Assessment and Mitigation of Bleeding Risk in Atrial Fibrillation and Venous Thromboembolism: Executive Summary of a European and Asia-Pacific Expert Consensus Paper

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Abstract

While there is a clear clinical benefit of oral anticoagulation 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 for initiating and continuing anticoagulation is often based on a careful assessment of both 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

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Keywords
► bleeding
► oral anticoagulation
► atrial fibrillation
► venous thromboembolism
► risk assessment
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, being influenced by aging, incident comorbidities, and drug therapies. In this executive summary of a European and Asia-Pacific Expert Consensus Paper, we comprehensively review the published evidence and propose a consensus on bleeding risk assessments in patients with AF and VTE, with a 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, and 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.

**Introduction and Scope**

While 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 may still occur and be devastating.\(^1\)

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 aging, incident comorbidities, and drug therapies. Another factor is ethnicity, where East Asians appear more sensitive to antithrombotic therapy-related bleeding.\(^2\)

In this Executive Summary of a European and Asia-Pacific Expert Consensus Paper, we consolidate the contents of the recently published Position Paper on the Assessment and Mitigation of Bleeding risk in Atrial fibrillation and Venous Thromboembolism from the ESC (European Society of Cardiology) Working Group on Thrombosis, in collaboration with the European Heart Rhythm Association (EHRA), Acute Cardiovascular Care Association, and Asia-Pacific Heart Rhythm Society.\(^3\)

**Systematic Review**

**Epidemiology of Bleeding with OAC in AF**

Major bleeding occurs in 1.4 to 3.4% of patients with AF treated with vitamin K antagonist (VKA), per annum.\(^4\) Intracranial hemorrhage (ICH) is rare, occurring in 0.1 to 2.5% patients per year,\(^5\) with more recent studies reporting a lower rate of 0.7 to 0.8% (Fig. 2).\(^6\) Non-vitamin K antagonist oral anticoagulants (NOACs) lower the incidence of major bleeding (−14%) and ICH (−52%) compared with warfarin.\(^6,7\) Several variables impact on the risk of anticoagulation-related bleeding in patients with AF, including time in the therapeutic range (TTR) and international normalized ratio (INR) variability which also impact the risk of ICH\(^8\) (Fig. 2).

**Epidemiology of Bleeding with OAC in VTE**

Anticoagulation is required for the treatment and prevention of VTE, whether deep vein thrombosis or pulmonary embolism, for a minimum of 3 months, with longer term treatment for patients with an unprovoked event or due to a persistent risk factor.\(^9,10\)

VKA-related major bleeding is approximately 2% during the initial 3 months of anticoagulation, with a fatal bleeding rate of 0.37 to 0.55%.\(^11,12\) Beyond the first 3 months, major bleeding occurs in 2.74% of patients on VKA.\(^11,13\)

NOACs are as effective as low-molecular-weight heparin (LMWH)/VKA but associated with less bleeding. 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% confidence interval [CI]: 0.51–0.77),\(^14\) as well as fatal bleeding (RR: 0.36%, 95% CI: 0.15–0.87), compared with VKA. During the extended phase, NOAC use was associated with a nonsignificant increase in major bleeding compared with placebo. Major or clinically relevant nonmajor bleeding events were similar with reduced-dose NOACs (apixaban\(^15\) and rivaroxaban\(^16\)) as with aspirin or placebo (RR: 1.19, 95% CI: 0.81–1.77), whereas there was no significant difference compared with full-dose NOAC, with a trend toward less bleeding with the reduced dose (RR: 0.74; 95% CI: 0.52–1.05).\(^17\)

**Definitions of Bleeding**

Several definitions are used to define bleeding events in patients on OAC (See Table 1), including qualitative or quantitative (such as drop in hemoglobin) definitions, or frequently both. The most widely used are the Thrombolysis in Myocardial Infarction (TIMI),\(^18\) Global Use of Strategies To Open occluded arteries (GUSTO),\(^19\) International Society of Thrombosis and Haemostasis (ISTH),\(^20,21\) and the Bleeding Academic Research Consortium (BARC)\(^22\) classifications, and all have been shown to predict mortality.\(^23,24\) Heterogeneity in bleeding definitions may in part account for the variability in the reported rate of hemorrhagic complications with OAC.\(^5\)
Clinical Bleeding Risk Factors with OAC for AF or VTE
Risk factors associated with bleeding on OAC are similar in VTE and AF, including age (Table 2), hypertension (Table 3), renal impairment (Table 4), prior stroke (Table 6), prior bleeding (Table 7), anemia (Table 8), and malignancy (Table 9).

Dynamic and Modifiable Nature of Bleeding Risk
Some bleeding risk factors are nonmodifiable, such as age, sex, prior bleeding, or stroke, whereas other risks may be correctable, such as uncontrolled blood pressure, transient renal or liver impairment, labile INR, excessive alcohol intake, or concomitant use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) in an anticoagulated patient.

Bleeding risk assessment cannot be a "one-off" and requires regular re-evaluation, due to the dynamic nature of some risk factors, including aging, comorbidities, and concomitant medications.

Advancing age increases the risk of bleeding on OAC (Table 2). The risk of ICH is higher with VKAs than with NOACs, and the benefit of NOAC over VKA in reducing ICH is consistent, independent of age.

Most studies show systolic hypertension to be a risk factor for bleeding with OAC, especially ICH, although others did not. Subanalysis of the ENGAGE-AF trial showed that major bleeding was more frequent in patients with a systolic blood pressure >140 mmHg compared with those with lower levels. Importantly, although the efficacy and safety of edoxaban were consistent across the full range of systolic blood pressures, the superior safety profile of edoxaban compared with VKA was most pronounced among patients with elevated diastolic blood pressure. In a nationwide Korean population registry, the risk of ICH was lowest with blood pressure <130/80 mmHg. It would therefore appear prudent to maintain good blood pressure control in patients on OAC.

Acquisition of new risk factors for bleeding over time is well recognized in patients on OAC. In an analysis of 19,566 anticoagulated AF patients, 76.6% of patients who experienced major bleeding had acquired new bleeding risk factors, compared with only 59.0% of those patients without major bleeding (p < 0.001). A Taiwanese registry of 24,990 AF patients showed that by 1 year, around 21% had acquired at least one new bleeding risk factor, including hypertension (5.84%), stroke (5.33%), bleeding (5.06%), concomitant use of antiplatelet agents or NSAIDs (4.34%), and renal (3.08%) or liver (2.22%) impairment.

Data from ORBIT AF shows that over a 2-year follow-up, about a quarter of patients had >20% decline in estimated glomerular filtration rate (eGFR) and...
<table>
<thead>
<tr>
<th>TIMI</th>
<th>GUSTO</th>
<th>ISTH</th>
<th>BARC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>Any intracranial bleeding (excluding microhemorrhages &lt;10 mm evident only on gradient-echo MRI) Clinically overt signs of hemorrhage associated with a drop in hemoglobin of $\geq 5$ g/dL Fatal bleeding (bleeding that directly results in death within 7 days)</td>
<td>Severe or life-threatening Intracerebral hemorrhage Resulting in substantial hemodynamic compromise requiring treatment</td>
<td>Major Fatal bleeding Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome. Bleeding causing a fall in hemoglobin level of $\geq 2$ g/dL or leading to transfusion of $\geq 2$ units of whole blood or red cells</td>
</tr>
<tr>
<td>Minor</td>
<td>Clinically overt (including imaging), resulting in hemoglobin drop of 3 to $&lt;$ 5 g/dL</td>
<td>Moderate Requiring blood transfusion but not resulting in hemodynamic compromise</td>
<td>Minor All nonmajor bleeds</td>
</tr>
<tr>
<td>Requiring medical attention</td>
<td>Any overt sign of hemorrhage that meets one of the following criteria and does not meet criteria for a major or minor bleeding event, as defined above Requiring intervention (medical practitioner-guided medical or surgical treatment to stop or treat bleeding, including temporarily or permanently discontinuing or changing the dose of a medication or study drug) Leading to or prolonging hospitalization Prompting evaluation (leading to an unscheduled visit to a health care professional and diagnostic testing, either laboratory or imaging)</td>
<td>Mild Bleeding that does not meet above criteria</td>
<td>Clinically relevant minor 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: Hospital admission for bleeding, or A physician-guided medical or surgical treatment for bleeding, or Change in antithrombotic therapy (including interruption or discontinuation of study drug)</td>
</tr>
<tr>
<td>Minimal</td>
<td>Any overt bleeding event that does not meet the criteria above</td>
<td></td>
<td>Type 0 No evidence of bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Type 1 Bleeding that is not actionable and does not cause the patient to seek an unscheduled performance of studies, hospitalization, or treatment by a health care professional; it may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a health care professional</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Type 2 Any overt, actionable sign of hemorrhage (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 nonsurgical, medical intervention by a health care professional; leading to hospitalization or increased level of care; or prompting evaluation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Type 3 Clinical, laboratory, and/or imaging evidence of bleeding with specific health care provider responses, as listed below: Type 3a Overt bleeding plus a hemoglobin drop of 3 to 5 g/dL (provided the...</td>
</tr>
</tbody>
</table>
3.7% of patients receiving NOACs had eGFR decline sufficient to warrant dose reductions. Real-world data from the PREFER in AF registry suggest that each single point decrease on a modifiable bleeding risk scale was associated with a 30% reduction in major bleeding.

### Laboratory-, Biomarker-, and Imaging-Based Risk Factors for Bleeding AF or VTE

Biomarkers can improve the accuracy of bleeding risk stratification based on clinical factors AF40–42 but their practical applicability remains limited.

### Table 1 (Continued)

<table>
<thead>
<tr>
<th>TIMIa</th>
<th>GUSTOb</th>
<th>ISTHc,d</th>
<th>BARCe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>hemoglobin drop is related to bleed; any transfusion with overt bleeding Type 3b Overt bleeding plus a hemoglobin drop of 5 g/dl (provided the hemoglobin drop is related to bleed); cardiac tamponade; bleeding requiring surgical intervention for control (excluding dental, nasal, skin, and hemorrhoid); bleeding requiring intravenous vasoactive agents Type 3c Intracranial hemorrhage (does not include microbleeds or hemorrhagic 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 hours 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-hour period Chest tube output 2 L within a 24-hour 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</td>
</tr>
</tbody>
</table>

Abbreviation: MRI, magnetic resonance imaging.


The ABC (Atrial fibrillation Better Care) bleeding risk score, which includes blood biomarkers of bleeding including growth differentiation factor-15 (GDF-15), troponin T, and hemoglobin, has been shown to statistically better predict bleeding than clinical factor-based bleeding risk scores in patients with AF receiving OAC or taking both OAC and antiplatelet therapy (APT), and in different geographic regions,43–46 but this was not confirmed in another study.47 The consecutive addition of different blood-based biomarkers only slightly enhanced the predictive ability of the HAS-BLED score for major bleeding.48 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.49,50 In patients with VTE on OAC, information on biomarkers and bleeding risk is sparse,51 and scores including biomarkers such as hemoglobin and/or creatinine (or creatinine clearance) have modest predictive performance.52,53

There are also 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 utmost importance. In many studies, biomarkers were assessed at baseline, and bleeding events determined many years later; notwithstanding that aging and incident comorbidities, modifiable bleeding risk factors and changes in drug therapies can dynamically influence bleeding. Furthermore, some biomarkers exhibit diurnal variation and inter-/intra-assay variability, may be expensive,54 and some (e.g., GDF-15) are not routinely available. Although improvement of risk prediction tools, for example, with inclusion of laboratory-based variables, may be desirable, this should not lead to loss of simplicity and practicality, deterring regular or easy bleeding risk estimation.55

In patients with AF on OAC, the presence of cerebral microbleed(s) on cerebral magnetic resonance imaging was independently associated with ICH,56 and addition of cerebral microbleeds to the HAS-BLED score significantly improved the prediction of ICH over the HAS-BLED score alone.56

### Current Published Bleeding Risk Schema in AF and VTE

Bleeding risk scores are important (1) to identify modifiable risk factors; (2) to identify people who require more regular monitoring; and (3) to estimate an individual’s bleeding risk on antithrombotic/OAC therapy.

Several bleeding risk scores (∼Table 10) are available for patients with AF and VTE.25,64–72 These incorporate numerous risk factors, including demographic and clinical information plus biomarkers, ranging from 343 to 1725 factors, with age included in most scores.49,53,51,72–83 The scores vary in the definitions of common risk factors and in their complexity, which can hinder clinical utility. Most scores stratify patients into low, intermediate, and high risk, demonstrating major bleeding rates ranging from <1743 to 30%60 and 0.170 to 12.2% per 100-patient years71 in low- and high-risk groups for AF and VTE bleeding risk scores, respectively (∼Table 10). Bleeding risk assessment only using

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of OAC</th>
<th>Subjects</th>
<th>Age groups</th>
<th>Subjects</th>
<th>Age groups</th>
<th>Subjects</th>
<th>Age groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPAF Investigators, 1996</td>
<td>VKA</td>
<td>433</td>
<td>Age &lt;75 vs. &gt;75 years</td>
<td>Papen et al, 2001</td>
<td>VKA</td>
<td>1,190</td>
<td>Age &gt;75 vs. &lt;75 years</td>
</tr>
<tr>
<td>Pisters et al, 2010</td>
<td>VKA</td>
<td>5,333</td>
<td>Age &gt;65 vs. ≤65 years</td>
<td>O'Brien et al, 2014</td>
<td>VKA/NOAC</td>
<td>14,264</td>
<td>Per decade increase in age</td>
</tr>
<tr>
<td>Hankey et al, 2014</td>
<td>VKA/NOAC</td>
<td>7,411</td>
<td>Age &gt;75 vs. ≤75 years</td>
<td>Chao et al, 2020</td>
<td>VKA</td>
<td>64,169</td>
<td>Age &gt;90, 75–89, and 65–74 years</td>
</tr>
</tbody>
</table>

**Table 2** Summary of "age" as a risk factor for bleeding in AF patients receiving OACs.
### Table 3 Summary of “hypertension” as a risk factor for bleeding in AF patients receiving OACs

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects (n)</th>
<th>Type of OACs</th>
<th>Definition of hypertension</th>
<th>Main findings</th>
<th>RR/HR (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPAF Investigators, 1996</td>
<td>555</td>
<td>VKA</td>
<td>Systolic BP &gt;160 mmHg or</td>
<td>Increase risk of ICH in patients with poor controlled hypertension</td>
<td>RR: 4.4 for systolic</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>diastolic BP &gt;90 mmHg</td>
<td></td>
<td>BP &gt;160 mmHg: RR:</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.6 for diastolic</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BP &gt;90 mmHg</td>
<td></td>
</tr>
<tr>
<td>Fang et al, 2011</td>
<td>9,186</td>
<td>VKA</td>
<td>Diagnosed hypertension as</td>
<td>Prevalence of hypertension in patients with or without major bleeding:</td>
<td>HR: 1.5 (1.2–1.9)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>per guideline</td>
<td>64.7 vs. 61.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hankey et al, 2014</td>
<td>14,264</td>
<td>VKA/rivaroxaban</td>
<td>Each 10 mmHg increase of</td>
<td>Increased diastolic BP is independently associated with ICH</td>
<td>HR: 1.17 (1.01–1.36)</td>
<td>0.042</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>diastolic BP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Park et al, 2019</td>
<td>19,679</td>
<td>VKA/edoxaban</td>
<td>≥150 mmHg</td>
<td>Major bleeding rate (per year)</td>
<td>≥150 mmHg: HR =</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>140 to &lt;150 mmHg</td>
<td>Edoxaban: 4.37 vs. 2.54 vs 1.88%</td>
<td>1.64 (1.26–2.12)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>130 to &lt;140 mmHg</td>
<td>VKA: 5.65 vs. 4.16 vs. 2.37%</td>
<td>140 to &lt;150 mmHg:</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR = 1.36 (1.13–1.62)</td>
<td>≤160 mmHg: HR =</td>
<td></td>
</tr>
<tr>
<td>Böhm et al, 2020</td>
<td>18,107</td>
<td>VKA/dabigatran</td>
<td>≥160 mmHg</td>
<td>Any bleeding rate (per year):</td>
<td>≥160 mmHg: HR =</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>140 to &lt;160 mmHg</td>
<td>24.99 vs. 17.30 vs. 14.71 vs. 14.61%</td>
<td>2.01 (1.73–2.32)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>130 to &lt;140 mmHg</td>
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<td>140 to &lt;160 mmHg:</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Systolic BP 120 to ≤130 mmHg</td>
<td></td>
<td>≤160 mmHg: HR =</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(reference)</td>
<td></td>
<td>1.23 (1.14–1.33)</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** AF, atrial fibrillation; BP, blood pressure; HR, hazard ratio; ICH, intracranial hemorrhage; NR, not reported; OACs, oral anticoagulants; RR, relative risk; SPAF, Stroke Prevention in Atrial Fibrillation; VKA, vitamin K antagonist.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects (n)</th>
<th>Type of OACs</th>
<th>Definition</th>
<th>Main findings</th>
<th>OR/HR (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pisters et al, 2010</td>
<td>5,333</td>
<td>VKA</td>
<td>Presence of chronic dialysis, renal transplantation, or serum creatinine &gt;200 mmol/L</td>
<td>The rate of major hemorrhage was 1.3% in patients without kidney failure versus 5.4% in those with kidney failure.</td>
<td>OR: 2.86 (1.33–6.18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fang et al, 2011</td>
<td>9,186</td>
<td>VKA</td>
<td>eGFR &lt; 30 mL/min</td>
<td>Prevalence of renal impairment in patients with or without major bleeding: 5.9 vs. 2.7%</td>
<td>HR: 4.3 (3.2–5.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fox et al, 2011</td>
<td>14,264</td>
<td>VKA/rivaroxaban</td>
<td>eGFR ≥ 50 mL/min</td>
<td>Major bleeding rate (per year) Rivaroxaban: 3.39 vs. 4.49% VKA: 3.17 vs. 4.70%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Hohnloser et al, 2012</td>
<td>18,122</td>
<td>VKA/apixaban</td>
<td>Divided into 3 groups:</td>
<td>Major bleeding rate (per year) Apixaban: 1.46 vs. 2.45 vs. 3.21% VKA: 1.84 vs. 3.21 vs. 6.44%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>O’Brien et al, 2015</td>
<td>7,411</td>
<td>VKA/dabigatran</td>
<td>eGFR &lt; 60 mL/min/1.73 m²</td>
<td>Prevalence of renal impairment in patients with or without major bleeding: 48.4 vs. 34.0%</td>
<td>HR: 1.44 (1.21–1.72)</td>
<td>NR</td>
</tr>
</tbody>
</table>

**Abbreviations:** AF, atrial fibrillation; HR, hazard ratio; eGFR, estimated glomerular filtration rate; NR, not reported; OACs, oral anticoagulants; OR, odds ratio; VKA, vitamin K antagonist.
modifiable bleeding risk factors is inferior to formal bleeding risk score calculation.73,79,80

Among the bleeding risk scores for AF,43,50,57–62 the HAS-BLED score59 has been most widely validated across the spectrum of the AF patient pathway, from OAC/antithrombotic-naïve patients to those established on OAC.77,78,84 and is predictive of ICH.81 In a contemporary cohort of AF patients treated with NOACs, the ORBIT was inferior to the HAS-BLED score.82

The HAS-BLED score has also been validated in non-AF populations, including those with VTE, or those undergoing bridging therapy.74–76,85 A systematic review83 evaluating the HAS-BLED,59 HEMORR2HAGES,37 ATRIA,50 and ABC-Bleeding43 scores concluded that HAS-BLED was the best for predicting major bleeding, albeit with modest evidence base.83 A prospective App-based intervention in a cluster-randomized trial, which included the HAS-BLED score, reduced major bleeding events, addressed modifiable risk factors, and increased OAC uptake, compared with usual care.86

Eight clinical risk scores for predicting major bleeding in patients with VTE (Table 10) have been developed,25,64–71 some focusing on the acute phase,64,67,70 long-term treatment,68,69 specific subgroups of VTE, for example, cancer-associated thromboembolism,87,88 and the elderly,71 with three,65,66,68 derived from cohorts treated with NOACs. Several prediction rules attempting to quantify the bleeding risk of an individual by adding weighted68–70 or unweighted25,59,61,75 risk factors have been derived from and/or tested in VTE patient cohorts (Table 10).

Bleeding risk scores for VTE have been less extensively validated than those for AF.72 Critical appraisal72 of seven bleeding risk scores developed for VTE (ACCP,25 EINSTEIN,65 Hokusai,58 Kuijer,69 RIETE,70 Seiler,71 VTE-BLEED68) and seven validated in VTE cohorts but derived in AF or mixed-indication cohorts (ATRIA,50 HAS-BLED59 HEMORR2HAGES,57 mOBRi,61 OBri,62 ORBIT,58 Shireman60) concluded that existing bleeding risk scores are not useful in assisting treatment decisions to cease or extend OAC after the initial 3-month period, with modest ability to predict bleeding (c-statistic: 0.68 [0.65–0.75]) and even lower in external validation studies (0.59 [0.52–0.71]).72 Bleeding risk scores derived in non-VTE populations have poor predictive ability (0.57 [0.52–0.71]); the only exception was the recalibrated HAS-BLED score (c-statistic: 0.69).72,75 External validation of the VTE-BLEED score,68 derived from a population treated with dabigatran or warfarin, demonstrated predictive ability across patient groups89–91 and for ICH and/or fatal bleeding.92 External validation of the EINSTEIN or Hokusai scores has not been undertaken.

In patients with VTE on NOAC, the prognostic precision of six bleeding risk scores (HAS-BLED,59 ORBIT,58 ATRIA-Bleed,69 Kuijer,69 RIETE,70 VTE-BLEED68) was found to be modest and similar, with c-statistics for VTE-BLEED of 0.674 (95% CI: 0.593–0.755), ORBIT of 0.645 (95% CI: 0.523–0.767), and RIETE of 0.604 (95% CI: 0.510–0.697).52 Another study of patients with VTE >65 years receiving VKA53 evaluating 10 clinical bleeding risk scores (VTE-BLEED58, RIETE70 ACCP,25 Seiler,71 Kuijer,69 Kearon, OBri,61,62 ATRIA,50 HAS-BLED,59 HEMORR2HAGES57) showed c-statistics ranging from 0.47 (OBri61,62) to 0.70 (Seiler71) for major bleeding and 0.52 (OBri61,62) to 0.67 (HEMORR2HAGES57) for clinically relevant bleeding. A recent review of bleeding risk assessment in patients with VTE93 concluded that the HAS-BLED or RIETE scores are beneficial in identifying patients at high bleeding risk (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 ability (c-indexes approximately 0.6). More complicated clinical bleeding risk scores modestly improve prediction (perhaps to 0.65) and the addition of biomarkers will always improve on clinical factor-based scores (with c-indexes around 0.7). Ultimately, bleeding risk scores need to balance statistical prediction against simplicity and practicality (incorporating both modifiable and nonmodifiable bleeding risks), for use in everyday busy clinical scenarios.

A limitation of current bleeding prediction tools is an unclear immediate actionability for treatment decisions; although in light of the importance of bleeding on prognosis,
Table 6  Summary of “stroke history” as a risk factor for bleeding in AF patients receiving OACs

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects (n)</th>
<th>Type of OACs</th>
<th>Definition</th>
<th>Main findings</th>
<th>RR/HR (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pengo et al, 2001</td>
<td>433</td>
<td>VKA</td>
<td>History of thromboembolism</td>
<td>A higher frequency of major primary bleeding in patients who had suffered a previous thromboembolic event</td>
<td>NR</td>
<td>0.03</td>
</tr>
<tr>
<td>Fang et al, 2004</td>
<td>1,190</td>
<td>VKA</td>
<td>History of cerebrovascular disease</td>
<td>Prevalence of cerebrovascular disease in patients with or without ICH: 37 vs. 20%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Fang et al, 2011</td>
<td>9,186</td>
<td>VKA</td>
<td>Prior stroke</td>
<td>Prevalence of prior stroke in patients with or without major bleeding: 17.4 vs. 12.4%</td>
<td>HR: 1.4 (1.1–1.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>Hankey et al, 2014</td>
<td>14,264</td>
<td>VKA/rivaroxaban</td>
<td>Previous stroke or TIA</td>
<td>Previous stroke or TIA is an independent factor associated with ICH</td>
<td>HR: 1.42 (1.02–1.96)</td>
<td>0.036</td>
</tr>
<tr>
<td>O’Brien et al, 2015</td>
<td>7,411</td>
<td>VKA/dabigatran</td>
<td>Prior stroke</td>
<td>Prevalence of prior stroke in patients with or without major bleeding: 13.1 vs. 9.2%</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Abbreviations: AF, atrial fibrillation; HR, hazard ratio; ICH, intracranial hemorrhage; NR, not reported; OACs, oral anticoagulants; OR, odds ratio; RR, relative risk; TIA, transient ischemic attack; VKA, vitamin K antagonist.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Type of OACs</th>
<th>Definition</th>
<th>Main findings</th>
<th>OR/HR (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pisters et al, 2010</td>
<td>5,333</td>
<td>VKA</td>
<td>Prior major bleeding (ICH, hospitalization, hemoglobin decrease &gt;2 g/L, and/or blood transfusion)</td>
<td>The rate of major hemorrhage was 1.3% in patients without prior major bleeding versus 14.8% in those with prior major bleeding</td>
<td>OR: 7.51 (3.00–18.78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fang et al, 2011</td>
<td>9,186</td>
<td>VKA</td>
<td>Prior GI hemorrhage</td>
<td>Prevalence of prior GI bleeding in patients with or without major bleeding: 12.1 vs. 6.8%</td>
<td>HR: 2.1 (1.5–2.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>O’Brien et al, 2015</td>
<td>7,411</td>
<td>VKA/dabigatran</td>
<td>Bleeding history</td>
<td>Bleeding history had good ability to identify those who bled versus not</td>
<td>HR: 1.73 (1.34–2.23)</td>
<td>NR</td>
</tr>
<tr>
<td>Šinigoj et al, 2020</td>
<td>2,260</td>
<td>Dabigatran, rivaroxaban, apixaban</td>
<td>Bleeding history</td>
<td>History of bleeding was a significant predictor of major bleeding</td>
<td>HR: 3.32 (1.87–5.90)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Abbreviations: AF, atrial fibrillation; GI, gastrointestinal; HR, hazard ratio; ICH, intracranial hemorrhage; NR, not reported; OACs, oral anticoagulants; OR, odds ratio; VKA, vitamin K antagonist.
### Table 8  Summary of “anemia” as a risk factor for bleeding in AF patients receiving OACs

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects (n)</th>
<th>Type of OACs</th>
<th>Definition</th>
<th>Main findings</th>
<th>HR (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fang et al, 2011</td>
<td>9,186</td>
<td>VKA</td>
<td>Hb &lt;13 g/dL in men and &lt;12 g/dL in women</td>
<td>The rate of major hemorrhage was 12.1% in patients without anemia versus 18.8% in those with anemia</td>
<td>HR: 4.2 (3.4–5.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>O’Brien et al, 2015</td>
<td>7,411</td>
<td>VKA/Dabigatran</td>
<td>Reduced Hb/hematocrit/history of anemia</td>
<td>Reduced hemoglobin/hematocrit/history of anemia had good ability to identify those who bled versus not</td>
<td>HR: 2.07 (1.74–2.47)</td>
<td>NR</td>
</tr>
</tbody>
</table>
| Bonde et al, 2019 | 18,734       | VKA/Dabigatran/Rivaroxaban | • No anemia (Hb >7.45 mmol/L for women and >8.07 mmol/L for men)  
• Mild anemia (Hb 6.83–7.45 mmol/L for women and 6.83–8.07 mmol/L for men)  
• Moderate/severe anemia (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 anemia | HR: 1.78 (1.30–2.48)         | NR      |
| Krittayaphong et al, 2021 | 1,562     | VKA/NOACs    | Hb <13 g/dL for male and <12 g/dL for female | Anemia was found to be an independent risk factor for major bleeding | HR: 2.96 (1.81–4.84)         | NR      |

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

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects (n)</th>
<th>Type of OACs</th>
<th>Definition</th>
<th>Main findings</th>
<th>HR (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fang et al, 2011</td>
<td>9,186</td>
<td>VKA</td>
<td>Any diagnosis of cancer</td>
<td>Prevalence of diagnosed cancer in patients with or without major bleeding: 18.0 vs. 15.1%</td>
<td>HR: 1.7 (1.3–2.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>O’Brien et al, 2015</td>
<td>7,411</td>
<td>VKA/dabigatran</td>
<td>History of cancer</td>
<td>The rate of major bleeding was 23.3% in patients without cancer versus 30.8% in those with cancer</td>
<td>NR</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Melloni et al, 2017</td>
<td>9,749</td>
<td>VKA/dabigatran</td>
<td>Any diagnosis of cancer</td>
<td>The rate of major bleeding was 3.45 per 100 patient-years in patients without cancer versus 5.13 per 100 patient-years in those with cancer</td>
<td>HR: 1.21 (1.04–1.40)</td>
<td>0.02</td>
</tr>
<tr>
<td>Vedovati et al, 2018</td>
<td>2,288</td>
<td>Dabigatran, rivaroxaban, apixaban</td>
<td>Patients with active cancer, at the 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</td>
<td>The higher bleeding risk found in cancer compared with noncancer patients was mainly due to an excess of bleeding at GI and at genitourinary sites</td>
<td>HR: 2.58 (1.08–6.16)</td>
<td>0.033</td>
</tr>
</tbody>
</table>

**Abbreviations:** AF, atrial fibrillation; GI, gastrointestinal; HR, hazard ratio; NR, not reported; OACs, oral anticoagulants; VKA, vitamin K antagonist.
### Table 10: Bleeding risk scores for atrial fibrillation and venous thromboembolism—risk factors and scoring, risk categories, and bleeding events in the validation cohorts (adapted from Konstantinides et al. and Noubiap et al.)

<table>
<thead>
<tr>
<th>Risk score</th>
<th>Number of risk factors</th>
<th>Risk factors (score for each factor)</th>
<th>Risk categories (bleeding events in the validation cohort per 100 patient-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Low</td>
<td>Intermediate</td>
</tr>
<tr>
<td><strong>Atrial fibrillation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAS-BLED 9</td>
<td>↑SBP (1); severe renal/hepatic disease (1 each); stroke (1); bleeding (1); labile INR (1); age &gt;65 (1); APT/NSAIDs (1); alcohol excess (1)</td>
<td>0–1 (1.02–1.13)</td>
<td>2 (1.88)</td>
</tr>
<tr>
<td>ORBIT 5</td>
<td>Age ≥75 (1); ↓Hb/Hct/anemia (2); bleeding history (2); ↓renal function (1); APT (1)</td>
<td>0–2 (2.4&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>3 (4.7)</td>
</tr>
<tr>
<td>ABC 3</td>
<td>Age&lt;sup&gt;b&lt;/sup&gt;; biomarkers&lt;sup&gt;b&lt;/sup&gt; (GDF-15 or cystatin C/CKD-EPI, cTnT-hs, and Hb); previous bleed&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;1% (0.62)</td>
<td>1–2% (1.67)</td>
</tr>
<tr>
<td>ATRIA 5</td>
<td>Anemia (3); severe renal disease (3); age ≥75 (2); prior bleed (1); hypertension (1)</td>
<td>0–3 (0.83)</td>
<td>4 (2.41)</td>
</tr>
<tr>
<td>HEMORRH2AGES 12</td>
<td>Hepatic/renal disease (1); ethanol abuse (1); malignancy; age &gt;75 (1); ↓Plt (1); re-bleeding risk (2); ↓BP (1); anemia (1); genetic factors (1); ↑falls risk (1); stroke (1)</td>
<td>0–1 (1.9–2.5)</td>
<td>2–3 (5.3–8.4)</td>
</tr>
<tr>
<td>Shireman et al 8</td>
<td>Age ≥70 (&lt;0.49); female (0.31); previous bleed (0.58); recent bleed (0.62); alcohol/drug abuse (0.71); DM (0.27); anemia (0.86); APT (0.32)</td>
<td>≤1.07 (0.9&lt;sup&gt;b&lt;/sup&gt;)</td>
<td>&gt;1.07 to &lt;2.19 (2.0&lt;sup&gt;b&lt;/sup&gt;)</td>
</tr>
<tr>
<td>OBRI 4</td>
<td>Age ≥65 (1); previous stroke (1); previous MI/anemia/DM/creatinine (1)</td>
<td>0 (3&lt;sup&gt;c&lt;/sup&gt;)</td>
<td>1–2 (8&lt;sup&gt;c&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACCP 17</td>
<td>Age 66–75 (1), &gt;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); anemia (1); APT (1); TTR &lt;60% (1); comorbidity (1); recent surgery (1); frequent falls (1); alcohol abuse (1); NSAIDs (1)</td>
<td>No risk factors (0.8&lt;sup&gt;d&lt;/sup&gt;)</td>
<td>1 risk factor (1.6&lt;sup&gt;d&lt;/sup&gt;)</td>
</tr>
<tr>
<td>VTE-BLEED 6</td>
<td>Active cancer (2); male with uncontrolled arterial hypertension (1); anemia (1.5); previous bleeding (1.5); age ≥60 (1.5), renal dysfunction (1.5)</td>
<td>&lt;2 (0.2&lt;sup&gt;e&lt;/sup&gt;) (0.4&lt;sup&gt;e&lt;/sup&gt;)</td>
<td>–</td>
</tr>
<tr>
<td>EINSTEIN score 6</td>
<td>Rivaroxaban (vs. VKA); age; Hb; male sex&lt;sup&gt;a&lt;/sup&gt;; Black (vs. Caucasian); Asian (vs. Caucasian); history of CVD</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Hokusai score 5</td>
<td>Female sex (1); APT (1); ↓Hb (1); history of hypertension (1); SBP &gt;160 mmHg (1)</td>
<td>0 (1.4&lt;sup&gt;f&lt;/sup&gt;) (1.1&lt;sup&gt;f&lt;/sup&gt;)</td>
<td>1 (1.0&lt;sup&gt;f&lt;/sup&gt;) (1.45&lt;sup&gt;f&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Seiler et al 7</td>
<td>Previous major bleeding (1); active cancer (1); low physical activity (2); anemia (1); thrombocytopenia (1); APT/NSAIDs (1); poor INR control (1)</td>
<td>0–1 (1.4)</td>
<td>2–3 (5.0)</td>
</tr>
</tbody>
</table>

(Continued)
Table 10 (Continued)

<table>
<thead>
<tr>
<th>Risk score</th>
<th>Number of risk factors</th>
<th>Risk factors (score for each factor)</th>
<th>Risk categories (bleeding events in the validation cohort per 100 patient-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMPROVE</td>
<td>10</td>
<td>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)</td>
<td>Low: &lt; 7 (2.7%)</td>
</tr>
<tr>
<td>RISTIE</td>
<td>6</td>
<td>Recent major bleed (2); ↓ creatinine (1.5); anemia (1.5); cancer (1); pulmonary embolism (1); age ≥ 75 (1)</td>
<td>Intermediate: 0 (0.1%)</td>
</tr>
<tr>
<td>Kuijer et al</td>
<td>3</td>
<td>Age ≥ 60 (1.6); female (1.3); malignancy (2.2)</td>
<td>High: 0 (0.6%)</td>
</tr>
</tbody>
</table>

Abbreviations: ↓ reduced/decreased; ↓ elevated/increased; 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; 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, hemoglobin; HEMORR2HAGES, hepatic/renal disease, ethanol abuse, malignancy, age, reduced platelet function, rebleeding risk [2 points]; (uncontrolled) hypertension, anemia, genetic factors, falls risk, stroke; Hct, hematocrit; ICU, intensive care unit; IMPROVE, International Medical Prevention Registry on Venous Thromboembolism; INR, international normalized ratio; NR, not reported; NSAIDs, nonsteroidal 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.

Note: 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 times upper limit of normal (ULN); AST/ALT/AlP > 3 times ULN; previous stroke (ischemic or hemorrhagic); previous major bleed or bleeding predisposition (anemia 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 hematocrit (<40% in men or 36% in women), or history of anemia; any previous GI, intracranial or hemorrhagic stroke; eGFR < 60 mg/dL/1.73 m²; APT.

ABC: As defined in the 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.

HEMORR2HAGES: 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; hematocrit <30% during hospitalization; APT.

OBR: Age ≥ 65; previous stroke; previous GI bleed; recent MI or anemia (hematocrit < 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), history of liver failure, thrombocytopenia (<100,000), previous stroke/TIA, diabetes, anemia (Hb < 10 g/dL), APT, TTR < 60%, comorbidity, recent surgery (<3 months), frequent falls (>2 in last year), history of alcohol abuse, NSAIDs.

VTE-BLED: 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 anticancer treatment within 6 months before the VTE was diagnosed), male with uncontrolled arterial hypertension (SBP > 140 mmHg at baseline); anemia (Hb < 13 g/dL -1 in men; <12 g/dL -1 in women); history of major or nonmajor clinically relevant bleeding, rectal bleeding, frequent nose bleeding or hematuria, age ≥ 60, eGFR < 60 ml/min/1.73 m².

EINSTEIN: Only criterion 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; anemia; thrombocytopenia; APT or NSAIDs; poor INR control.

IMPROVE: Active GI ulcer; recent bleed (<3 months); Plt (<50 × 10⁹/L); age ≥ 75; hepatic failure (INR > 1.5) or renal failure (moderate GFR 30–59 ml/min/m² or severe <30 ml/min/m²); ICU/CCU admission; central venous catheter; rheumatic disease; current cancer; male.

RIETE: Recent major bleeding; creatinine >1.2 mg/dL; anemia (Hb < 13 g/dL -1 in men; <12 g/dL -1 in women); cancer; clinically overt pulmonary embolism.

Kuijer: Age ≥ 60; male; malignancy.

* Bleeding event in original derivation cohort.

† At 3 months; ↓ reduced/decreased; † elevated/increased.

$ Score for each variable in ABC score is based on a nomogram (see reference 3).

$ Annualised risk.

Dabigatran arm.

Edoxaban arm.

Warfarin arm.
bleeding risk assessment should inform decision making in clinical practice, especially for mitigation of modifiable bleeding risks and scheduling HBR patients for early review and follow-up as part of the holistic or integrated care approach to AF management.56

**Patient Values and Preferences**

Shared decision making54 is important to enable health care professionals to inform patients about treatment options, risks, benefits, and length of treatment, and to allow open dialogue to increase the uptake of OAC and long-term adherence.95–102 Patients with AF would generally accept a higher risk of bleeding for a corresponding reduction in stroke risk but there is considerable variability in the number of bleeds which would be accepted.103–108 In contrast, physicians generally worry more about the harm from bleeding.106,109,110 A reduction in major bleeding was second to stroke prevention as the most valued attribute of OAC.111,112 Similarly, patients with VTE96 appear to value reduction in VTE risk over potential bleeding risk.96,113–117 Among cancer patients, risk of bleeding was less important than ensuring that VTE prophylaxis did not interfere with cancer treatment and OAC efficacy.118,119

Studies assessing patient preferences toward VKAs versus NOACs105,120–125 indicate that when efficacy and safety are similar, patients with AF and VTE commonly favored simpler, more convenient treatment regimens, less frequent dosing, fixed-dose medication, without need for regular monitoring or bridging, or drug–food interactions.103,111,112,117,121,130–135

**Approach to Assessment and Bleeding Risk Mitigation**

**General AF Population**

After the evaluation of thromboembolic risk, bleeding risk should also be evaluated. Quality indicators 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.136

The appropriate use of a validated score is essential. All clinical guidelines for the management of AF recommend bleeding risk assessment prior to or on OAC, with the HAS-BLED score recommended by the ESC.97 American College of Chest Physicians,101 and Asia-Pacific Heart Rhythm Society,137 given its simplicity and evidence base.56 The ACC/AHA/HRS AF guidelines did not propose any specific bleeding risk scheme.138

The 2021 NICE guideline acknowledged low to very low quality evidence for its recommended use of the ORBIT score based on better calibration in NOAC users,139 but also emphasized attention to modifiable risk factors for bleeding, including uncontrolled hypertension, poor INR control, concurrent medication, excessive alcohol consumption, and addressing reversible causes of anemia. Of note, all these modifiable risk factors listed are already included in the HAS-BLED score.

The 2020 ESC AF guideline emphasizes that, irrespective of the score used, the main aim is to identify modifiable bleeding risk factors,97 including controlling blood pressure, cessation of nonessential APT or NSAIDs, improving TTR, and reduction/cessation of alcohol (→Fig. 3). Most modifiable bleeding risk factors in the ESC AF guideline are incorporated into the HAS-BLED score. Since an individual’s bleeding risk is composed of both nonmodifiable and modifiable risk factors, simply focusing on modifiable risk factors alone is inferior to formal assessment with a bleeding risk score.73,79,80

Generally, HBR should not be a reason to withhold OAC, except for situations in which the risk/benefit ratio excessively favors no antithrombotic treatment.97,138,140–142 Instead, efforts should be made to identify and address all modifiable bleeding risks and provide more frequent risk assessment.

**General VTE Population**

Notwithstanding the limitations of bleeding risk scores for VTE discussed earlier, bleeding risk assessment is recommended both upon initiation of anticoagulation and at follow-up, with more frequent re-assessment when bleeding risk is high.144

Most current VTE guidelines leave the choice of bleeding risk score to the clinician.10,144 Although the 2020 NICE VTE guideline145 recommends the HAS-BLED score and advises stopping anticoagulation if the score is ≥4 and cannot be modified. In case of persistent HBR, the patient’s personalized risk:benefit ratio for OAC should be assessed and if judged to favor 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.

**Surgery and Endoscopic and Endovascular Procedures**

- **Peri-​ablation of atrial arrhythmias**: Catheter ablation, especially left-sided ablation, is associated with a small but relevant approximately 0.5% risk of severe bleeding,146 including cardiac tamponade and 1 to 2% access-site bleeds,147,148 related to vascular access and peri-​interventional anticoagulation.148 Ablation also carries a risk of thrombotic events, with left-sided procedures carrying an approximately 1% risk of thrombosis and stroke.147,148 Continuation of OAC for AF ablation is safe with a trend toward fewer bleeding events and may also help in preventing periprocedural stroke (→Table 1).149 Most guidelines agree on three main points:97,101,141,142,150; (1) uninterrupted OAC is recommended for patients undergoing ablation; (2) after the procedure, OAC is essential for at least 8 weeks in all patients; and (3) long-term OAC beyond the first 8 weeks should be considered on the basis of risk profile (CHA2DS2-VASc). Regarding the type of OAC, both NOACs and VKAs are options, although meta-analyses report a trend favoring NOACs with respect to major bleeding.151

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

A study comparing patients undergoing CIED implantation with interrupted (for 2 days) versus uninterrupted NOAC was prematurely stopped for futility, with far fewer bleeding events than anticipated. Therefore, both stopping and continuing NOAC are possible options (► Table 12). For patients on a NOAC undergoing low bleeding risk interventions (i.e., infrequent bleeding or with nonsevere clinical impact), last dose intake the day before the procedure is appropriate in most cases, with resumption of NOAC on the first postoperative day. Procedures with uninterrupted OAC should be performed by an experienced operator, paying close attention to achieving good hemostasis.

- **Surgical procedures**: The periprocedural management of patients with AF or VTE with a clinical indication for OAC who require elective surgery or an endoscopic or endovascular procedure represents a frequent clinical challenge, with most recommendations based on expert consensus. An individualized approach by local physicians is mandatory. Management needs to balance the procedural bleeding risk and the thromboembolic risk associated with the underlying condition.

The procedural bleeding risk classification must consider both the prevalence of hemorrhagic complications and its consequences, with several attempts to categorize the risk of bleeding related to different interventional procedures. Procedures with low rates of bleeding but relevant associated sequelae (e.g., intracranial or spinal surgery) should be classified as high risk. In addition, comorbid conditions (e.g., older age, kidney or liver dysfunction) that can increase the risk of periprocedural bleeding should be considered.

The thromboembolic risk associated with the indication for OAC is classified according to the annual risk of arterial thromboembolism or VTE: high if the risk is >10%, moderate between 5 and 10%, and low when <5% (► Table 13). Generally, temporary interruption without bridging is recommended for low or moderate thromboembolic risk patients, with bridging only for high-risk patients. Bridging is rarely needed with NOacs, given their short half-life. When temporary interruption is required, the duration for

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**Fig. 3** A in the Atrial fibrillation Better Care pathway. ABC, Atrial fibrillation Better Care; APT, antiplatelet therapy; BP, blood pressure; CHA2DS2-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, nonsteroidal anti-inflammatory drugs; OAC, oral anticoagulation; OSA, obstructive sleep apnea; TTR, time in the therapeutic range; VKA, vitamin K antagonist. (Adapted from Lother et al.)
Table 11 Randomized controlled trial of uninterrupted oral anticoagulation in atrial fibrillation catheter ablation

<table>
<thead>
<tr>
<th></th>
<th>COMPARE&lt;sup&gt;4&lt;/sup&gt;</th>
<th>VENTURE-AF&lt;sup&gt;10&lt;/sup&gt;</th>
<th>RE-CIRCUIT-AF&lt;sup&gt;11&lt;/sup&gt;</th>
<th>AXAFA-AFNET&lt;sup&gt;5,12&lt;/sup&gt;</th>
<th>ELIMINATE-AF&lt;sup&gt;13&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>OAC treatment</td>
<td>Heparin bridging vs. warfarin (1:1)</td>
<td>Rivaroxaban vs. warfarin (1:1)</td>
<td>Dabigatran vs. warfarin (1:1)</td>
<td>Apixaban vs. warfarin (1:1)</td>
<td>Edoxaban vs. warfarin (2:1)</td>
</tr>
<tr>
<td>Number of patient (n)</td>
<td>790/793</td>
<td>124/124</td>
<td>317/318</td>
<td>318/315</td>
<td>411/203</td>
</tr>
<tr>
<td>Age (y), mean or median</td>
<td>61/24</td>
<td>58.6/60.5</td>
<td>59.1/59.3</td>
<td>64.0/64.0</td>
<td>60.0/61.0</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>76/74</td>
<td>68.4/72.6</td>
<td>72.6/77</td>
<td>69/65</td>
<td>70.6/73.4</td>
</tr>
<tr>
<td>BMI, kg/m&lt;sup&gt;2&lt;/sup&gt;, mean or median</td>
<td>NA</td>
<td>29.8/28.9</td>
<td>28.5/28.8</td>
<td>28.4/28.2</td>
<td>28.1/27.8</td>
</tr>
<tr>
<td>CHA&lt;sub&gt;2&lt;/sub&gt;DS&lt;sub&gt;2&lt;/sub&gt;-VASc score</td>
<td>1: 29/26</td>
<td>1.5/1.7</td>
<td>2/2.2</td>
<td>2.4/2.2</td>
<td>0: 23.4/21.7</td>
</tr>
<tr>
<td></td>
<td>2: 34/36</td>
<td>3.2/2.8</td>
<td>7.5/7.3</td>
<td>5.4/3.9</td>
<td>1: 26.5/28.1</td>
</tr>
<tr>
<td></td>
<td>≥3: 37/38</td>
<td>100</td>
<td>84.6</td>
<td>74.6</td>
<td>≥2: 50.1/50.2</td>
</tr>
<tr>
<td>Prior stroke or TIA (%)</td>
<td>7/8</td>
<td>0/2.4</td>
<td>3.2/2.8</td>
<td>7.5/7.3</td>
<td>5.4/3.9</td>
</tr>
<tr>
<td>Congestive heart failure (%)</td>
<td>15/17</td>
<td>9.7/7.3</td>
<td>9.8/10.7</td>
<td>24.5/22.9</td>
<td>17.3/19.2</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>81/83</td>
<td>47.6/46</td>
<td>52.4/55.7</td>
<td>89/91.4</td>
<td>60.8/59.6</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>38/40</td>
<td>6.5/11.3</td>
<td>9.5/10.7</td>
<td>12.9/11.1</td>
<td>13.4/15.8</td>
</tr>
<tr>
<td>Types of AF (%)</td>
<td>29/25</td>
<td>76.6/70.2</td>
<td>67.2/68.9</td>
<td>59.4/56.5</td>
<td>69.1/64.5</td>
</tr>
<tr>
<td></td>
<td>71/75</td>
<td>23.4/29.8</td>
<td>32.8/31.2</td>
<td>40.6/43.6</td>
<td>25.5/30</td>
</tr>
<tr>
<td></td>
<td>• Paroxysmal AF</td>
<td>23.4/29.8</td>
<td>32.8/31.2</td>
<td>40.6/43.6</td>
<td>25.5/30</td>
</tr>
<tr>
<td></td>
<td>• Persistent AF</td>
<td>23.4/29.8</td>
<td>32.8/31.2</td>
<td>40.6/43.6</td>
<td>25.5/30</td>
</tr>
<tr>
<td>TEE prior to ablation (%)</td>
<td>NA</td>
<td>100</td>
<td>84.6</td>
<td>74.6</td>
<td></td>
</tr>
<tr>
<td>Duration of OAC before ablation</td>
<td>3–4 wk</td>
<td>3 wk</td>
<td>4–8 wk</td>
<td>30 d</td>
<td>21–28 d</td>
</tr>
<tr>
<td>Estimated NOAC compliance (%)</td>
<td>NA</td>
<td>99.9</td>
<td>97.6</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>INR, time in therapeutic range (%)</td>
<td>NA</td>
<td>79.8</td>
<td>84.5</td>
<td>302/332</td>
<td></td>
</tr>
<tr>
<td>ACT (s), mean or median</td>
<td>NA</td>
<td>85.7</td>
<td>84</td>
<td>302/332</td>
<td></td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Thromboembolic events (stroke/TIA/systemic thromboembolism)</td>
<td>Major bleeding events (ISTH)</td>
<td>Major bleeding events (ISTH)</td>
<td>All-cause mortality, stroke, or major bleeding (BARC≥2)</td>
<td>All-cause mortality, stroke, or major bleeding event (ISTH)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>48 h</td>
<td>30 d</td>
<td>8 wk</td>
<td>3 mo</td>
<td>90 d</td>
</tr>
<tr>
<td>Primary outcome event (%)</td>
<td>4.9/0.25&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0/0.8</td>
<td>1.6/6.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6.9/7.3</td>
<td>2.7/1.7</td>
</tr>
<tr>
<td>Death (%)</td>
<td>0/0</td>
<td>0/0.8</td>
<td>0/0</td>
<td>0.3/0.3</td>
<td>0/0</td>
</tr>
<tr>
<td>Ischemic stroke (%)</td>
<td>3.7/0.25</td>
<td>0/0.8</td>
<td>0/0.3</td>
<td>0.6/0</td>
<td>0.3/0</td>
</tr>
<tr>
<td>Major bleeding (%)</td>
<td>0.76/0.38</td>
<td>0/0.8</td>
<td>1.6/6.9</td>
<td>3.1/4.4</td>
<td>2.4/1.7</td>
</tr>
<tr>
<td>Death/ischemic stroke/major bleeding (%)</td>
<td>5.7/0.63</td>
<td>0/2.4</td>
<td>1.6/7.2</td>
<td>4/0.4/7</td>
<td>2.7/1.7</td>
</tr>
</tbody>
</table>

Abbreviations: AF, atrial fibrillation; ACT, activated clotting time; BARC, Bleeding Academic Research Consortium; BMI, body mass index; INR, international Normalized ratio; ISTH, International society on Thrombosis and Hemostasis; NOAC, non-vitamin K antagonist oral anticoagulant; NA, not available; OAC, oral anticoagulant; TIA, transient ischemic attack.

<sup>a</sup>Significant with \( p < 0.01 \).
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Subjects (n)</th>
<th>Age (y), mean</th>
<th>Continued OAC (%)</th>
<th>Interrupted OAC (%)</th>
<th>Timing of OAC interruption (h), mean or median</th>
<th>Timing of OAC resumption</th>
<th>Antiplatelet therapy (%)</th>
<th>Clinically significant hematoma (%)</th>
<th>Other device-related bleeding (%)</th>
<th>Thromboembolic and other complications (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birnie et al</td>
<td>BRUISE CONTROL 1 prospective randomized control trial</td>
<td>Warfarin 681</td>
<td>72 y</td>
<td>50.3%</td>
<td>Heparin bridging 49.7</td>
<td>NA</td>
<td>NA</td>
<td>Warfarin</td>
<td>3.5%</td>
<td>Pericardial effusion: Warfarin: 0%</td>
<td>Stroke/TIA: Warfarin: 0.6% Heparin bridging: 0% AF Warfarin: 0% Heparin bridging: 0.3%</td>
</tr>
<tr>
<td>Black-Maier et al [7]</td>
<td>Retrospective analysis of ORBIT-AF</td>
<td>Warfarin 284 NOAC 60</td>
<td>Warfarin 77 y NOAC 36%</td>
<td>Warfarin 70.5 y NOAC 36%</td>
<td>Warfarin 64% NOAC 65%</td>
<td>NA</td>
<td>NA</td>
<td>Warfarin</td>
<td>35%</td>
<td>Major bleeding: –ve warfarin: 1% +ve warfarin: 1% –ve NOAC: 0% +ve NOAC: 0%</td>
<td>Stroke/TIA: –ve warfarin: 1% –ve warfarin: 1% –ve NOAC: 0% –ve NOAC: 0%</td>
</tr>
<tr>
<td>Essesbag et al</td>
<td>Post-hoc analysis of RE-LY trial</td>
<td>VKA 201 Dabigatran 410</td>
<td>73 y</td>
<td>0%</td>
<td>100%</td>
<td>VKA: 144 h (total pre- + post-) NOAC: 53 h</td>
<td>NOAC: 34 h</td>
<td>Aspirin: 44%</td>
<td>2.7%</td>
<td>Major bleeding: VKA, bridging: 2.7% VKA, no bridging: 6% NOAC: 1.0%</td>
<td>Stroke: VKA, bridging: 0% VKA, no bridging: 0.6% NOAC: 0.2%</td>
</tr>
<tr>
<td>Leef et al</td>
<td>Post-hoc analysis of ROCKET-AF trial</td>
<td>VKA 211 Rivaroxaban 242</td>
<td>75 y</td>
<td>25%</td>
<td>75%</td>
<td>VKA: 5 d NOAC: 3 d</td>
<td>VKA: 3 d NOAC: 2 d</td>
<td>–</td>
<td>NOAC: 0.4%</td>
<td>Major bleeding: NOAC: 1.2% VKA: 1.0% –ve NOAC: 1.2% +ve OAC: 0.9%</td>
<td>Stroke: SE NOAC: 1.3% VKA: 0.5% –ve OAC: 0.6% +ve OAC: 1.8%</td>
</tr>
<tr>
<td>Ricciardi et al</td>
<td>Prospective randomized pilot trial</td>
<td>NOAC 101 (dabigatran = 37, rivaroxaban = 33, apixaban = 31)</td>
<td>76 y</td>
<td>49.5%</td>
<td>50.5%</td>
<td>Dabigatran: 24–48 h Rivaroxaban/ apixaban: 24 h</td>
<td>≥24 h</td>
<td>Aspirin: 15.8%</td>
<td>–ve NOAC: 0%</td>
<td>Any hematoma: –ve NOAC: 4% +ve NOAC: 3.9% Loss of HB &gt;2 g/dl –ve NOAC: 6% +ve NOAC: 9.8%</td>
<td>Pocket infection: –ve NOAC: 1%</td>
</tr>
<tr>
<td>Birnie et al</td>
<td>BRUISE CONTROL 2 prospective randomized control trial</td>
<td>NOAC 647 (dabigatran = 96, rivaroxaban = 106, apixaban = 125)</td>
<td>74</td>
<td>49.3%</td>
<td>50.5%</td>
<td>Dabigatran: 24–48 h Rivaroxaban/ apixaban: 24 h</td>
<td>≥24 h</td>
<td>Aspirin: 17.4%</td>
<td>–ve NOAC: 2.1%</td>
<td>Any hematoma: –ve NOAC: 4.8% +ve NOAC: 5.5% Pericardial effusion: –ve NOAC: 0.3% +ve NOAC: 0.3%</td>
<td>Stroke: –ve NOAC: 0.3% –ve NOAC: 0.3%</td>
</tr>
<tr>
<td>Tsai et al</td>
<td>Retrospective analysis</td>
<td>NOAC 100 (dabigatran = 28, rivaroxaban = 61, apixaban = 10, edoxaban = 1)</td>
<td>78 y</td>
<td>100%</td>
<td>0%</td>
<td>NA</td>
<td>NA</td>
<td>Aspirin: 6%</td>
<td>–ve NOAC: 1%</td>
<td>Pericardial effusion: +ve NOAC: 1%</td>
<td>0%</td>
</tr>
<tr>
<td>Steffel et al</td>
<td>Post-hoc analysis of ENGAGE AF trial</td>
<td>VKA 324 Edoxaban 549</td>
<td>74 y</td>
<td>26%</td>
<td>74%</td>
<td>Median 7 days (pre- + post-)</td>
<td>NA</td>
<td>Aspirin: 32%</td>
<td>2.5%</td>
<td>Major bleeding: –ve VKA: 0% +ve VKA: 0% +ve NOAC: 0% +ve NOAC: 0.5%</td>
<td>Stroke: –ve VKA: 1.1% –ve VKA: 0.9% –ve NOAC: 0.5% –ve NOAC: 0.4%</td>
</tr>
</tbody>
</table>

Abbreviations: MI, myocardial infarction; NOAC, non-vitamin K antagonist oral anticoagulant; NA, not available; OAC, oral anticoagulant; SE, systemic embolism; TIA, transient ischemic attack; VKA, vitamin K antagonist; –ve, interrupted; +ve, continued.
withholding OAC is mostly based on the procedural bleeding risk and the INR values 5 to 7 days before the procedure in case of VKAs, or renal function with NOACs (Table 14). For some procedures with low hemorrhagic risk (e.g., diagnostic endoscopy without biopsy), uninterrupted OAC is safe both in patients on VKA (INR/C20) or NOACs. When treatment on uninterrupted OAC is not feasible, the perioperative strategy will depend on the patient’s risk of thromboembolism (Fig. 4) and is discussed in more detail in the section on “Bridging” later.

Postprocedure, OAC may be re-initiated once hemostasis is achieved in the absence of bleeding. In most situations with low postprocedural bleeding risk, OAC can be resumed within 24 hours (generally on the day following the procedure), whereas it is reasonable to wait 48 to 72 hours if the risk of postprocedural bleeding is high. Measures to mitigate bleeding in patients on OAC requiring emergency procedures is beyond the scope of this manuscript and can be found elsewhere, including possible use of a reversal agent, such as intravenous vitamin K, idarucizumab for dabigatran or andexanet alfa for factor Xa inhibitors, or 4-factor prothrombin complex concentrate (PCC) and PCC as first options for VKAs and NOACs, respectively.

**Presentation with ACS and/or Requiring PCI**

In patients requiring combined OAC and APT, such as those with AF or VTE presenting with acute coronary syndrome (ACS) and/or undergoing percutaneous coronary intervention (PCI), the risk of bleeding is increased. In this setting, the predictive value of scores is generally poor, with the HAS-BLED score performing best and shown to predict

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

<table>
<thead>
<tr>
<th>Risk</th>
<th>Indication for OAC</th>
<th>AF</th>
<th>VTE</th>
</tr>
</thead>
</table>
| High  | • CHA₂DS₂-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 20210 mutation, protein C, protein S, or antithrombin deficiency, antiphospholipid syndrome, multiple defects) | • VTE within the past 3–12 months  
• Nonsevere thrombophilia (e.g., heterozygous factor V Leiden or prothrombin gene mutation)  
• Recurrent VTE  
• Active cancer + VTE | |
| Moderate | • CHA₂DS₂-VASc 5–6  
• Stroke/TIA >3 months | • VTE >12 months and no other risk factors | |
| Low   | • CHA₂DS₂-VASc 1–4  
• No history of stroke/TIA | | |

Abbreviations: AF, atrial fibrillation; OAC, oral anticoagulation; TIA, transient ischemic attack; VTE, venous thromboembolism.

Source: Modified from Vivas et al.161.

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

<table>
<thead>
<tr>
<th>NOAC</th>
<th>Procedural bleed risk</th>
<th>CrCl (mL/min)</th>
<th>INR 5–7 days prior to the procedure</th>
<th>Warfarin&lt;sup&gt;5&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CrCl (mL/min)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>≥96 h&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;15</td>
<td>2–3</td>
<td>3–4 d</td>
</tr>
<tr>
<td>Intermediate, high, or uncertain</td>
<td>≥72 h</td>
<td>15–29</td>
<td>&gt;3</td>
<td>5 d</td>
</tr>
<tr>
<td>Apixaban, rivaroxaban, or edoxaban</td>
<td>≥72 h</td>
<td>≥30</td>
<td></td>
<td>&gt;5 d</td>
</tr>
<tr>
<td>VKA</td>
<td>≥72 h</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CrCl, creatinine clearance; DOAC, direct acting oral anticoagulant; dTT, dilute thrombin time; INR, international normalized ratio; VKA, vitamin K antagonist.

<sup>a</sup>Consider measuring dTT.
<sup>b</sup>Consider measuring agent-specific anti-Xa level.
<sup>c</sup>INR must be measured again 24 hours before the procedure.
<sup>d</sup>If other VKA than warfarin is used, the durations may be adjusted according to the drug half-life.
significant bleeding in AF patients undergoing PCI. The Academic Research Consortium has defined HBR (BARC 3 or 5 bleeding) for patients undergoing PCI as the presence of one major or two minor characteristics (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 postdischarge periods and strategies to minimize such risk should therefore be applied before, during, and after PCI. Pre-PCI approaches include avoidance of routine pretreatment with APT, with P2Y12 inhibitor generally given only after coronary angiography has confirmed the decision to proceed to PCI. 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 whereas North American guidelines recommend uninterrupted VKA if INR <2 with interruption of VKA considered when INR is above these thresholds. Intra-PCI administration of reduced-dose unfractionated heparin (UFH) is recommended.

In patients on NOAC, timely interruption in elective patients may be considered, as indicated in the European guidelines and is clearly recommended by North American guidelines. Both guidelines recommend administration of weight-adjusted dose UFH for patients on NOAC undergoing both elective and emergency PCI owing to the uncertain protection of NOAC against PCI-related ischemic events.

Following PCI, the type and duration of APT should be carefully considered to minimize bleeding. An initial short course of triple antithrombotic therapy (TAT) with OAC and dual APT (DAPT) of aspirin and clopidogrel is warranted to early ischemic events. To mitigate the increased risk of bleeding with TAT, the more potent P2Y12 inhibitors prasugrel and ticagrelor should be avoided, with European guidelines indicating that ticagrelor or prasugrel...
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

<table>
<thead>
<tr>
<th>Major</th>
<th>Minor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticipated use of long-term oral anticoagulation&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Age ≥75 years</td>
</tr>
<tr>
<td>Severe or end-stage CKD (eGFR &lt;30 mL/min)</td>
<td>Moderate CKD (eGFR 30–59 mL/min)</td>
</tr>
<tr>
<td>Hemoglobin &lt;11 g/dL</td>
<td>Hemoglobin 11–12.9 g/dL for men and 11–11.9 g/dL for women</td>
</tr>
<tr>
<td>Spontaneous bleeding requiring hospitalization and/or transfusion in the past 6 months or at any time, if recurrent</td>
<td>Spontaneous bleeding requiring hospitalization and/or transfusion within the past 12 months not meeting the major criterion</td>
</tr>
<tr>
<td>Moderate or severe baseline thrombocytopenia&lt;sup&gt;b&lt;/sup&gt; (platelet count &lt;100 × 10&lt;sup&gt;9&lt;/sup&gt; per liter)</td>
<td>Chronic use of oral NSAIDs or steroids</td>
</tr>
<tr>
<td>Chronic bleeding diathesis</td>
<td>Any ischemic stroke at any time not meeting the major criterion</td>
</tr>
<tr>
<td>Liver cirrhosis with portal hypertension</td>
<td>Nondeferrable major surgery on DAPT</td>
</tr>
<tr>
<td>Active malignancy&lt;sup&gt;c&lt;/sup&gt; (excluding nonmelanoma skin cancer) within the past 12 months</td>
<td>Recent major surgery or major trauma within 30 days prior to PCI</td>
</tr>
<tr>
<td>Previous spontaneous ICH (at any time)</td>
<td></td>
</tr>
<tr>
<td>Previous traumatic ICH within the past 12 months</td>
<td></td>
</tr>
<tr>
<td>Presence of a bAVM</td>
<td></td>
</tr>
<tr>
<td>Moderate or severe ischemic stroke&lt;sup&gt;d&lt;/sup&gt; within the past 6 months</td>
<td></td>
</tr>
<tr>
<td>Nondeferrable major surgery on DAPT</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: bAVM, brain arteriovenous malformation; CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate; HBR, high bleeding risk; ICH, intracranial hemorrhage; NSAID, nonsteroidal anti-inflammatory drug; PCI, percutaneous coronary intervention.

<sup>a</sup>This excludes dual pathway inhibition doses.
<sup>b</sup>Baseline thrombocytopenia defined as thrombocytopenia prior to PCI.
<sup>c</sup>Active malignancy defined as diagnosis within 12 months and/or ongoing requirement for treatment (including surgery, chemotherapy, or radiotherapy).
<sup>d</sup>National Institutes of Health Stroke Scale [NIHSS] score ≥5.

be used as part of TAT only in exceptional circumstances such as stent thrombosis, and North American guidelines suggesting that ticagrelor can be considered in patients at high stent thrombosis risk although prasugrel should be avoided.

The duration of TAT should be minimized to 1 to 4 weeks (Fig. 5). 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 to 12 months, based on the patient’s bleeding and ischemic risks. Prolongation of DAT beyond 1 year may be considered in selected patients with both clinical and/or anatomical features for increased ischemic cardiac events (Fig. 5). In contrast, in patients with a first episode of VTE, in whom OAC is discontinued after 3 months, DAPT comprising aspirin and clopidogrel should be resumed upon OAC cessation with duration tailored to type of event and procedural characteristics.

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, aiming for TTR >65–70%. NOACs are preferable to VKA as part of combination therapy and switching from warfarin should be routinely considered. 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 favorable safety and efficacy profile compared with TAT including warfarin. In the AUGUSTUS trial, among patients with AF and either ACS or PCI treated with a P2Y<sub>12</sub> Inhibitor, treatment with apixaban, without aspirin, resulted in less bleeding and fewer hospitalizations than regimens that included a VKA, aspirin, or both. Subanalysis of data from the RE-DUAL PCI trial, which compared DAT (dabigatran 110 or 150 mg twice daily, 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.
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.\textsuperscript{175}

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: (1) in the setting of NSTEMI, avoidance of DAPT pretreatment in patients at HBR reduces bleeding risk\textsuperscript{187,188}; (2) radial is preferred over femoral access to reduce bleeding complications\textsuperscript{188,189}; (3) in patients not pretreated with oral APT, during urgent/emergency PCI, intravenous antiplatelet agents may be used, and the intravenous P\_Y\_12 inhibitor cangrelor may be preferred over glycoprotein IIb/IIIa inhibitors;\textsuperscript{190} (4) 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,\textsuperscript{191} and finally (5) administration of proton-pump inhibitors and avoidance of NSAIDs.\textsuperscript{192}

\textbf{Patients with Cancer}

Patients with cancer, particularly gastric or urothelial tumors, have an increased risk of bleeding on OAC compared with patients without cancer,\textsuperscript{193–195} and proton-pump inhibitors should be routinely considered to mitigate this risk.

Patients with AF and cancer experience similar or lower bleeding with NOAC compared with VKA,\textsuperscript{195–198} with the exception of patients with gastrointestinal cancers or active gastrointestinal mucosal abnormalities.\textsuperscript{199}

In cancer patients with VTE, NOACs significantly reduce bleeding compared with VKA.\textsuperscript{200} Apixaban and edoxaban have similar safety profile to LMWH,\textsuperscript{15,201} with excess bleeding mainly observed in patients with gastrointestinal cancer.\textsuperscript{201,202} A meta-analysis showed no difference in major bleeding between LMWH and VKA treatment, whereas NOACs significantly lowered bleeding risk compared with 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

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\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig5.png}
\caption{Management of antithrombotics in patients presenting with ACS and/or requiring PCI or stents. ACS, acute coronary syndrome; PCI, percutaneous coronary intervention.}
\end{figure}
showed significantly higher incidence of major bleeding with NOACs (6.5 vs. 3.7%, RR: 1.75, 95% CI: 1.10–2.77).203

Bridging Therapy

Patients Treated with OAC Undergoing Interventional or Surgical Procedures

While bridging with either UFH or LMWH may theoretically reduce the periprocedural thrombotic risk, it substantially increases periprocedural bleeding.163 Irrespective of the periprocedural anticoagulation strategy used, the incidence of thromboembolic events is 0 to 1% (Table 12). In patients undergoing CIED implantation, uninterrupted VKA without bridging is associated with lower thromboembolic and bleeding rates162 and reduced length of stay.162,204 Heparin-bridging results in a 4.5-fold increase in postoperative hematoma compared with a continued warfarin strategy,162 and a sizeable hematoma is an independent risk factor for subsequent device infection.205,206

In AF patients, bridging significantly increased bleeding, with no ischemic benefit.163,207 Postoperatively, bridging with parenteral agents is not required with NOACs, but could be considered in selected high thromboembolic risk patients when resuming VKA.

A routine bridging strategy is not recommended in the current 2020 ESC AF Guideline37 and an ESC/EHRA document on the use of NOACs.208 emphasized that bridging should be avoided.

Patients Treated with OAC with Prior Stent Requiring Surgery

In patients with prior coronary stenting, antithrombotic therapy is required to reduce the risk of stent thrombosis. The decision on APT bridging requires careful evaluation of bleeding and ischemic (stent thrombosis) risk. The thrombotic risk falls with time from PCI, being relatively high in the first 3 to 6 months, intermediate at 6 to 12 months, and low beyond 12 months.209 While 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 such that the bridging APT strategy may be required. There are specific clinical and angiographic risk factors which increase ischemic risk.209,210

The risk of perioperative hemorrhage is very high with hepatic resection, and with many other surgical procedures including splenectomy, gastrectomy, thyroid surgery, nephrectomy, prostatectomy, and aortic or redo cardiac surgery.209 Additionally, the site of potential bleeding is critical, for example, even relatively minor bleeding with neurosurgery or ophthalmic surgery can be catastrophic. Bridging of APT usually involves starting (or continuing with) aspirin, and consideration should be given to temporary transition with an intravenous antiplatelet agent in patients who would otherwise require DAPT (if they were not on OAC).

For patients with high ischemic 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 the use of DAPT with clopidogrel rather than more potent P2Y12 inhibitors, or preferably using intravenous cangrelor, which has a short half-life in case of major bleeding.161,209

Consensus Statements

• Bleeding risk reflects the interaction of nonmodifiable and modifiable bleeding risks. Simply focusing on modifiable bleeding risk factors is an inferior strategy to the use of formal bleeding risk scores.
• Bleeding risk is not a static “one-off” assessment but is dynamic, being influenced by aging, 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 have modest predictive value and calibration for bleeding events, and 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 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 nonmodifiable risk factors 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. 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.
• In VTE patients, the choice of the bleeding risk score is at the discretion of the clinician. The 2020 NICE VTE guideline recommends use of the HAS-BLED score.

Conflict of Interest

None declared.

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