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

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Abbreviations

ACS – Acute coronary syndrome
AF – Atrial fibrillation
APT – Antiplatelet therapy
ARC – Academic Research Consortium
BARC – Bleeding Academic Research Consortium
CI – Confidence interval
CIED – cardiac implantable electronic device
DAPT – Dual antiplatelet therapy
DAT – Double antithrombotic therapy
DVT – Deep vein thrombosis
eGFR – estimated glomerular filtration rate
ESC – European Society of Cardiology
GUSTO – Global Use of Strategies To Open occluded arteries
HBR – High bleeding risk
ICH – Intracranial haemorrhage
INR – International normalised ratio
ISTH – International Society of Thrombosis and Haemostasis
LAA – Left atrial appendage
LMWH – Low molecular weight heparin
MI – Myocardial infarction
NOAC – Non-vitamin K antagonist oral anticoagulant
NSTEMI – Non ST-segment elevation myocardial infarction
OAC – Oral anticoagulant
PCC – Prothrombin complex concentrate
PCI – Percutaneous coronary intervention
PE – Pulmonary embolism
RR – Risk ratio
SAPT – Single antiplatelet therapy
STEMI – ST-segment elevation myocardial infarction
TAT – Triple antithrombotic therapy
TIMI – Thrombolysis in Myocardial Infarction
TTR – Time in therapeutic range
UFH – Unfractionated heparin
VKA – Vitamin K antagonist

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 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 variable INR 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 ageing, incident comorbidities and drug therapies.

In this executive summary of our Consensus Document, we comprehensively review the published evidence and propose a consensus on bleeding risk assessments in patients with AF and VTE, with a view to summarising '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 summarise 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.

KEY WORDS

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 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 ageing, 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, we consolidate the Position Paper on the Assessment and Mitigation of Bleeding risk in Atrial fibrillation and Venous Thromboembolism from the ESC Working Group on Thrombosis, in collaboration with the EHRA, Acute Cardiovascular Care Association and Asia-Pacific Heart Rhythm Society [ref].

Systematic review

Epidemiology of bleeding with OAC in AF

Major bleeding occurs in 1.4-3.4% of patients with AF treated with VKA, per annum.[3] Intracranial haemorrhage (ICH) is rare, occurring in 0.1-2.5% patients per year,[4] with more recent studies reporting a lower rate of 0.7-0.8%.[5] NOACs lower the incidence of major bleeding (-14%) and ICH (-52%) compared to warfarin.[5,6] [5]. A number of variables impact on the risk of anticoagulation-related bleeding in patients with AF, including TTR and INR variability which also impact the risk of ICH[7] (Figure 3).

Epidemiology of bleeding with OAC in VTE

Anticoagulation is required for the treatment and prevention of VTE, whether deep vein thrombosis (DVT) or pulmonary embolism (PE), for a minimum of three months, with longer term treatment for patients with an unprovoked event or due to a persistent risk factor [8,9]. VKA-related major bleeding is approximately 2% during the initial 3 months of anticoagulation, with a fatal bleeding rate of 0.37-0.55%.[10] [11]. Beyond the first 3 months, major bleeding occurs in 2.74% of patients on VKA.[10] [12].

NOACs are as effective as 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%CI 0.51-0.77)[13], as well as fatal bleeding (RR 0.36%, 95%CI 0.15-0-87), compared to VKA. During the extended phase, NOAC use was associated with a non-significant increase in major bleeding compared to placebo. Major or clinically relevant non-major bleeding events were similar with reduced-dose NOACs (apixaban[14] and rivaroxaban[15]) as with aspirin or placebo (RR 1.19, 95%CI 0.81–1.77), whereas the 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)[16].

Definitions of bleeding

Several definitions are used to define bleeding events in patients on OAC (Table 1), including qualitative or quantitative (such as drop in haemoglobin) definitions, or frequently both. The most widely used are the Thrombolysis in Myocardial Infarction (TIMI),[17] Global Use of Strategies To Open occluded arteries (GUSTO),[18] International Society of Thrombosis and Haemostasis (ISTH),[19,20] and the Bleeding Academic Research Consortium (BARC)[21] classifications, and all have been shown to predict mortality.[22,23] Heterogeneity in bleeding definitions may in part account for the variability in the reported rate of haemorrhagic complications with OAC.[4]

Clinical bleeding risk factors with OAC for AF or VTE

Risk factors associated with bleeding on OAC are similar in VTE and AF[8,9,24] (Tables 2 to 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, 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.
Bleeding risk assessment cannot be a ‘one-off’ and requires regular re-evaluation, due to the dynamic nature of some risk factors, including ageing, comorbidities and concomitant medications.[25-27]

Advancing age increases the risk of bleeding on OAC (Table 2).[28-30] 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.[29,31,32]

Most studies show systolic hypertension to be a risk factor for bleeding with OAC, especially ICH,[33,34] although others did not.[35,36] Sub-analysis of the ENGAGE-AF trial showed that major bleeding was more frequent in patients with a systolic blood pressure >140 mmHg compared to those lower levels.[34] 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 to VKA was most pronounced among patients with elevated diastolic blood pressure.[34] In a nationwide Korean population registry, the risk of ICH was lowest with BP<130/80 mmHg.[37] 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).[25] 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%), renal (3.08%) or liver (2.22%) impairment [27]. 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 3.7% of patients receiving NOACs had eGFR decline sufficient to warrant dose reductions.[38] 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% reduction in major bleeding.[30]

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 AF [39-41] but their practical applicability remains limited.

The ABC-bleeding risk score which includes blood biomarkers of bleeding including growth differentiation factor-15 [GDF-15], troponin T and haemoglobin, 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 APT, and in different geographic regions,[42-45] but this was not confirmed in another study.[46] The consecutive addition of different blood-based biomarkers only slightly enhanced the predictive ability of the HAS-BLED score for major bleeding.[47] 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.[48,49] In patients with VTE on OAC, information on biomarkers and bleeding risk is sparse,[50] and scores including biomarkers such as haemoglobin and/or creatinine (or creatinine clearance), have modest predictive performance.[51,52]

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 ageing 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[53] 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.[54]

In patients with AF on OAC, the presence of cerebral microbleed(s) on cerebral MRI imaging was independently associated with ICH,[55] and addition of cerebral microbleeds to the HAS-BLED score significantly improved the prediction of ICH over the HAS-BLED score alone.[55]

Current published bleeding risk schema in AF and VTE

Bleeding risk scores are important: i) to identify modifiable risk factors; ii) to identify people who require more regular monitoring; and iii) to estimate an individual's bleeding risk on antithrombotic/OAC therapy.

Several bleeding risk scores (Table 10) are available for patients with AF [42,49,56-62] and VTE.[24,63-71] These incorporate numerous risk factors, including demographic and clinical information plus biomarkers, ranging from 3[42,68] to 17 [24] 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, which can hinder clinical utility. Most scores stratify patients into low, intermediate and high risk, demonstrating major bleeding rates ranging from <1% [42] to 30% [59] and 0.1%[69] to 12.2 per 100-patient years [70] in low- and high-risk groups for AF and VTE bleeding risk scores, respectively (Table 10). Bleeding risk assessment only using modifiable bleeding risk factors is inferior to formal bleeding risk score calculation.[72-74]

Among the bleeding risk scores for AF,[42,49,56-61] the HAS-BLED score[58] has been most widely validated across the spectrum of the AF patient pathway, from OAC/antithrombotic-naïve patients to those established on OAC [75] [76,77], and is predictive of ICH.[78] In a contemporary cohort of AF patients treated with NOACs, the ORBIT was inferior to the HAS-BLED score.[79]

The HAS-BLED score has also been validated in non-AF populations, including those with VTE, or those undergoing bridging therapy.[80-83] A systematic review[84] evaluating the HAS-BLED,[58] HEMORR$_2$HAGES,[56] ATRIA,[49] and ABC-Bleeding[42] scores concluded that HAS-BLED was the best for predicting major bleeding, albeit with modest evidence base.[84] A prospective App-based intervention in a cluster radomised trial, which included the HAS-BLED score, reduced major bleeding events, addressed modifiable risk factors and increased OAC uptake, compared to usual care.[85]

Eight clinical risk scores for predicting major bleeding in patients with VTE (Table 10) have been developed,[24,63-70] some focusing on the acute phase,[63,66,69] long-term treatment,[67,68], specific sub-groups of VTE, for example, cancer-associated thromboembolism,[86,87] and the elderly,[70] with three[64,65,67] derived from cohorts treated with NOACs. A number of prediction rules attempting to quantify the bleeding risk of an individual by adding weighted[67-69] or unweighted[24,58,60,81] 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.[71] Critical appraisal[71] of 7 bleeding risk scores developed for VTE (ACCP[24], EINSTEIN[64], Hokusai[65], Kuijer[68], RIETE[69], Seiler[70], VTE-BLEED[67]) and 7 validated in VTE cohorts but derived in AF or mixed-indication cohorts (ATRIA[49], HAS-BLED[58], HEMORR$_2$HAGES[56], mOBRI[60], OBRI[61], ORBIT[57], Shireman[59]) 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]).[71] 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).[81 71] External validation of the VTE-BLEED score,[67] derived from a population treated with dabigatran or warfarin, demonstrated predictive ability across patient groups [88],[89 90], and for ICH and/or fatal bleeding [91]. External validation of the EINSTEIN or Hokusai scores has not been undertaken.

In patients with VTE on NOAC, the prognostic precision of 6 bleeding risk scores (HAS-BLED [58], ORBIT [57], ATRIA-Bleeding [49], Kuijer [68], RIETE [69], VTE-BLEED[67]) found to be modest and similar, 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).[51] Another study of patients with VTE ≥65 years receiving VKA[52] evaluating 10 clinical bleeding risk scores (VTE-BLEED [67], RIETE [69], ACCP [24], Seiler [70], Kuijer [68], Kearon, OBRI [60,61], ATRIA,[49] HAS-BLED,[58] HEMORR$_2$HAGES[56]) showed c-statistics ranging from 0.47 (OBRI [60,61]) to 0.70 (Seiler [70]) for major bleeding and 0.52 (OBRI [60,61]) to 0.67 (HEMORR$_2$HAGES [56]) for clinically relevant bleeding. A recent review of bleeding risk assessment in patients with VTE [92] 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 ability (c-indexes approx. 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 non-modifiable 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, bleeding risk assessment should inform decision making in clinical practice, especially for mitigation of modifiable bleeding risks and scheduling high bleeding risk patients for early review and followup as part of the holistic or integrated care approach to AF management.[85]

Patient values and preferences

Shared decision-making[93] is important to enable healthcare 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.[94-99 96,100,101] 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.[102 103-107] In contrast, physicians generally worry more about the harm from bleeding.[105,108,109] A reduction in major bleeding was second to stroke prevention as the most valued attribute of OAC.[110,111] Similarly, patients with VTE[95] appear to value reduction in VTE risk over potential bleeding risk.[95,112,113 95 114-116] Among cancer patients, risk of bleeding was less important than ensuring that VTE prophylaxis did not interfere with cancer treatment and OAC efficacy.[117,118]

Studies assessing patient preferences towards VKAs versus NOACs[104,119-128] indicate that when efficacy and safety are similar, patients with AF and VTE commonly favoured simpler, more convenient treatment regimens, less frequent dosing, fixed-dose medication, without need for regular monitoring or bridging, or drug-food interactions.[102 129,130 110,111,131 116,120,132-134]

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 [135].

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,[96] American College of Chest Physicians,[100] and Asia-Pacific Heart Rhythm Society,[136] given its simplicity and evidence base.[85] The ACC/AHA/HRS AF guidelines did not propose any specific bleeding risk scheme.[137]

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,[138] 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 anaemia. Of note, all these modifiable risk factors listed are already included in the HAS-BLED score.

The 2020 ESC AF guideline emphasizes that, irrespectively of the score used, the main aim is to identify modifiable bleeding risk factors,[96] including controlling blood pressure, cessation of non-essential antiplatelet therapy (APT) or NSAIDs, improving TTR, and reduction/cessation of alcohol (Figure 4). 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 non-modifiable and modifiable risk factors, simply focusing on modifiable risk factors alone is inferior to formal assessment with a bleeding risk score.[72-74]

Generally, HBR should not be a reason to withhold OAC, except for situations in which the risk/benefit ratio excessively favours no antithrombotic treatment.[96,137,139-141] Instead, efforts should be made to identify and address all modifiable bleeding risk and provide more frequent risk assessment.[25,96,100,142]

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.[143]
Most current VTE guidelines leave the choice of bleeding risk score to the clinician,[9,143] although the 2020 NICE VTE guideline[144] 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 personalised risk:benefit ratio for OAC 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..

Surgery and endoscopic and endovascular procedures

(i) Peri-ablation of atrial arrhythmias

Catheter ablation, especially left-sided ablation, is associated with a small but relevant ~0.5% risk of severe bleeding,[145] including cardiac tamponade and 1-2% access site bleeds,[146,147] related to vascular access and peri-interventional anticoagulation.[147] Ablation also carries a risk of thrombotic events, with left-sided procedures carrying a ~1% risk of thrombosis and stroke.[146,147] 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).[148] Most guidelines agree on 3 main points [96,100,140,141,149]: 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 (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.[150]

(ii) 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 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.[151] Therefore both stopping or continuing NOAC are possible options (Table 12).[152-156] For patients on a NOAC undergoing low bleeding risk interventions (i.e. infrequent bleeding or with non-severe clinical impact), last dose intake the day before the procedure is appropriate in most cases,[141] with resumption of NOAC on the first postoperative day. Procedures with uninterrupted OAC should be carried out by an experienced operator, paying close attention to achieving good haemostasis.

(iii) 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 are based on expert consensus.[4,157-160] 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 haemorrhagic complications and its consequences, with several attempts to categorize the risk of bleeding related to different interventional procedures.[158-160] 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 peri-procedural bleeding, should be considered. 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 5-10%, and low when < 5% (Table 13).[157,158,160]

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 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 haemorrhagic risk (e.g. diagnostic endoscopy without biopsy), uninterrupted OAC is a safe both in patients on VKA (INR≤3) or NOACs.[151,161] When treatment on uninterrupted OAC is not feasible, the peri-procedural strategy will depend on 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 in the absence of bleeding. In most situations with low post-procedural bleeding risk, OAC can be resumed within 24 hours (generally on the day following the procedure), whereas it is reasonable to wait 48-72 hours if the risk of post-procedural bleeding is high [158,160,162].
Measures to mitigate bleeding in patients on OAC requiring emergency procedures is beyond the scope of this manuscript and can be found elsewhere,[141,160,163] including possible use of a reversal agent, such as intravenous vitamin K, idarucizumab[164] for dabigatran or andexanet alfa for factor Xa inhibitors,[165,166] or 4-factor prothrombin complex concentrate (PCC) and PCC as first options for VKAs and NOACs, respectively.[163,167]

Presentation with ACS and/or requiring PCI

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.[168] In this setting, the predictive value of scores is generally poor, with the HAS-BLED score performing best[169,170] and shown

to predict significant bleeding in AF patients undergoing PCI.[171] 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[172] (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 [173]. 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.[173,174] 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, [174] whereas North American guidelines recommend uninterrupted VKA if INR<2,[175] with interruption of VKA considered when INR is above these thresholds. Intra-PCI administration of reduced-dose UFH is recommended.[174,175]

In patients on NOAC, timely interruption in elective patients may be considered, as indicated in the European guidelines[174] and is clearly recommended by North American guidelines.[175] Both guidelines recommend administration of weight-adjusted dose UFH for patients on NOAC undergoing both elective and emergency PCI,[176,177 174] owing to the uncertain protection of NOAC against PCI-related ischaemic events.

Following PCI, the type and duration of APT should be carefully considered to minimize bleeding.[173] An initial short course of triple antithrombotic therapy (TAT) with OAC and dual APT (DAPT) of aspirin and clopidogrel is warranted to early ischaemic events (Figure 6).[96] To mitigate the increased risk of bleeding 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,[174] and North American guidelines suggesting that ticagrelor can be considered in patients at high stent thrombosis risk although prasugrel should be avoided.[175]

The duration of TAT should be minimized to 1-4 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[174,175] (Figure 6), followed by OAC alone indefinitely.[174,175,178,179] Prolongation of DAT beyond 1 year may be considered in selected patients with both clinical and/or anatomical features for increased ischaemic cardiac events[174,175] (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.[175]

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 [174], aiming for TTR >65-70% [180]. NOACs are preferable to VKA as part of combination therapy and switching from warfarin should be routinely considered.[174] 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.[181-184] In the AUGUSTUS trial, amongst 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.[183] 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.[185] 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.[174]

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 pre-treatment in patients at HBR reduces bleeding risk [186,187]; 2) radial is preferred over femoral access to reduce bleeding complications [187,188]; 3) in patients not pretreated with oral APT, during urgent/emergency PCI, intravenous antiplatelet agents may be used, and the intravenous $P2Y_{12}$-inhibitor cangrelor may be preferred over glycoprotein IIb/IIIa inhibitors [189]; 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 [190], and finally 5) administration of proton-pump inhibitors and avoidance of NSAIDs.[191]

Patients with cancer

Patients with cancer, particularly gastric or urothelial tumours, have an increased risk of bleeding on OAC compared to patients without cancer,[192-194] 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 to VKA,[195 194,196,197] with the exception of patients with gastrointestinal cancers or active gastrointestinal mucosal abnormalities.[198]
In cancer patients with VTE, NOACs significantly reduce bleeding compared to VKA.[199] Apixaban and edoxaban have similar safety profile to LMWH [14,200], with excess bleeding mainly observed in patients with gastrointestinal cancer.[200,201] A meta-analysis showed no difference in major bleeding between LMWH and VKA treatment 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).[202]

Bridging therapy

(i) Patients treated with OAC undergoing interventional or surgical procedures

While bridging with either UFH or LMWH may theoretically reduce the peri-procedural thrombotic risk, it substantially increases peri-procedural bleeding.[162] Irrespective of the perioperative anticoagulation strategy used, the incidence of thromboembolic events is 0-1% (Table 12). In patients undergoing CIED implantation, uninterrupted VKA without bridging is associated with lower thromboembolic and bleeding rates[161] and reduced length of stay.[161,203] Heparin-bridging results in a 4.5-fold increase in postoperative haematoma compared to a continued warfarin strategy,[161] and a sizeable haematoma is an independent risk factor for subsequent device infection.[204,205]

In AF patients, bridging significantly increased bleeding, with no ischaemic benefit.[162 206]

Post-operatively, 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 Guideline[96] and an ESC/EHRA document on the use of NOACs[207] emphasized that bridging should be avoided.

(ii) 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 ischaemic (stent thrombosis) risk. 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.[208] 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 such that bridging APT strategy may be required. There are specific clinical and angiographic risk factors which increase ischaemic risk.[208,209]

The risk of peri-operative haemorrhage is very high with hepatic resection, and with many other surgical procedures including splenectomy, gastrectomy, thyroid surgery, nephrectomy and prostatectomy, aortic or redo cardiac surgery.[208] 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 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 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.[160,208]

Consensus statements

- Bleeding risk reflects the interaction of non-modifiable 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 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 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 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. 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.

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