies.[38–40] Therefore, bleeding risk assessment needs to be performed and repeated frequently over the course of the patient journey, in response to change in clinical characteristics and treatments.

Increasing age is associated with increasing risk of bleeding on OAC (*Table 2*).[41–43] The risk of ICH is higher with VKAs than with NOACs, and the benefit of NOAC over VKA in reducing ICH is consistent irrespective of advanced age.[42,44,45]

Most studies show systolic hypertension to be a risk factor for bleeding in patients on OAC, especially ICH,[46,47] although others did not show a relationship between BP at trial entry and subsequent bleeding.[48,49] In the sub-analysis of the ENGAGE-AF trial, patients with a systolic BP above 140 mmHg experienced a higher risk of major bleeding compared to those with a systolic BP between 130 and 140 mmHg.[47] Importantly, although the efficacy and safety of edoxaban were consistent across the full range of systolic BPs, the superior safety profile of edoxaban compared to VKA was most pronounced among patients with elevated diastolic BP.[47] In a nationwide Korean population registry, the risk of ICH was found to be lowest with BP <130/80 mmHg.[50] Based on these associations, it appears prudent to maintain good control of BP in patients on OAC.

Table 1 Most frequently used bleeding definitions

TIMI[30]	GUSTO[31]	ISTH[32,33]	BARC[34]
Major	**Severe or life-threatening**	**Major**	**Type 0**
Any intracranial bleeding (excluding microhaemorrhages <10 mm evident only on gradient-echo magnetic resonance imaging)	Intracerebral haemorrhage	Fatal bleeding	No evidence of bleeding
Clinically overt signs of haemorrhage associated with a drop in haemoglobin of ≥5 g/dL	Resulting in substantial haemodynamic compromise requiring treatment	Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome.	
Fatal bleeding (bleeding that directly results in death within 7 days)		Bleeding causing a fall in haemoglobin level of ≥2 g/dL or leading to transfusion of ≥2 units of whole blood or red cells	
Minor	**Moderate**	**Minor**	
Clinically overt (including imaging), resulting in haemoglobin drop of 3 to <5 g/dL	Requiring blood transfusion but not resulting in haemodynamic compromise	All non-major bleeds	
Requiring medical attention	**Mild**	**Clinically relevant minor**	**Type 1**
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	Bleeding that does not meet above criteria	Acute or subacute clinically overt bleed that does not meet the criteria for a major bleed but prompts a clinical response, in that it leads to at least one of the following:	Bleeding that is not actionable and does not cause the patient to seek an unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; it may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional
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)		A. hospital admission for bleeding, or	
Leading to or prolonging hospitalization		B. a physician guided medical or surgical treatment for bleeding, or	
Prompting evaluation (leading to an unscheduled visit to a healthcare professional and diagnostic testing, either laboratory or imaging)		C. change in antithrombotic therapy (including interruption or discontinuation of study drug)	
Minimal			**Type 2**
Any overt bleeding event that does not meet the criteria above			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, type 4, or type 5 but does meet at least one of the following criteria: requiring non-surgical, medical intervention by a healthcare professional; leading to hospitalization or increased level of care; or prompting evaluation
			Type 3
			Clinical, laboratory, and/or imaging evidence of bleeding with specific healthcare provider responses, as listed below:

Continued

Table 1 *Continued*

TIMI[30]	GUSTO[31]	ISTH[32,33]	BARC[34]
			Type 3a Overt bleeding plus a haemoglobin drop of 3–5 g/dL[a] (provided the haemoglobin drop is related to bleed); any transfusion with overt bleeding **Type 3b** Overt bleeding plus a haemoglobin drop of 5 g/dL (provided the haemoglobin drop is related to bleed); cardiac tamponade; bleeding requiring surgical intervention for control (excluding dental, nasal, skin, and 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 lumbar puncture; intraocular bleed compromising vision **Type 4** Coronary artery bypass grafting-related bleeding Perioperative intracranial bleeding within 48 h; reoperation after closure of sternotomy for the purpose of controlling bleeding; Transfusion of 5 U of whole blood or packed red blood cells within a 48-h period; Chest tube output 2 L 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

In an analysis of 19 566 anticoagulated AF patients, 76.6% of the 3032 patients who experienced major bleeding (ICH or bleeding requiring hospitalization and blood transfusion) had acquired new bleeding risk factors, compared with only 59.0% of those patients without major bleeding ($P < 0.001$).[38] A recent study from Taiwan enrolling 24 990 AF patients with low bleeding, showed that ~21% of patients acquired at least one new bleeding risk factor at 1 year, including hypertension (5.84%), stroke (5.33%), bleeding (5.06%), concomitant use of antiplatelet agents or NSAIDs (4.34%), abnormal renal function (3.08%), and abnormal liver function (2.22%).[40] In the data from ORBIT AF, about a quarter of patients had >20% decline in estimated glomerular filtration rate (eGFR) during 2 years of follow-up, and 3.7% of patients receiving NOACs had eGFR decline sufficient to warrant recommended dose reductions.[51] Real-world data from the PREFER in AF registry suggests that each single point decrease on a modifiable bleeding risk scale was associated with a 30% lower risk of major bleeding.[43]

Laboratory-, biomarker-, and imaging-based risk factors for bleeding in patients with atrial fibrillation or venous thromboembolism

Many blood, urine, and imaging biomarkers have been shown to improve the accuracy of bleeding risk stratification in AF[52–54] but their clinical applicability remains limited.

The blood biomarker-based ABC-bleeding risk score [including growth differentiation factor-15 (GDF-15), troponin T, and haemoglobin] has been shown to perform better at bleeding prediction than clinical factor-based bleeding risk scores in patients with AF

Table 2 Summary of 'age' as a risk factor for bleeding in AF patients receiving OACs

Study	Subjects (*n*)	Type of OACs	Age groups	Main findings	RR/OR/HR (95% CI)	*P* value
SPAF Investigators, 1996	555	VKA	Age >75 vs. ≤75 years	Major bleeding (per year): 4.2% vs. 1.7%	RR 2.6	0.009
Pengo *et al.*, 2001	433	VKA	Age >75 vs. ≤75 years	Major bleeding (per year): 5.1% vs. 1.0%	RR 6.6 (1.2–3.7)	0.032
Fang *et al.*, 2004	1190	VKA	Incremental risk per 5 years	The risk for intracranial haemorrhage increased at ≥85 years of age.	adjusted OR 2.5 (1.3–4.7) compared to age 70–74 years	NR
Pisters *et al.*, 2010	5333	VKA	Age >65 vs. ≤65 years	1-year event rate of major bleeding: 2.3% vs. 0.7%	OR 2.66 (1.33–5.32)	<0.001
Hankey *et al.*, 2014	14 264	VKA/rivaroxaban	Per decade increase in age	Age is an important risk factor of ICH	HR 1.35 (1.13–1.63)	0.001
O'Brien *et al.*, 2015	7411	VKA/dabigatran	Age >75 vs. ≤75 years	Older age had good ability to identify those who bled vs. not.	HR 1.38 (1.17–1.61)	NR
Chao *et al.*, 2020	64 169	VKA/NOACs	Age >90, 75–89 and 65–74 years	Major bleeding (per year): 10.53% vs. 6.11% vs. 3.48% ICH (pear year): 1.33% vs. 0.99% vs. 0.74%	NR	NR

AF, atrial fibrillation; HR, hazard ratio; ICH , intra-cranial haemorrhage; NR, not reported; OACs, oral anticoagulants; OR, odds ratio; NOAC, non-vitamin K antagonist oral anticoagulant; RR, relative risk; SPAF, Stroke Prevention in Atrial Fibrillation; VKA, vitamin K antagonists.

Table 3 Summary of 'hypertension' as a risk factor for bleeding in AF patients receiving OACs

Study	Subject (*n*)	Type of OACs	Definition of hypertension	Main findings	RR/HR (95% CI)	*P* value
SPAF Investigators, 1996	555	VKA	Systolic BP >160 mmHg or diastolic BP >90 mmHg	Increase risk of ICH in patients with poor controlled hypertension	RR 4.4 for systolic BP >160 mmHg RR 3.6 for diastolic BP > 90 mmHg	0.02 0.04
Fang *et al.*, 2011	9186	VKA	Diagnosed hypertension as per guideline	Prevalence of hypertension in patients with or without major bleeding: 64.7% vs. 61.9%	HR 1.5 (1.2–1.9)	0.001
Hankey *et al.*, 2014	14 264	VKA/rivaroxaban	Each 10 mmHg increase of diastolic BP	Increased diastolic BP is independently associated with ICH	HR 1.17 (1.01–1.36)	0.042
Park *et al.*, 2019	19 679	VKA/edoxaban	>150 mmHg 140–<150 mmHg 130–<140 mmHg (reference)	Major bleeding rate (per year) Edoxaban: 4.37% vs. 2.54% vs. 1.88% VKA: 5.65% vs. 4.16% vs. 2.37%	>150 mmHg: HR 1.64 (1.26–2.12) 140–<150 mmHg: HR 1.36 (1.13–1.62)	<0.001 <0.001
Böhm *et al.*, 2020	18 107	VKA/ Dabigatran	>160 mmHg 140–<160 mmHg 130–<140 mmHg Systolic BP 120–<130 mmHg (reference)	Any bleeding rate (per year): 24.99% vs. 17.30% vs. 14.71% vs. 14.61%	>160 mmHg: HR = 2.01 (1.73–2.32) 140–<160 mmHg: HR = 1.23 (1.14–1.33)	NR

AF, atrial fibrillation; BP, blood pressure; HR, hazard ratio; ICH , intra-cranial haemorrhage; NR, not reported; OACs, oral anticoagulants; RR, relative risk; SPAF, Stroke Prevention in Atrial Fibrillation; VKA, vitamin K antagonists.

Table 4 Summary of 'abnormal renal function' as a risk factor for bleeding in AF patients receiving OACs

Study	Subjects (*n*)	Type of OACs	Definition	Main findings	OR/HR (95% CI)	*P* value
Pisters *et al.*, 2010	5333	VKA	Presence of chronic dialysis, renal transplantation, or serum creatinine >200 mmol/L	The rate of major haemorrhage was 1.3% in patients without kidney failure vs. 5.4% in those with kidney failure.	OR 2.86 (1.33–6.18)	<0.001
Fang *et al.*, 2011	9186	VKA	eGFR <30 mL/min	Prevalence of renal impairment in patients with or without major bleeding: 5.9% vs. 2.7%	HR 4.3 (3.2–5.8)	<0.001
Fox *et al.*, 2011	14 264	VKA/rivaroxaban	eGFR >50 mL/min eGFR 30–49 mL/min	Major bleeding rate (per year) Rivaroxaban: 3.39% vs. 4.49% VKA: 3.17% vs. 4.70%	NR	NR
Hohnloser *et al.*, 2012	18 122	VKA/apixaban	Divided into three groups (1) eGFR >80 mL/min (2) eGFR 50–80 mL/min (3) eGFR <50 mL/min	Major bleeding rate (per year) Apixaban: 1.46% vs. 2.45% vs. 3.21% VKA: 1.84% vs. 3.21% vs. 6.44%	NR	NR
O'Brien *et al.*, 2015	7411	VKA/dabigatran	eGFR <60 mL/min/1.73 m^2	Prevalence of renal impairment in patients with or without major bleeding: 48.4% vs. 34.0%	HR 1.44 (1.21–1.72)	NR

AF, atrial fibrillation; HR, hazard ratio; eGFR, estimated glomerular filtration rate; NR, not reported; OACs, oral anticoagulants; OR, odds ratio; VKA, vitamin K antagonists.

Table 5 Summary of 'abnormal liver function' as a risk factor for bleeding in AF patients receiving OACs

Study	Subjects (*n*)	Type of OACs	Study population	Main findings	HR (95% CI)	*P* value
Fang *et al.*, 2011	9186	VKA	Diagnosed cirrhosis	Prevalence of liver cirrhosis in patients with or without major bleeding: 1.2% vs. 0.5%	HR 2.6 (1.1–6.1)	0.03
Efird *et al.*, 2014	103 897	VKA	Patients were defined as having liver disease if there was record ≥1 of the ICD9 codes for chronic liver disease, recorded either in the inpatient or outpatient setting, during the study period.	Patients with liver disease had more haemorrhages when compared with patients without.	HR 2.02 (1.69–2.42)	<0.001
Hylek *et al.*, 2014	18 122	Apixaban/VKA	Patients with AF randomized to apixaban/VKA. Liver dysfunction not defined in paper	Only 8 patients with liver dysfunction experienced a major haemorrhage, precluding any definitive conclusion regarding this subgroup	HR 0.44 (0.22–0.88)	0.020

AF, atrial fibrillation; HR, hazard ratio; ICD9, International Classification of Diseases-Ninth Revision; OACs, oral anticoagulants; VKA, vitamin K antagonists.

receiving OAC or both OAC and APT, and in different geographic regions,[55–58] but this finding was not confirmed in another study.[59] Only marginal enhancement in predictive ability of the HAS-BLED score for major bleeding was observed, after consecutively adding different blood-based biomarkers.[60] Blood (e.g. eGFR) and urine (e.g. proteinuria) based biomarkers of renal dysfunction have been used to improve clinical risk stratification for bleeding (as well as stroke) in AF.[61,62]

In patients with VTE, information on biomarkers and bleeding risk is sparse.[63] Bleeding risk scores evaluated in VTE patients receiving OAC treatment, including biomarkers, such as haemoglobin and/or creatinine (or creatinine clearance), generally have modest predictive performance.[64,65]

There are limitations to using laboratory-based biomarkers at any one time point, to assess bleeding risk, due to the dynamic nature of bleeding risk such that regular re-evaluation of bleeding risk is of

Table 6 Summary of 'stroke history' as a risk factor for bleeding in AF patients receiving OACs

Study	Subjects (*n*)	Type of OACs	Definition	Main findings	RR/HR (95% CI)	*P* value
Pengo *et al.*, 2001	433	VKA	History of thromboembolism	A higher frequency of major primary bleeding in patients who had suffered a previous thromboembolic event	NR	0.03
Fang *et al.*, 2004	1190	VKA	History of cerebrovascular disease	Prevalence of cerebrovascular disease in patients with or without ICH: 37% vs. 20%	NR	NR
Fang *et al.*, 2011	9186	VKA	Prior stroke	Prevalence of prior stroke in patients with or without major bleeding: 17.4% vs. 12.4%	HR 1.4 (1.1–1.9)	0.01
Hankey *et al.*, 2014	14 264	VKA/rivaroxaban	Previous stroke or TIA	Previous stroke or TIA is an independent factor associated with ICH	HR 1.42 (1.02–1.96)	0.036
Hylek *et al.*, 2014	18 122	Apixaban/VKA	Prior stroke/TIA/SE	Rate of ISTH major haemorrhage was 18.9% in patients without history vs. 24.5% in those with history (apixaban) and 19.5% vs. 23.4% (warfarin).	HR 1.23 (1.038–1.45)	0.016
O'Brien *et al.*, 2015	7411	VKA/dabigatran	Prior stroke	Prevalence of prior stroke in patients with or without major bleeding: 13.1% vs. 9.2%	NR	NR

AF, atrial fibrillation; HR, hazard ratio; ICH , intra-cranial haemorrhage; NR, not reported; OACs, oral anticoagulants; OR, odds ratio; RR, relative risk; TIA, transient ischaemic attack; VKA, vitamin K antagonists.

Table 7 Summary of 'bleeding history' as a risk factor for bleeding in AF patients receiving OACs

Study	*n*	Type of OACs	Definition	Main findings	OR/HR (95% CI)	*P* value
Pisters *et al.*, 2010	5333	VKA	Prior major bleeding (ICH, hospitalization, haemoglobin decrease >2 g/L, and/or blood transfusion)	The rate of major haemorrhage was 1.3% in patients without prior major bleeding vs. 14.8% in those with prior major bleeding.	OR 7.51 (3.00–18.78)	<0.001
Fang *et al.*, 2011	9186	VKA	Prior GI haemorrhage	Prevalence of prior GI bleeding in patients with or without major bleeding: 12.1% vs. 6.8%	HR 2.1 (1.5–2.9)	<0.001
Hylek *et al.*, 2014	18 122	Apixaban/VKA	Bleeding history	Rate of ISTH major haemorrhage was 16.5% in patients without bleeding history vs. 25.2% in those with prior bleeding history (apixaban) and 16.4% vs. 22.5% (warfarin).	HR 1.38 (1.17–1.63)	0.002
O'Brien *et al.*, 2015	7411	VKA/dabigatran	Bleeding history	Bleeding history had good ability to identify those who bled vs. not.	HR 1.73 (1.34–2.23)	NR
Šinigoj *et al.*, 2020[a]	2260	Dabigatran Rivaroxaban Apixaban	Bleeding history	History of bleeding was a significant predictor of major bleeding.	HR 3.32 (1.87–5.90)	<0.001

AF, atrial fibrillation; GI, gastrointestinal; HR, hazard ratio; ICH , intra-cranial haemorrhage; NR, not reported; OACs, oral anticoagulants; OR, odds ratio; VKA, vitamin K antagonists.
[a]Šinigoj *et al.* is restricted to individuals aged 85 and older.

Table 8 Summary of 'anaemia' as a risk factor for bleeding in AF patients receiving OACs

Study	Subjects (*n*)	Type of OACs	Definition	Main findings	HR (95% CI)	*P* value
Fang *et al.*, 2011	9186	VKA	Hb <13 g/dL in men and <12 g/dL in women	The rate of major haemorrhage was 12.1% in patients without anaemia vs. 18.8% in those with anaemia.	HR 4.2 (3.4–5.3)	<0.001
O'Brien *et al.*, 2015	7411	VKA Dabigatran	Reduced Hb/haematocrit/history of anaemia	Reduced haemoglobin/haematocrit/history of anaemia had good ability to identify those who bled vs. not.	HR 2.07 (1.74–2.47)	NR
Bonde *et al.*, 2019	18 734	VKA Dabigatran Rivaroxaban	(1) No anaemia (Hb >7.45 mmol/L for women and >8.07 mmol/L for men) (2) Mild anaemia (Hb 6.83–7.45 mmol/L for women and 6.83–8.07 mmol/L for men) (3) Moderate/severe anaemia (Hb <6.83 mmol/L for women and men).	OAC was associated with a 5.3% (95% CI 2.1–8.7%) increased standardized absolute risk of major bleeding among AF patients with moderate/severe anaemia.	HR 1.78 (1.30–2.48)	NR
Krittayaphong *et al.*, 2021	1562	VKA NOACs	Hb <13 g/dL for male and <12 g/dL for female	Anaemia was found to be an independent risk factor for major bleeding.	HR 2.96 (1.81–4.84)	NR

AF, atrial fibrillation; Hb, haemoglobin; HR, hazard ratio; NR, not reported; OACs, oral anticoagulants; NOAC, non-vitamin K antagonist oral anticoagulant; VKA, vitamin K antagonists.

Table 9 Summary of 'malignancy' as a risk factor for bleeding in AF patients receiving OACs

Study	Subjects (*n*)	Type of OACs	Definition	Main findings	HR (95% CI)	*P* value
Fang *et al.*, 2011	9186	VKA	Any diagnosis of cancer	Prevalence of diagnosed cancer in patients with or without major bleeding: 18.0% vs. 15.1%	HR 1.7 (1.3–2.2)	<0.001
O'Brien *et al.*, 2015	7411	VKA/dabigatran	History of cancer	The rate of major bleeding was 23.3% in patients without cancer vs. 30.8% in those with cancer.	NR	<0.0001
Melloni *et al.*, 2017	9749	VKA/dabigatran	Any diagnosis of cancer	The rate of major bleeding was 3.45 per 100 patient-years in patients without cancer vs. 5.13 per 100 patient-years in those with cancer.	HR 1.21 (1.04–1.40)	0.02
Vedovati *et al.*, 2018	2288	Dabigatran Rivaroxaban Apixaban	Patients with active cancer, at time of inclusion in the study, in presence of a diagnosis of cancer or any anticancer treatment within 6 months before the study inclusion, or recurrent locally advanced or metastatic cancer; patients with history of cancer	The higher bleeding risk found in cancer compared to non-cancer patients was mainly due to an excess of bleeding at GI and at genitourinary sites.	HR 2.58 (1.08–6.16)	0.033

AF, atrial fibrillation; GI, gastrointestinal; HR, hazard ratio; NR, not reported; OACs, oral anticoagulants; VKA, vitamin K antagonists.

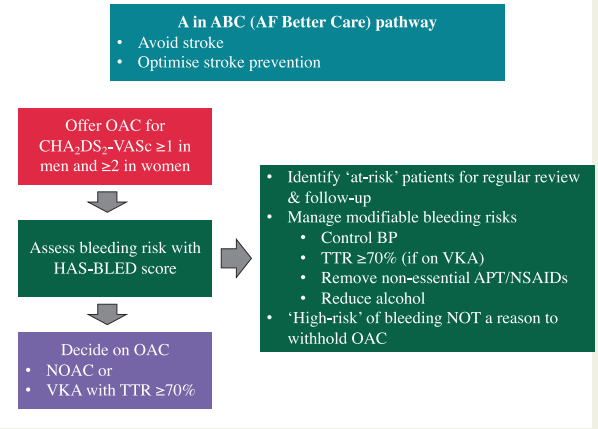

Figure 4 A in the atrial fibrillation better care pathway. ABC, Atrial fibrillation Better Care; APT, antiplatelet therapy; BP, blood pressure; CHA_2DS_2-VASc, congestive heart failure, hypertension, age 75 years (2 points), diabetes, stroke/TIA/thromboembolism (2 points), vascular disease, age 65–74 years, sex category (female); DM, diabetes mellitus; HAS-BLED, (uncontrolled) hypertension, abnormal renal, or liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs/drink (alcohol); HF, heart failure; NOAC, non-vitamin K antagonist oral anticoagulant; NSAIDs, non-steroidal anti-inflammatory drugs; OAC, oral anticoagulation; OSA, obstructive sleep apnoea; TTR, time in the therapeutic range; VKA, vitamin K antagonist. Adapted from Ref.[83]

utmost importance. Also, some biomarkers are non-specific and predictive of various non-bleeding outcomes.[66–69] Furthermore, some biomarkers exhibit diurnal variation and inter-/intra-assay variability and may be expensive.[70] Some, such as GDF-15, are not routinely available. Although every effort should be made to improve current risk prediction tools and inclusion of laboratory-based variables is of upmost importance, especially when these are widely available, incorporation of these should not lead to loss of simplicity that ultimately detracts from regular or easy bleeding risk estimation.[71]

In patients with AF on OAC, small vessel disease on magnetic resonance imaging cerebral imaging is an independent risk factor for ischaemic stroke[72] and the presence of cerebral microbleed(s) was independently associated with ICH.[73] The addition of cerebral microbleeds to the HAS-BLED score (c-index 0.66, 95% CI 0.53–0.80) significantly improved the prediction of ICH significantly over the HAS-BLED score alone (c-index 0.41, 95% CI 0.29–0.53).[73]

Current published bleeding risk schema in atrial fibrillation and venous thromboembolism

The purpose of a bleeding risk score is three-fold: (i) to identify risk factors that are modifiable, that can be addressed to reduce bleeding risk; (ii) to identify people who require more regular monitoring and follow-up; and (iii) to estimate an individual's risk of bleeding on antithrombotic/OAC therapy. Bleeding risk assessment using only modifiable bleeding risk factors alone is an inferior strategy to formal bleeding risk scores.[74–76]

Numerous bleeding risk scores (*Table 10*) are available for patients with AF[55,62,77–83] and VTE.[37,84–92] These incorporate numerous risk factors, including demographic and clinical information plus biomarkers, ranging from 3[55,89] to 17[37] factors, with age included in most scores.[48,52,60,71–76,78,79,81–84] The scores vary in the definitions of common risk factors and in their complexity and ease of calculation, which can hinder clinical utility. Most scores stratify patients into low, intermediate, and high risk, demonstrating major bleeding rates ranging from <1%[55] to 30%[80] and 0.1%[90] to 12.2 per 100 patient-years[91] in the low- and high-risk groups for AF and VTE bleeding risk scores, respectively, in validation cohorts (*Table 10*).

Among the seven bleeding risk scores for AF,[55,62,77–82] the HAS-BLED score[79] has been most widely validated across the spectrum of the AF patient pathway, from OAC/antithrombotic-naïve newly-diagnosed patients to those established on OAC[93] (both VKA and NOAC),[94,95] and is predictive of ICH.[96] In a recent contemporary cohort of AF patients from the ESC EHRA EORP-AF registry who were treated with NOACs, the ORBIT score did not provide reclassification improvement, showing even poorer calibration compared to HAS-BLED.[97] These findings do not support the preferential use of ORBIT in NOAC-treated AF patients.

The HAS-BLED score has also been validated in non-AF populations, including those with VTE, acute coronary syndrome (ACS), or percutaneous coronary interventions (PCI), or those undergoing bridging therapy.[98–101] A Patient Centred Outcomes Research Institute (PCORI) systematic review of 38 studies[102] evaluated the prognostic precision of HAS-BLED,[79] $HEMORR_2HAGES$,[77] ATRIA,[62] and ABC-Bleeding,[55] concluded that HAS-BLED was the best score for predicting major bleeding but with a modest strength of evidence.[102] In a prospective cluster randomized (mAFA-II) trial using App-based mHealth intervention, using the HAS-BLED score, dynamic bleeding risk monitoring and scheduling of high bleeding risk (HBR) patients for review and follow-up reduced major bleeding events (mAFA 2.1% vs. usual care 4.3%, $P = 0.004$), addressed modifiable bleeding risk and increased OAC uptake, compared to a decrease of 25% amongst those receiving usual care.[103]

Eight[37,84–91] clinical risk scores for predicting major bleeding in patients with VTE (*Table 10*) have been developed, some focusing on the acute phase,[84,87,90] long-term treatment,[88,89] specific sub-groups of VTE, for example, cancer-associated thromboembolism,[104,105] and the elderly,[91] with three[85,86,88] derived from cohorts treated with NOACs. A number of prediction rules attempting to quantify the bleeding risk of an individual by adding weighted[88–90] or unweighted[37,79,81,99] risk factors have been derived from and/or tested in VTE patient cohorts (*Table 10*).

The bleeding risk scores for VTE have been less extensively validated than those for AF.[92] The main weakness of these scores remains the lack of prospective independent validation in large, real-world contemporary populations treated with NOACs. Trials have not prospectively tested the efficacy and safety of coagulation regimens tailored to bleeding risk. De Winter *et al.*[92] critically appraised the prognostic ability of seven of the bleeding risk scores developed for VTE (ACCP,[37] EINSTEIN,[85] Hokusai,[86] Kuijer,[89] RIETE,[90] Seiler,[91] VTE-BLEED[88]) and seven validated in VTE cohorts but derived in AF or mixed-indication cohorts

Table 10 Bleeding risk scores for atrial fibrillation and venous thromboembolism—risk factors and scoring, risk categories, and bleeding events in the validation cohorts

Risk score	Number of risk factors	Risk factors (score for each factor)	Risk categories (bleeding events in validation cohort per 100 patient-years)		
			Low	Intermediate	High
Atrial fibrillation					
HAS-BLED[5]	9	↑SBP (1); severe renal/hepatic disease (1 each); stroke (1); bleeding (1); labile INR (1); age >65 (1); APT/NSAIDs (1); alcohol excess (1)	0–1 (1.02–1.13)	2 (1.88)	≥3 (≥3.74)
ORBIT[4]	5	Age ≥75 (1); ↓Hb/Hct/anaemia (2); bleeding history (2); ↓ renal function (1); APT (1)	0–2 (2.4[*])	3 (4.7)	≥4 (8.1)
ABC[3]	3	Age[b]; biomarkers[b] (GDF-15 or cystatin C/CKD-EPI, cTnT-hs, and Hb); previous bleed[b]	<1% (0.62)	1–2% (1.67)	>3% (4.87)
ATRIA[1]	5	Anaemia (3); severe renal disease (3); age ≥75 (2); prior bleed (1); hypertension (1)	0–3 (0.83)	4 (2.41)	5–10 (5.32)
HEMORR$_2$HAGES[2]	12	Hepatic/renal disease (1); ethanol abuse (1); malignancy; age >75 (1); ↓Plt (1); re-bleeding risk (2); ↑BP (1); anaemia (1); genetic factors (1); ↑ falls risk (1); stroke (1)	0–1 (1.9–2.5)	2–3 (5.3–8.4)	≥4 (10.4–12.3)
Shireman *et al.*[6]	8	Age ≥70 (0.49); female (0.31); previous bleed (0.58); recent bleed (0.62); alcohol/drug abuse (0.71); DM (0.27); anaemia (0.86); APT (0.32)	≤1.07 (0.9%[a])	>1.07/<2.19 (2.0%[a])	≥2.19 (5.4%[a])
OBRI[7,8]	4	Age ≥ 65 (1); previous stroke (1); previous GI bleed (1); recent MI/anaemia/DM/↑creatinine (1)	0 (3%[b])	1–2 (8%[b])	3–4 (30%[b])
Venous thromboembolism					
ACCP[14]	17	Age 66–75 (1), >75 (1); previous major bleed (1); active cancer (1); metastatic cancer (1); renal failure (1); liver failure (1); thrombocytopenia (1); previous stroke (1); diabetes mellitus (1); anaemia (1); APT (1); TTR < 60% (1); comorbidity (1); recent surgery (1); frequent falls (1); alcohol abuse (1); NSAIDs (1)	No risk factors (0.8%[c])	1 risk factor (1.6%[c])	≥2 risk factors (≥6.5%[c])
VTE-BLEED[15]	6	Active cancer (2); male with uncontrolled arterial hypertension (1); anaemia (1.5); previous bleeding (1.5); age ≥60 (1.5), renal dysfunction (1.5)	<2 (0.2%[d]) (0.4%[w])	—	≥2 (1.4%[d]) (2.8%[w])
EINSTEIN score[11]	6	Rivaroxaban (vs. VKA); age; Hb; male sex[*]; Black (vs. Caucasian); Asian (vs. Caucasian); history of CVD	NR	NR	NR
Hokusai score[12]	5	Female sex (1); APT (1); ↓Hb (1); history of hypertension (1); SBP > 160 mmHg (1)	0 (1.4%[e]) (1.1%[w])	1 (1.0%[e]) (1.45 [w])	2 (2.1% [e]) (2.1% [w])
Seiler *et al.*[18]	7	Previous major bleeding (1); active cancer (1); low physical activity (2); anaemia (1); thrombocytopenia (1); APT/NSAIDs (1); poor INR control (1)	0–1 (1.4)	2–3 (5.0)	>3 (12.2)
IMPROVE[10,13]	10	Active GI ulcer (4.5); Recent bleed (4); ↓Plt (4); Age ≥75 (3.5); Hepatic/renal failure (2.5 each); ICU/CCU admission (2.5); CV catheter (2); Rheumatic disease (2); current cancer (2); Male (1)	<7 (2.7%)	-	≥7 (6.5%)
RIETE[17]	6		0 (0.1%)	1–4 (2.8%)	>4 (6.2%)

Continued

Table 10 *Continued*

Risk score	Number of risk factors	Risk factors (score for each factor)	Risk categories (bleeding events in validation cohort per 100 patient-years)		
			Low	Intermediate	High
Kuijer *et al.*[16]	3	Recent major bleed (2); ↑Creatinine (1.5); Anaemia (1.5); Cancer (1); Pulmonary embolism (1); Age >75 (1) Age ≥60 (1.6); Female (1.3); Malignancy (2.2)	0 (0.6%)	1–3 (1.7%)	>3 (6.7%)

Definitions for risk factors included in scores (where specified).
HAS-BLED: SBP >160 mmHg; dialysis, renal transplant, or serum creatinine >200 μmol/L; cirrhosis, bilirubin > ×2 upper limit of normal (ULN), AST/ALT/ALP > ×3 ULN; previous stroke (ischaemic or haemorrhagic); previous major bleed or bleeding predisposition (anaemia and/or severe thrombocytopenia); TTR <60%; age >65; APT/NSAIDs; >8 units/week of alcohol.
ORBIT: Age ≥75; Hb <13 g/dL in men or <12 g/dL in women, or haematocrit (<40% in men or 36% in women), or history of anaemia; any previous GI, intracranial or haemorrhagic stroke; eGFR <60 mg/dL/1.73 m^2; APT.
ABC: as defined in table.
ATRIA: Hb <13 g/dL in men or <12 g/dL in women; eGFR <30 mL/min or dialysis dependent; Age ≥ 75; any previous bleed; hypertension.
$HEMORR_2HAGES$: no further detail on specific definitions given in derivation paper.
Shireman: Age ≥70; female; history of bleeding; recent bleed; alcohol or drug abuse; diabetes mellitus; haematocrit <30% during hospitalization; APT.
OBRI: Age ≥65; previous stroke; previous GI bleed; Recent MI or anaemia (haematocrit < 30%) or diabetes mellitus or serum creatinine >1.5 mg/dL.
ACCP: Age 66–75 and >75; previous major bleed; active cancer; metastatic cancer, renal failure (CrCL < 30–60 mL/min^{-1}), history of liver failure, thrombocytopenia (<100 000), previous stroke/TIA, diabetes, anaemia (Hb < 10 g/dL), APT, TTR < 60%, comorbidity, recent surgery (<3 months), frequent falls (≥2 in last year), history of alcohol abuse, NSAIDs.
VTE-BLEED: Active cancer (≤6 months of VTE, excluding basal cell or squamous cell carcinoma of skin; recently recurrent or progressive cancer or any cancer that required anti-cancer treatment within 6 months before the VTE was diagnosed), male with uncontrolled arterial hypertension (SBP ≥ 140 mmHg at baseline); anaemia (Hb < 13 g/dL^{-1} in men; <12 g/dL^{-1} in women); history of major or non-major clinically relevant bleeding, rectal bleeding, frequent nose bleeding or haematuria, age ≥ 60, eGFR < 60 mL/min^{-1}.
EINSTEIN: Only criteria further specified was male sex if Hb <12 g/dL.
Hokusai: Female; APT, Hb ≤ 10 g/dL, history of hypertension; SBP > 160 mmHg.
Seiler: Previous major bleed; active cancer; low physical activity; anaemia; thrombocytopenia; APT or NSAIDs; poor INR control.
IMPROVE: Active GI ulcer; recent bleed (≤3 months); Plt (<50 × 10^9/L); age ≥75; hepatic failure (INR > 1.5) or renal failure (moderate GFR 30–59 mL/min/m^2 or severe <30 mL/min/m^2); ICU/CCU admission; central venous catheter; rheumatic disease; current cancer; male.
RIETE: Recent major bleeding; creatinine >1.2 mg/dL; anaemia (Hb < 13 g/dL^{-1} in men; <12 g/dL^{-1} in women); cancer; clinically overt pulmonary embolism.
Kuijer: Age ≥ 60; male; malignancy.
Adapted from Refs.[9,41]
ABC, age, biomarkers, clinical history; ACCP, American College of Chest Physicians; APT, antiplatelet therapy; ATRIA, Anticoagulation and Risk Factors in Atrial fibrillation; BP, blood pressure; CCU, coronary care unit; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; cTnT-hs, high-sensitivity cardiac troponin T; CV, central venous; CVD, cardiovascular; EINSTEIN; GDF-15, growth differentiation factor-15; GI, gastrointestinal; HAS-BLED, (uncontrolled) hypertension, abnormal renal or liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs/drink (alcohol); Hb, haemoglobin; $HEMORR_2HAGES$, Hepatic/renal disease, ethanol abuse, malignancy, age, reduced platelet function, re-bleeding risk (2 points), (uncontrolled) hypertension, anaemia, genetic factors, falls risk, stroke; Hb, haemoglobin; Hct, haematocrit; HAS-BLED, (uncontrolled) hypertension, abnormal renal or liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs/drink (alcohol); $HEMORR_2HAGES$, Hepatic/renal disease, ethanol abuse, malignancy, age, reduced platelet function, re-bleeding risk (2 points), (uncontrolled) hypertension, anaemia, genetic factors, falls risk, stroke; ICU, intensive care unit; IMPROVE, International Medical Prevention Registry on Venous Thromboembolism; INR, international normalized ratio; NR, not reported; NSAIDs, non-steroidal anti-inflammatory drugs; ORBIT-AF, Outcomes Registry for Better Informed Treatment of Atrial Fibrillation; Plt, platelet count or function; RIETE, Registro Informatizado de la Enfermedad ThromboEmbolica; SBP, systolic blood pressure; TTR, time in the therapeutic range; VKA, vitamin K antagonist; VTE-BLEED.
*Bleeding event in original derivation cohort. [a]At 3 months; ↓ reduced/decreased; ↑ elevated/increased; [b]score for each variable in ABC score is based on a nomogram (see reference[3]); [c]annualized risk; [d]dabigatran arm; [e]edoxaban arm; [w]warfarin arm.

(ATRIA,[62] HAS-BLED,[79] $HEMORR_2HAGES$,[77] mOBRI,[81] OBRI,[82] ORBIT,[78] Shireman[80]) The predictive ability, evidenced by the c-statistic, in the derivation and internal validation studies ranged from 0.65 to 0.75 (median 0.68) but was lower in the external validation studies (range 0.52–0.71, median 0.59).[92] Bleeding risk scores derived in non-VTE populations have poor discriminative ability (c-statistic 0.52–0.71; median 0.57); the only exception was the recalibrated HAS-BLED score (c-statistic 0.69).[99] They concluded that the current evidence does not support the implementation of existing bleeding risk scores to assist in treatment decisions to cease or extend OAC after the initial 3-month period.[92] External validation of the VTE-BLEED score,[88] derived from a population treated with dabigatran or warfarin, demonstrated predictive ability across patient groups,[106–108] and for ICH and/or fatal bleeding.[109] External validation of the EINSTEIN or Hokusai scores has not been undertaken.

More recently, the prognostic precision of six bleeding risk scores (HAS-BLED,[79] ORBIT,[78] ATRIA-Bleeding,[62] Kuijer,[89] RIETE,[90] and VTE-BLEED[88]) for predicting major bleeding was compared in a prospective multicentre cohort of 1034 people receiving a NOAC for VTE and found to be modest, with c-statistics for VTE-BLEED 0.674 (95% CI 0.593–0.755), ORBIT 0.645 (95% CI 0.523–0.767), and RIETE 0.604 (95% CI 0.510–0.697), with no significant difference between bleeding scores in predicting major bleeding.[64] Another study[65] compared the predictive ability of 10 clinical bleeding risk scores (VTE-BLEED,[88] RIETE,[90] ACCP,[37] Seiler,[91] Kuijer,[89] Kearon, OBRI,[81,82] ATRIA,[62] HAS-BLED,[79] and $HEMORR_2HAGES$[77]) for major and clinically relevant bleeding, in 743 patients ≥65 years receiving extended (≥3 months) VKA therapy following VTE. The c-statistics ranged from 0.47 (OBRI[81,82]) to 0.70 (Seiler[91]) for major bleeding and 0.52 (OBRI[81,82]) to 0.67 ($HEMORR_2HAGES$[77]) for clinically relevant bleeding. A recent review of bleeding risk assessment in patients

Table 11 Randomized controlled trial of uninterrupted oral anticoagulation in atrial fibrillation catheter ablation

	COMPARE[4]	VENTURE-AF[10]	RE-CIRCUIT-AF[11]	AXAFA-AFNET 5[12]	ELIMINATE-AF[13]
OAC treatment	Heparin bridging vs. warfarin (1:1)	Rivaroxaban vs. warfarin (1:1)	Dabigatran vs. warfarin (1:1)	Apixaban vs. warfarin (1:1)	Edoxaban vs. warfarin (2:1)
Number of patient (*n*)	790/793	124/124	317/318	318/315	411/203
Age (years), mean or median	61/24	58.6/60.5	59.1/59.3	64.0/64.0	60.0/61.0
Male gender (%)	76/74	68.4/72.6	72.6/77	69/65	70.6/73.4
BMI, kg/m^2, mean or median	NA	29.8/28.9	28.5/28.8	28.4/28.2	28.1/27.8
CHA_2DS_2-VASc score	1: 29/26 2: 34/36 ≥3: 37/38	1.5/1.7	2/2.2	2.4/2.2	0: 23.4/21.7 1: 26.5/28.1 ≥2: 50.1/50.2
Prior stroke or TIA (%)	7/8	0/2.4	3.2/2.8	7.5/7.3	5.4/3.9
Congestive heart failure (%)	15/17	9.7/7.3	9.8/10.7	24.5/22.9	17.3/19.2
Hypertension (%)	81/83	47.6/46	52.4/55.7	89/91.4	60.8/59.6
Diabetes (%)	38/40	6.5/11.3	9.5/10.7	12.9/11.1	13.4/15.8
Types of AF (%)					
Paroxysmal AF	29/25	76.6/70.2	67.2/68.9	59.4/56.5	69.1/64.5
Persistent AF	71/75	23.4/29.8	32.8/31.2	40.6/43.6	25.5/30
TEE prior to ablation (%)	NA	NA	100	84.6	74.6
Duration of OAC before ablation	3–4 weeks	3 weeks	4–8 weeks	30 days	21–28 days
Estimated NOAC compliance (%)	NA	99.9	97.6	97	97
INR, time in therapeutic range (%)	NA	79.8	85.7	84	84
ACT (s), mean or median	NA	302/332	330/340	310/348	3014/322.6
Primary outcome	Thromboembolic events (stroke/TIA/systemic thromboembolism)	Major bleeding events (ISTH)	Major bleeding events (ISTH)	All-cause mortality, stroke or major bleeding (BARC ≥ 2)	All-cause mortality, stroke or major bleeding event (ISTH)
Follow-up	48 h	30 days	8 weeks	3 months	90 days
Primary outcome event (%)	4.9/0.25*	0/0.8	1.6/6.9*	6.9/7.3	2.7/1.7
Death (%)	0/0	0/0.8	0/0	0.3/0.3	0/0
Ischaemic stroke (%)	3.7/0.25	0/0.8	0/0.3	0.6/0	0.3/0
Major bleeding (%)	0.76/0.38	0/0.8	1.6/6.9	3.1/4.4	2.4/1.7
Death/ischaemic stroke/major bleeding (%)	5.7/0.63	0/2.4	1.6/7.2	4.0/4.7	2.7/1.7

AF, atrial fibrillation; ACT, activated clotted time; BARC, Bleeding Academic Research Consortium; BMI, body mass index; INR, international normalized ratio; ISTH, International Society on Thrombosis and Haemostasis; NOAC, non-vitamin K antagonist oral anticoagulant; NA, not available; OAC, oral anticoagulant; TEE, transoesophageal echocardiogram; TIA, transient ischaemic attack.
*$P < 0.01$.

with VTE[110] concluded that the HAS-BLED or RIETE scores are beneficial in identifying patients at HBR during early phase OAC treatment, with VTE-BLEED advantageous in identifying low-risk patients who could benefit from extended OAC for secondary prophylaxis.

In summary, simple bleeding risk scores based on clinical factors generally have modest predictive value and calibration for bleeding events (c-indexes ~0.6). More complicated clinical bleeding risk scores modestly improve prediction (perhaps to 0.65) and the addition of biomarkers will always statistically improve on clinical factor-based scores (with c-indexes ~0.7). All these approaches offer far from perfect prediction (c-indexes <0.9) but ultimately, bleeding risk scores need to balance statistical prediction against simplicity and practicality (incorporating both modifiable and non-modifiable bleeding risks), for use in everyday busy clinical scenarios. In contrast to ischaemic risk prediction tools, a limitation of current bleeding prediction tools is an unclear immediate actionability for treatment decisions, which may explain lower implementation in clinical practice. However, as illustrated in the mAFA-II trial,[103] where appropriate use of the HAS-BLED score is associated with lowered major bleeds and increased OAC uptake, the increasing recognition of the importance of bleeding on prognosis should inform decision-making based on bleeding risk assessment in clinical practice.

Patient values and preferences

Clinical guidelines advocate inclusion of patient preferences in treatment decisions, particularly for OAC.[11,14,111] A 2017 systematic review of OAC preferences among AF patients found 27 studies conducted across 12 countries.[112] Sixteen studies (106–121)

Table 12 Prospective and retrospective cohort studies (sample size ≥100) of peri-procedural oral anticoagulation in atrial fibrillation patients undergoing cardiac rhythm device procedures

Study	Design	Subjects (*n*)	Age (years), mean	Continued OAC (%)	Interrupted OAC (%)	Timing of OAC Interruption (h), mean or median	Timing of OAC resumption	Antiplatelet therapy (%)	Clinically significant haematoma (%)	Other device-related bleeding (%)	Thromboembolic and other complications (%)
Birnie *et al.*[16]	BRUISE CONTROL 1 prospective randomized control trial	Warfarin 681	72 years	50.3%	Heparin bridging 49.7%	NA	NA	*Warfarin* Aspirin: 38.2% P2Y12: 6.2% *Heparin bridging* aspirin: 40.5% P2Y12: 6.1%	Warfarin: 3.5% Heparin bridging: 16.0%	*Pericardial effusion* Warfarin: 0% Heparin bridging: 0.3%	*Stroke/TIA* Warfarin: 0.6% Heparin bridging: 0% *MI* Warfarin: 0% Heparin bridging: 0.3%
Black-Meier *et al.*[7,23]	Retrospective analysis of ORBIT-AF	Warfarin 284 NOAC 60	Warfarin 77 years NOAC 70.5 year	Warfarin 36% NOAC 35%	Warfarin 64% NOAC 65%	NA	NA	*Warfarin* Aspirin: 35% P2Y12: 7.4% *NOAC* Aspirin: 51.7% P2Y12: 8.3%		*Major bleeding* −ve warfarin: 1% +ve warfarin: 3% −ve NOAC: 0% +ve NOAC: 0%	*Stroke/TIA* −ve warfarin: 1% +ve warfarin: 1% −ve NOAC: 0% +ve NOAC: 0%
Essebag *et al.*[19]	Post-hoc analysis of RE-LY trial	VKA 201 Dabigatran 410	73 years	0%	100%	VKA: 144 h (total pre + post) NOAC: 53 h	NOAC: 34 h	Aspirin: 44% P2Y12: 8%	VKA, bridging: 10.8% VKA, no bridging: 2.4% NOAC: 2.2%	*Major bleeding* VKA, bridging: 2.7% VKA, no bridging: 0.6% NOAC: 1.0%	*Stroke* VKA, bridging: 0% VKA, no bridging: 0.6% NOAC: 0.2%
Leef *et al.*[20]	Post-hoc analysis of ROCKET-AF trial	VKA 211 Rivaroxaban 242	75 years	25%	75%	VKA: 5 days NOAC: 3 days	VKA: 3 days NOAC: 2 days	—	NOAC: 0.4% VKA: 2.9% −ve OAC: 1.2% +ve OAC: 2.7%	*Major bleeding* NOAC: 1.2% VKA: 1.0% −ve OAC: 1.2% +ve OAC: 0.9%	*Stroke/SE* NOAC: 1.3% VKA: 0.5% −ve OAC: 0.6% +ve OAC: 1.8%
Ricciardi *et al.*[24]	Prospective randomized pilot trial	NOAC 101 (Dabigatran = 37, Rivaroxaban = 33, Apixaban = 31)	76 years	49.5%	50.5%	Dabigatran: 24–48 h Rivaroxaban/apixaban: 24 h	≥24 h	Aspirin: 15.8% P2Y12: 5.9% Both: 3%	−ve NOAC: 0% +ve NOAC: 2%	*Any* haematoma −ve NOAC: 4% +ve NOAC: 3.9% *Loss of Hb > 2 g/dL* −ve NOAC: 6% +ve NOAC: 9.8%	*Pocket infection* +ve NOAC: 1%
Birnie *et al.*[18]	BRUISE CONTROL 2 prospective randomized control trial	NOAC 647 (Dabigatran = 96, Rivaroxaban = 106, Apixaban = 125)	74	49.3%	50.5%	Dabigatran: 24–48 h Rivaroxaban/apixaban: 48 h	≥24 h	Aspirin 17.4% P2Y12: 3.6%	−ve NOAC: 2.1% +ve NOAC: 2.1%	*Any* haematoma −ve NOAC: 4.8% +ve NOAC: 5.5% *Pericardial effusion* −ve NOAC: 0.3% +ve NOAC: 0.3%	*Stroke* −ve NOAC: 0.3% +ve NOAC: 0.3%
Tsai *et al.*[22]	Retrospective analysis	NOAC 100 (Dabigatran = 28, Rivaroxaban = 61,	78 years	100%	0%	NA	NA	Aspirin: 6% P2Y12: 2%	+ve NOAC: 1%	*Pericardial effusion* +ve NOAC: 1%	0%

Continued

Table 12 *Continued*

Study	Design	Subjects (*n*)	Age (years), mean	Continued OAC (%)	Interrupted OAC (%)	Timing of OAC Interruption (h), mean or median	Timing of OAC resumption	Antiplatelet therapy (%)	Clinically significant haematoma (%)	Other device-related bleeding (%)	Thromboembolic and other complications (%)
		Apixaban = 10, Edoxaban = 1)									
Steffel *et al.*[21]	Post-hoc analysis of ENGAGE AF trial	VKA 324	74 years	26%	74%	median 7 days (pre + post)	NA	Aspirin: 32%	NA	*Major bleeding*	*Stroke*
		Edoxaban 549						P2Y12: 2.5%		−ve VKA: 0%	+ve VKA: 1.1%
										+ve VKA: 0%	−ve VKA: 0.9%
										−ve NOAC: 0%	+ve NOAC: 0.5%
										+ve NOAC: 0.5%	−ve NOAC: 0.4%

−ve , interrupted; +ve, continued; MI, myocardial infarction; NA, not available; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; SE , systemic embolism; TIA, transient ischaemic attack; VKA , vitamin K antagonist.

examined patients' general perceptions of OAC, predominantly in those already receiving OAC, utilizing standard trade-off scenarios or conjoint or discrete choice analysis, or preference questionnaires.[112] Most patients would accept a higher risk of bleeding for a corresponding reduction in stroke risk, but there was considerable variability in the number of bleeds that would be accepted.[113–117] This contrasted with the perception of physicians, who generally worried more about the harm from bleeding.[115,118,119] Eleven studies[114,120–129] assessed patient preferences towards VKAs vs. NOACs. Where efficacy and safety were similar, patients commonly favoured simpler, more convenient treatment regimens, preferring less frequent dosing, fixed-dose medication, without need for regular monitoring or bridging, or drug–food interactions.[112] These results are supported by two previous systematic reviews[130,131] and more recent studies,[132–134] including an international survey (USA, Canada, France, Germany, and Japan) of 934 AF patients receiving OAC for stroke prevention.[132] A reduction in major bleeding was second to stroke prevention as the most valued attribute of OAC; preferences were the same regardless of demographic characteristics, stroke knowledge, stroke concern, perception of AF severity, or medication burden.[132,133]

A recent systematic review of values and preferences amongst VTE patients evaluating 49 studies (34 quantitative and 15 qualitative)[135] concluded that patients valued reduction in VTE risk over the potential risks associated with OAC treatment (i.e. bleeding)[135–137] and preferred oral medication.[135] Most studies indicated that although VTE patients preferred to avoid adverse events, only one-fifth to one-quarter feared bleeding events[135] and among those who had experienced deleterious consequences, most 'were not afraid' of adverse outcomes.[138–140] Among cancer patients, risk of major bleeding was the third most important consideration related to VTE treatment, after ensuring that VTE prophylaxis did not interfere with cancer treatment and OAC efficacy.[141,142] As with AF patients, convenience attributes (e.g. OAC monitoring, dosing frequency, and dietary restrictions) were less important than efficacy[121,140,143–145] and safety. Venous thromboembolism patients who were made aware of the need for OAC treatment and understood the risks/benefits were more accepting of OAC.[146–150]

Shared decision-making[151] is important to enable healthcare professionals to inform and educate patients and their family/caregivers about the treatment options, risks, benefits, and length of treatment (which may differ depending on the indication, VTE vs. AF), and to allow open dialogue to discuss patients' concerns and treatment preferences and goals, barriers/enablers to implementation, and how patients will incorporate OAC into their daily routine, to increase the uptake of OAC and long-term adherence.[11,135,152–155]

Approach to assessment and bleeding risk mitigation

General atrial fibrillation population

After the evaluation of thromboembolic risk, most guidelines suggest paying attention to the evaluation of bleeding risk. Quality indicators

Table 13 Stratification of thromboembolic risk according to clinical indication for oral anticoagulation

Risk	Indication for OAC	
	AF	VTE
High	• CHA_2DS_2-VASc ≥7 • Recent (within 3 months) stroke/TIA • Rheumatic mitral valve disease	• Recent (within 3 months) VTE • Severe thrombophilia (e.g. homozygous factor V Leiden or prothrombin 20 210 mutation, protein C, protein S, or antithrombin deficiency, antiphospholipid syndrome, multiple defects)
Moderate	• CHA_2DS_2-VASc 5–6 • Stroke/TIA >3 months	• VTE within the past 3–12 months • Non-severe thrombophilia (e.g. heterozygous factor • V Leiden or prothrombin gene mutation) • Recurrent VTE • Active cancer + VTE
Low	• CHA_2DS_2-VASc 1–4 • No history of stroke/TIA	• VTE >12 months and no other risk factors

Modified from Ref.[179]
AF, atrial fibrillation; OAC, oral anticoagulation; TIA, transient ischaemic attack; VTE, venous thromboembolism.

Table 14 Recommended duration for withholding OAC prior to a procedure when temporary interruption is needed

NOAC						
	Procedural bleed risk					
CrCl (mL/min)		<15	15–29	30–49	50–79	≥80
Dabigatran	Low	≥96 h[a]	≥72 h	≥48 h	≥36 h	≥24 h
	Intermediate, high or uncertain	No data[a]	≥120 h	≥96 h	≥72 h	≥48 h
CrCl (mL/min)		<15	15–29	≥30		
Apixaban, rivaroxaban, or edoxaban	Low	≥48 h	≥36 h	≥24 h		
	Intermediate, high, or uncertain	≥72 h[b]	≥72 h[b]	≥48 h		
VKA						
INR 5–7 days prior to the procedure[c]		<2	2–3	>3		
Warfarin[d]		3–4 days	5 days	>5 days		

CrCl, creatinine clearance; DOAC, direct acting oral anticoagulant; dTT, dilute thrombin time; INR, international normalized ratio; VKA, vitamin K antagonist.
[a]Consider measuring dTT.
[b]Consider measuring agent-specific antiXa level.
[c]INR must be measured again 24 h before the procedure.
[d]If other VKA than warfarin is used, the durations may be adjusted according to the drug half-life.

for the care and outcomes of adults with AF published by EHRA include the proportion of patients with bleeding risk assessment using a validated method, such as the HAS-BLED score.[156]

The important aspect is the appropriate use of a validated score, given the limitations of all bleeding risk scores highlighted above, and the dynamic nature of bleeding risk. All clinical guidelines for the management of AF recommend bleeding risk assessment for people prior to, or on OAC, with the HAS-BLED score recommended by the ESC,[11] American College of Chest Physicians,[14] and Asia-Pacific Heart Rhythm Society,[12] given its simplicity and evidence base, including evaluation in a prospective cluster RCT.[103] The ACC/AHA/HRS AF guidelines did not propose any specific bleeding risk scheme.[157]

The 2021 NICE guideline acknowledged low- to very low-quality evidence for its recommended use of the ORBIT risk score, based on better calibration in NOAC users,[158] but also further emphasized attention to modifiable risk factors for bleeding, including uncontrolled hypertension; poor INR control; concurrent medication, including antiplatelets, selective serotonin reuptake inhibitors (SSRIs), and NSAIDs; excessive alcohol consumption; and addressing reversible causes of anaemia. Of note, all these modifiable risk factors listed are already included within the HAS-BLED score.

The 2020 ESC AF guideline emphasizes that, irrespectively of the score used, the main aim is to identify patients with modifiable or potentially modifiable bleeding risk factors.[11] This may include controlling BP, cessation of non-essential antiplatelet therapy (APT) or NSAIDs, improving TTR, and reduction/cessation of alcohol (*Figure 4*). Most of the modifiable bleeding risk factors listed in the ESC AF guideline are components of the HAS-BLED score. Often an individual patient's bleeding risk is based on the interaction of non-modifiable and modifiable bleeding risks. Simply focusing on modifiable bleeding risk factors alone as a measure of predicting bleeding

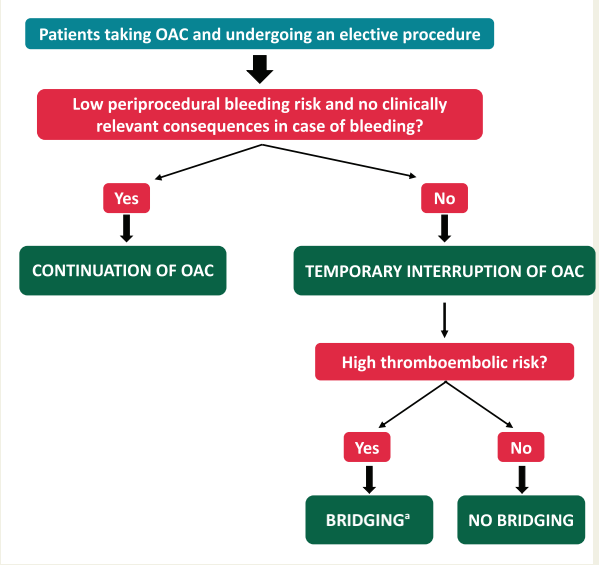

Figure 5 Simplified algorithm for selecting the periprocedural management strategy of OAC in patients undergoing an elective surgery or invasive procedure. [a]Bridging with parenteral heparin is generally not necessary with DOACs. DOAC, direct oral anticoagulant; OAC, oral anticoagulation.

risk is an inferior strategy to formal assessment with a bleeding risk score.[74–76]

Generally, HBR should not a reason to withhold OAC, except for specific situations in which the risk/benefit ratio excessively favours no antithrombotic treatment.[11,157,159–161] Instead, efforts should be made to identify and address all modifiable bleeding risk and provide more regular review, to assess bleeding risk frequently since it is dynamic.[11,14,38,162]

General venous thromboembolism population

Notwithstanding the limitations of bleeding risk scores for VTE discussed earlier, bleeding risk assessment is recommended both upon initiation of anticoagulation for VTE and at follow-up visits, the frequency of which should increase if the bleeding risk is high.[21] Of note, the aim is not to withhold OAC if one or more bleeding risk factors are found, but (like in AF) to identify and address potentially modifiable factors.

Consequently, current VTE guidelines leave the choice of the tool for assessing bleeding risk to the discretion of the clinician, with many guidelines avoiding endorsement of a particular score.[21,22] However, the 2020 NICE VTE guideline[163] recommends using the HAS-BLED score and advises stopping anticoagulation if the HAS-BLED score is 4 or more and cannot be modified. In case of persistent HBR, the patient's personalized risk: benefit ratio of anticoagulant treatment should be assessed and if judged to favour extended anticoagulation, a reduced dose of the NOACs apixaban (2.5 mg twice daily) or rivaroxaban (10 mg once daily) should be considered after 6 months of therapeutic anticoagulation. Aspirin is not an alternative to anticoagulation for extended secondary VTE prevention and may be considered only in patients who refuse to take or are unable to tolerate OAC.[21]

Surgery and endoscopic and endovascular procedures

Peri-ablation of atrial arrhythmias

Catheter ablation, especially left-sided ablation, is associated with a small but relevant ~0.5% risk of severe bleeding[164] related to vascular access and peri-interventional anticoagulation.[165] It also carries a risk of thrombotic events, with left-sided procedures carrying a higher risk of thrombosis and stroke.

The incidence of vascular complications depends on type of vascular access (arterial, venous, or both), site and size of vascular access (i.e. femoral vs. subclavian or jugular), number of introduced catheters, length of the procedure, patient profile (i.e. obesity and baseline coagulation parameters), type of anticoagulation used, management of catheterization site during and after the procedure, and operator experience. The stroke and transient ischaemic attack rate are ~1% in large studies, with reported bleeding rates of 1% for cardiac tamponade and 1–2% for access site bleeds.[165] The risk of perforation even with AF ablation is reported to occur in <1% of cases in contemporary series, with use of intracardiac echo shown to reduce the risk.[165,166]

Continuation of OAC for AF ablation is safe with a trend towards fewer bleeding events and may also help to prevent peri-procedural stroke (*Table 11*).[167] Most guidelines agree on three main points[11,14,160,161,168]: (i) uninterrupted OAC is recommended for patients undergoing ablation; (ii) after the procedure, OAC is essential for at least 8 weeks in all patients; and (iii) long-term OAC beyond the first 8 weeks, should be considered on the basis of risk profile (CHA_2DS_2-VASc). Regarding the type of OAC, NOACs, and VKAs are both options, although meta-analyses report a trend favouring NOACs with respect to major bleeding.[169]

Cardiovascular implantable electronic device

In patients without mechanical valves, anticoagulation may be briefly interrupted for cardiovascular implantable electronic device (CIED) implantation, without bridging. In patients with mechanical valves, uninterrupted VKA is preferable to interruption of VKA with heparin bridging (see section on bridging).

In patients on NOACs, the BRUISE-CONTROL 2 trial compared patients with a last intake 2 days before the implantation for rivaroxaban, apixaban, and (based on glomerular filtration rate) dabigatran vs. continued NOAC until the morning of the procedure. The study was prematurely stopped due to futility because of the far lower rate of events than anticipated and similar rates of bleeding and embolic events.[170] Therefore, both stopping or continuing NOAC are possible options and supported by subgroup analyses from the pivotal Phase III trials and large observational analyses (*Table 12*).[171–175] For patients on a NOAC, a strategy as for low bleeding risk interventions (i.e. infrequent bleeding or with non-severe clinical impact) with intake of the last dose the day before the procedure is appropriate in most cases,[161] with resumption of NOAC intake on the first post-

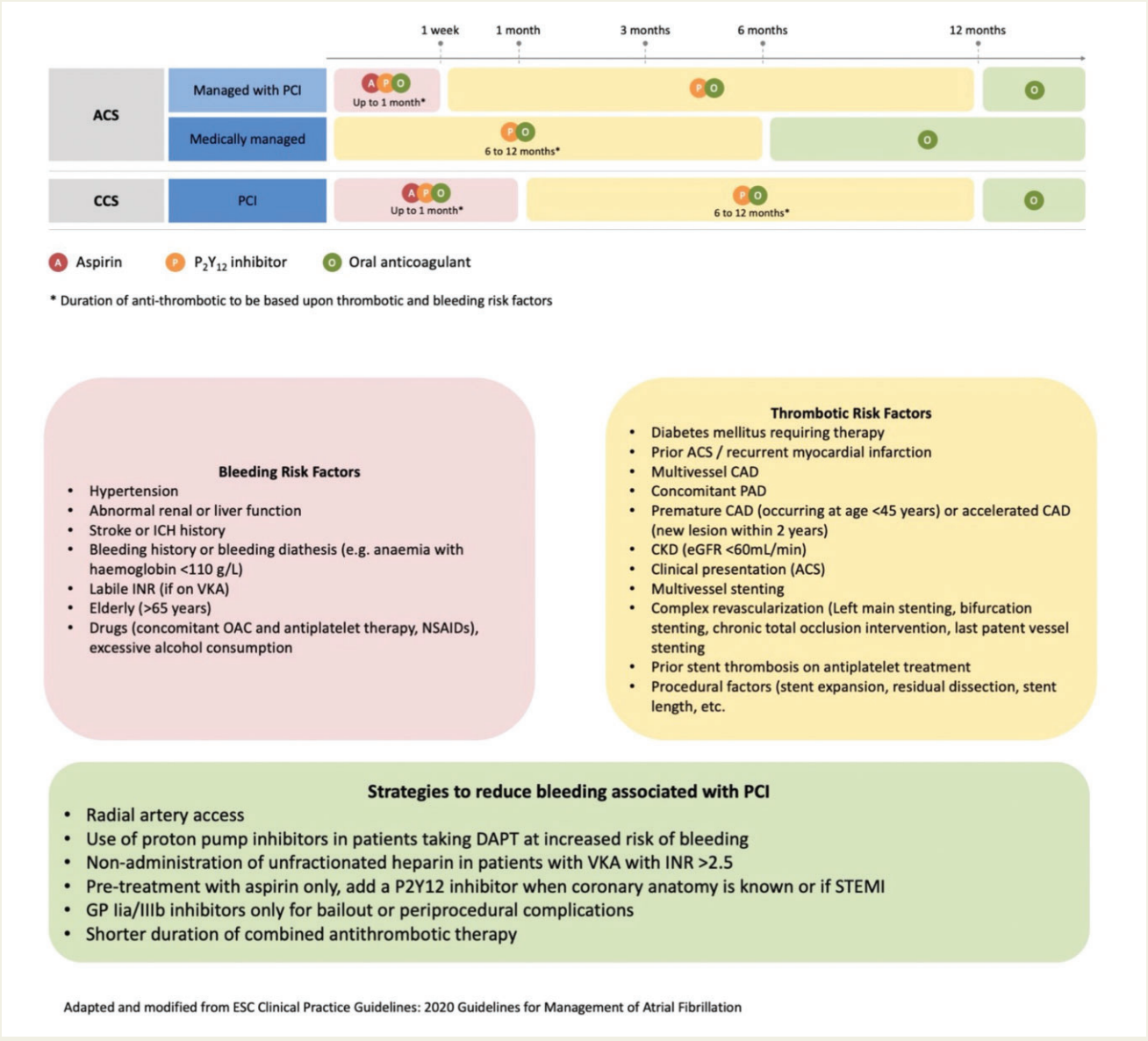

Figure 6 Management of antithrombotics in patients presenting with ACS and/or requiring PCI or stents. ACS, acute coronary syndrome; PCS, percutaneous coronary interventions.

operative day. Procedures with uninterrupted OAC should be carried out by an experienced operator, with close attention paid to achieving good haemostasis.

Surgical procedures

The periprocedural management of patients receiving OAC represents a frequent clinical challenge for physicians. Given the relatively scarce evidence-base on this subject, most available recommendations are based on expert consensus.[16,176–179] This section focuses on recommendations regarding patients with AF or VTE with a clinical indication for OAC who require elective surgery or an endoscopic or endovascular procedure. Briefly, the periprocedural strategy to reduce the risk of adverse outcomes is based on careful assessment of two risks: (i) the bleeding risk associated with the procedure, and (ii) the thromboembolic risk associated with the condition that underlies the indication for OAC.

The risk of bleeding with a given procedure must consider both the prevalence of haemorrhagic complications and its consequences. Thus, procedures with low rates of bleeding but relevant associated sequelae (e.g. intracranial or spinal surgery) should be classified as high risk. In addition, it is also pertinent to contemplate comorbid conditions (e.g. older age, kidney or liver dysfunction) that can increase the risk of peri-procedural bleeding. Different professional societies have made several attempts to categorize the risk of bleeding related to different interventional procedures.[177–179]

The thromboembolic risk associated with the indication for OAC is classified according to the annual risk of arterial or venous thromboembolism: high if the risk is >10%, moderate between 5% and 10%, and low when <5% (*Table 13*).[176,177,179]

Despite general recommendations, an individualized approach by the local physicians (surgeons, anaesthesiologists, etc.) involved in the procedure is mandatory. For some procedures with low haemorrhagic risk (e.g. diagnostic endoscopy without biopsy), uninterrupted OAC is a safe strategy both in patients on VKA (INR ≤3 on the day of the procedure) or NOACs.[170,180] The general recommendation is to consider peri-procedural temporary interruption without bridging for patients with low or moderate thromboembolic risk and reserve bridging only for patients at high risk. Bridging is rarely needed in patients on NOACs, given the short half-life of these agents. When a temporary interruption is required, the recommended duration for withholding OAC before the procedure is mostly based on the procedural bleeding risk and the INR values 5–7 days before the procedure in case of VKAs or the renal function in case of NOACs (*Table 14*).

When treatment on uninterrupted OAC is not feasible, the peri-procedural strategy will depend on the assessment of the patient's risk of thromboembolism (*Figure 5*) and is discussed in more detail in the section on 'Bridging' later.

Post-procedure, OAC may be re-initiated once haemostasis is achieved and in the absence of a bleeding complication. In most situations with low post-procedural bleeding risk, OAC can be resumed within 24 h (generally on the day following the procedure), whereas it is reasonable to wait for 48–72 h if the risk of post-procedural bleeding is high.[177,179,181]

A detailed explanation regarding measures to mitigate bleeding in patients on OAC requiring emergency surgery or invasive procedure is beyond the scope of this manuscript and can be found elsewhere.[161,179,182] Notably, depending on the type of procedure and its associated bleeding risk, such patients may require a reversal agent, such as intravenous vitamin K for VKAs (INR reduction in 4–6 h), idarucizumab for dabigatran or andexanet alfa for factor Xa inhibitors,[183,184] although it should be noted that idarucizumab was evaluated in patients requiring urgent surgery in only one small study[185] and andexanet has not been studied in this setting. If antidotes are not available for an emergency procedure or the patient has active major or life-threatening bleeding, administration of haemostatic agents should be considered, with four-factor prothrombin complex concentrate (PCC) and PCC as first options for VKAs and NOACs, respectively.[182,186]

Presentation with acute coronary syndrome and/or requiring percutaneous coronary intervention

In patients requiring combined OAC and APT, such as those with AF or VTE presenting with ACS and/or undergoing PCI, the risk of bleeding is increased.[187] In this setting, the predictive value of scores is generally poor, with the HAS-BLED score performing best[188,189] and shown to predict significant bleeding in AF patients undergoing PCI.[190] The Academic Research Consortium (ARC) has defined HBR (BARC 3 or 5 bleeding) for patients undergoing PCI as the presence of one major or two minor characteristics[191] (*Table 15*), which can be found in up to 40% of patients.

An increased risk of bleeding is apparent in both the peri-PCI and post-discharge periods and strategies to minimize such risk should therefore be applied before, during, and after PCI.[192] Pre-PCI approaches include avoidance of routine pre-treatment with APT, with $P2Y_{12}$-inhibitor generally given only after coronary angiography has confirmed the decision to proceed to PCI.[192,193]

Peri-PCI strategies include the preferential use of the radial approach and avoidance of glycoprotein IIb/IIIa inhibitors.

For elective procedures, European guidelines recommend uninterrupted VKA if the INR < 2.5,[193] whereas North American guidelines recommend uninterrupted VKA if INR < 2,[194] with interruption of VKA considered when INR is above these thresholds. Intra-PCI administration of reduced-dose UFH is recommended.[193,194]

In patients on NOAC, timely interruption in elective patients may be considered, as indicated in the European guidelines[193] and is clearly recommended by North American guidelines[194] with both guidelines recommending administration of weight-adjusted dose UFH, owing to the uncertain protection of NOAC against PCI-related ischaemic events.[195,196] Because of that, UFH should be also administered to patients on NOAC undergoing PCI in the emergency setting.[193]

Following PCI, the type and duration of APT should be carefully considered to minimize bleeding.[192] An initial short course of triple antithrombotic therapy (TAT) with OAC and dual APT (DAPT) of aspirin and clopidogrel is warranted to limit the early hazard of ischaemic events (*Figure 6*).[11] To mitigate the increased risk of bleeding associated with TAT, the more potent $P2Y_{12}$-inhibitors prasugrel and ticagrelor should be avoided, with European guidelines indicating that ticagrelor or prasugrel be used as part of TAT only in exceptional circumstances such as stent thrombosis whilst on TAT with clopidogrel, aspirin and OAC,[193] and North American guidelines suggesting that ticagrelor can be considered in patients at particularly high stent thrombosis risk although prasugrel should be avoided.[194]

The duration of TAT should be minimized, generally ranging from 1 to 4 weeks (*Figure 6*). Subsequent antithrombotic management is determined by whether long-term OAC is indicated. In most AF and VTE patients for whom indefinite OAC is warranted, double antithrombotic therapy (DAT) with OAC and single APT (SAPT), preferably clopidogrel, should follow initial TAT and be maintained up to 6–12 months, based on the patient's bleeding and ischaemic risks[193,194] (*Figure 6*), followed by OAC alone indefinitely.[193,194,197,198] Prolongation of DAT beyond 1 year may be considered in selected patients with both clinical and/or anatomical features for increased ischaemic cardiac events, including diabetes, multi-vessel disease, incomplete revascularization, and left main or last remaining vessel stenting, and, importantly, low risk of bleeding[193,194] (*Figure 6*). In contrast, in patients with a first episode of VTE, in whom OAC is discontinued after 3 months, DAPT comprising of aspirin and clopidogrel should be resumed upon OAC cessation with duration tailored to type of event and procedural characteristics.[194]

In addition to limiting the duration of TAT, as well as of DAT, strategies to minimize the risk of bleeding should also aim to reduce the intensity of OAC. A target INR at the lower end of the therapeutic range (2.0–2.5) is recommended with VKA,[193] aiming for TTR >65–70%.[199] NOACs are preferable to VKA as part of combination therapy and switching from warfarin should be routinely considered.[193] To date, no specific NOAC appears preferable since no head-to-head comparisons have been performed and all of them given as part of DAT have shown a favourable safety and efficacy profile compared to TAT including warfarin.[200–203] In the AUGUSTUS trial, amongst

Table 15 ARC major and minor criteria for HBR at time of PCI High bleeding risk defined as at least one major or two minor criteria

Major	Minor
	Age ≥75 years
Anticipated use of long-term oral anticoagulation[a]	
Severe or end-stage CKD (eGFR <30 mL/min)	Moderate CKD (eGFR 30–59 mL/min)
Haemoglobin <11 g/dL	Haemoglobin 11–12.9 g/dL for men and 11–11.9 g/dL for women
Spontaneous bleeding requiring hospitalization and/or transfusion in the past 6 months or at any time, if recurrent	Spontaneous bleeding requiring hospitalization and/or transfusion within the past 12 months not meeting the major criterion
Moderate or severe baseline thrombocytopenia[b] (platelet count $<100 \times 10^9$ per litre)	
Chronic bleeding diathesis	
Liver cirrhosis with portal hypertension	
	Chronic use of oral NSAIDs or steroids
Active malignancy[c] (excluding non-melanoma skin cancer) within the past 12 months	
Previous spontaneous ICH (at any time)	Any ischaemic stroke at any time not meeting the major criterion
Previous traumatic ICH within the past 12 months	
Presence of a bAVM	
Moderate or severe ischaemic stroke[d] within the past 6 months	
Non-deferrable major surgery on DAPT	
Recent major surgery or major trauma within 30 days prior to PCI	

bAVM, brain arterio-venous malformation; CKD, chronic kidney disease; DAPT, dual-antiplatelet therapy; eGFR, estimated glomerular filtration rate; HBR, high bleeding risk; ICH, intracranial haemorrhage; NSAID, non-steroidal anti-inflammatory drug; PCI, percutaneous coronary intervention.
[a]This excludes dual pathway inhibition doses.
[b]Baseline thrombocytopenia defined as thrombocytopenia prior to PCI.
[c]Active malignancy is defined as diagnosis within 12 months and/or ongoing requirement for treatment (including surgery, chemotherapy, or radiotherapy).
[d]National Institutes of Health Stroke Scale (NIHSS) score ≥5.

patients with AF and either ACS or PCI treated with a $P2Y_{12}$ inhibitor, treatment with apixaban, without aspirin, resulted in less bleeding and fewer hospitalizations than regimens that included a VKA, aspirin, or both.[202] Sub-analysis of data from the RE-DUAL PCI trial, which compared DAT (dabigatran 110 or 150 mg bid, clopidogrel or ticagrelor) with TAT (warfarin, clopidogrel or ticagrelor, and aspirin), showed that DAT with dabigatran reduced bleeding both in non-HBR and HBR patients, with a greater magnitude of benefit among non-HBR patients.[204] NOACs should be given at the recommended doses, with the possible exceptions of dabigatran and rivaroxaban for which the lower doses of 110 mg twice daily and 15 mg once daily respectively, are preferable when used as part of TAT.[193]

In patients at HBR not on OAC when presenting for PCI, but developing an indication for OAC later, several bleeding-avoidance strategies should be considered: (i) while in patients with ST-elevation myocardial infarction (STEMI) DAPT (aspirin plus ticagrelor or prasugrel, clopidogrel only if the stronger $P2Y_{12}$-inhibitors are contraindicated, not available, or in patents at HBR) should be started when the diagnosis is confirmed at first medical contact, 'pre-treatment' is not routine strategy in patients with non-ST-elevation MI (NSTEMI) and a planned early invasive strategy. Therefore, in the setting of NSTEMI, avoidance of DAPT pre-treatment in patients at HBR reduce bleeding risk[205,206]; (ii) radial is preferred over femoral access and is associated with significantly reduced bleeding complications[206,207]; (iii) in patients not pre-treated with oral APT, during urgent/emergency PCI, intravenous antiplatelet agents may be used, and due to better safety profile, the intravenous $P2Y_{12}$-inhibitor cangrelor may be preferred over glycoprotein IIb/IIIa inhibitors[208]; (iv) newer generation drug eluting stents have displaced bare metal stents also in HBR patients as their quick re-endothelialization allows a shorter duration of DAPT after PCI[209]; and finally, (v) administration of proton-pump inhibitors and avoidance of NSAIDs is recommended to minimize bleeding risk.[210]

Patients with cancer

Patients with cancer, particularly gastric or urothelial tumours, have an increased risk of bleeding on OAC compared to patients without cancer,[211–213] and proton-pump inhibitors should be routinely considered to mitigate this risk.

In patients with AF, registry data[214] and Subgroup analyses of pivotal phase 3 trials[213,215,216] indicate similar or lower bleeding with NOAC compared to VKA in patients with cancer, with the exception of patients with gastrointestinal cancers or active gastrointestinal mucosal abnormalities.[217]

In cancer patients in whom OAC is indicated for the treatment or prevention of VTE, NOACs have been shown to significantly reduce bleeding compared with VKA.[218] In comparison to LMWH, apixaban and edoxaban appear to have similar safety profile to LMWH,[27,219] with excess bleeding mainly observed in patients with gastrointestinal cancer.[219,220] A meta-analysis of 23 RCTs including 6980 patients, showed no difference in major bleeding between LMWH and VKA treatment (4.7% vs. 4.8%, RR 0.99, 95% CI 0.67–1.45), whereas NOACs significantly lowered bleeding risk compared to VKA (2.5% vs. 4.2%, RR 0.58, 95% CI 0.35–0.99). Pooled data from the only two RCTs comparing NOACs against LMWH showed significantly higher incidence of major bleeding with NOACs (6.5% vs. 3.7%, RR 1.75, 95% CI 1.10–2.77).[221]

Bridging therapy

Patients treated with oral anticoagulant undergoing interventional or surgical procedures

There may be specific clinical scenarios, when temporary interruption of OAC may be necessary, such as when an interventional procedure or surgery is planned.

While bridging with either UFH or LMWH, may theoretically reduce the peri-procedural thrombotic risk, this substantially increases peri-procedural bleeding.[181]

In patients undergoing CIED implantation, randomized data in VKA-treated patients indicate lower thromboembolic and bleeding rates[180] and reduced length of stay[180,222] if the VKA is uninterrupted, without bridging. Heparin-bridging results in a 4.5-fold increase in postoperative haematoma compared to a continued warfarin strategy.[180] A clinically meaningful pocket haematoma after the implantation of a CIED is an independent risk factor (7- to 8-fold risk) for subsequent device infection.[223,224] Irrespective of the perioperative anticoagulation strategy used, the incidence of thromboembolic events is 0–1% (*Table 12*).

In AF patients, the randomized, double-blind, placebo-controlled BRIDGE trial demonstrated no ischaemic benefit but significantly increased bleeding in patients randomized to bridging.[181] A meta-analysis of 18 studies (6 randomized and 12 observational studies) including 23 364 patients,[225] bridging significantly increased overall bleeding events (RR: 2.83, 95% CI: 2.00–4.01) including major bleeding (RR: 3.00, 95% CI: 1.78–5.06), without significant reduction in ischaemic risk (RR: 1.26, 95% CI: 0.61–2.58).

Post-operatively, bridging with parenteral agents is not required with NOACs, but could be considered in selected high thromboembolic risk patients when resuming VKA. Thus, a routine bridging strategy is not recommended in the current 2020 ESC AF Guideline[11] and a recent ESC/EHRA document on the use of NOACs[226] which emphasize that this approach should be avoided.

Patients treated with oral anticoagulant with prior stent requiring surgery

In patients with prior coronary stenting, antithrombotic therapy is required to reduce the risk of stent thrombosis. The thrombotic risk falls with time from PCI, being relatively high in the first 3–6 months, intermediate at 6–12 months, and low beyond 12 months.[227] Whilst OAC may be discontinued for elective or urgent surgery, there is concern that patients with prior stenting on single or no APT, may be left with insufficient antithrombotic protection to prevent stent thrombosis. In such patients, a bridging APT strategy may be required for those at high ischaemic risk although there are no large clinical trial data in AF patients *per se*.

The decision on APT bridging requires a careful evaluation of bleeding risk and perioperative ischaemic (stent thrombosis) risk. The risk of perioperative haemorrhage should also be considered, being very high with hepatic resection, and high with many other surgical procedures including splenectomy, gastrectomy, thyroid surgery, nephrectomy and prostatectomy, and among cardiac surgical procedures, relatively high when re-intervention and aortic surgery is performed.[227] Additionally, the site of potential bleeding is critical, for example even relatively minor bleeding in patients undergoing neurosurgery or ophthalmic surgery can be catastrophic. Bridging of APT indicates a strategy of usually starting (or continuing with) aspirin, and consideration given to temporary transition with an intravenous antiplatelet agent in patients who would otherwise require DAPT (if they were not on OAC).

There are specific clinical (including ACS as indication for PCI, prior stent thrombosis, diabetes, and CKD) and angiographic (including long stented segment length, bifurcation stenting, small stent diameter, last remaining conduit) risk factors which increase ischaemic risk.[227,228]

For patients with high ischaemic and HBR, consideration should be given to postponing elective surgery beyond 6 months post-PCI, when SAPT with aspirin may be considered or if this is not possible, every effort should be made to employ bridging strategies that mitigate risk, with use DAPT with clopidogrel rather than more potent $P2Y_{12}$ inhibitors, or preferably using intravenous cangrelor, which has a short half-life in case of major bleeding.[179,227]

Consensus statements

- Bleeding risk reflects the interaction of non-modifiable and modifiable bleeding risks. Simply focusing on modifiable bleeding risk factors alone as a measure of predicting bleeding risk is an inferior strategy to the use of formal bleeding risk scores.
- Bleeding risk is not a static 'one off' assessment based on baseline factors but is dynamic, being influenced by ageing, incident comorbidities, surgical/interventional procedures, and use of modifiers (such as proton pump inhibitors) or drug therapies.
- Simple bleeding risk scores based on clinical factors generally have modest predictive value and calibration for bleeding events. More complex clinical bleeding risk scores can improve prediction, at least statistically, and the addition of biomarkers improves the performance of clinical factor-based bleeding risk scores. Ultimately, the use of bleeding risk scores needs to balance statistical prediction against simplicity and practicality (incorporating both modifiable and non-modifiable bleeding risks), for use in everyday busy clinical scenarios.
- In patients with AF, a formal structured risk-score-based bleeding risk assessment is recommended to help identify non-modifiable and address modifiable bleeding risk factors, and to identify patients potentially at high risk of bleeding who should be scheduled for more frequent clinical review. For a formal risk-score-

based assessment of bleeding risk, the HAS-BLED score should be used.

- Treatment of patients with AF according to an integrated care or holistic approach, based on the ABC (Atrial fibrillation Better Care) pathway, is associated with a lower risk of major bleeding and this should be applied. Appropriate use of the HAS-BLED score as part of the ABC pathway is associated with less major bleeding and an increase in OAC uptake.
- In VTE patients, the choice of the bleeding risk score for assessing the individual's bleeding risk is at the discretion of the clinician. The 2020 NICE VTE guideline recommends use of the HAS-BLED score.

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