Bleeding risk assessment and management in atrial fibrillation patients

Executive Summary# of a Position Document from the European Heart Rhythm Association [EHRA], endorsed by the European Society of Cardiology [ESC] Working Group on Thrombosis

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Summary
In this executive summary of a Consensus Document from the European Heart Rhythm Association, endorsed by the European Society of Cardiology Working Group on Thrombosis, we comprehensively review the published evidence and propose a consensus on bleeding risk assessments in atrial fibrillation (AF) patients. The main aim of the document was to summarise ‘best practice’ in dealing with bleeding risk in AF patients when approaching antithrombotic therapy, by addressing the epidemiology and size of the problem, and review established bleeding risk factors. We also summarise definitions of bleeding in the published literature. Patient values and preferences balancing the risk of bleeding against thromboembolism as well as the prognostic implications of bleeding are reviewed. We also provide an overview of published bleeding risk stratification and bleeding risk schema. Brief discussion of special situations (e.g. periablation, peri-devices such as implantable cardioverter defibrillators [ICD] or pacemakers, presentation with acute coronary syndromes and/or requiring percutaneous coronary interventions/stents and bridging therapy) is made, as well as a discussion of the prevention of bleeds and managing bleeding complications. Finally, this document puts forwards consensus statements that may help to define evidence gaps and assist in everyday clinical practice.

Keywords
Bleeding, oral anticoagulation, atrial fibrillation, risk assessment

1. Introduction and scope
Prevention of stroke and thromboembolism is one of the main therapeutic goals in atrial fibrillation (AF) (1, 2). Oral anticoagulation (OAC) is highly effective in preventing ischaemic strokes in patients with AF and conveys a clear net clinical benefit despite a potential risk for major bleeding events (3).

Current OAC in common use are essentially the vitamin K antagonists (VKA), most often warfarin or acenocoumarol or phenprocoumon, which are dose-adjusted to achieve an international normalised ratio (INR) of 2.0–3.0 (2). The VKA have many limitations, including a significant inter- and intra-patient variability of effective dose, and various food and drug interactions. New OAC, broadly divided into two categories, the oral direct thrombin inhibitors and the oral direct factor Xa inhibitors, are in advanced clinical development, and may offer alternative therapies to patients who suffer from the limitations and dis-utility associated with VKA (4). Indirect comparisons show how well these new OAC may perform relative to VKA, aspirin-clopidogrel combination therapy, aspirin monotherapy or placebo (5).
Anticoagulant therapy with VKA carries a risk for bleeding, including severe bleeding events, but the clinical benefit of OAC clearly outweighs the risk of OAC therapy, especially in patients at high risk for stroke: indeed, bleeding events are 5–8 times less likely than ischaemic strokes reported among AF patients from trials and registry data (6).

Estimation of the stroke risk in an individual patient with AF can be achieved using easily applicable clinical stroke risk estimators such as the CHADS2 score (7) and an increasingly more refined score that considers additional stroke risk factors, the CHA2DS2-VASC score (2, 8, 9).

Despite the clear net clinical benefit of OAC in AF patients at risk for stroke, major bleeding events, especially intracranial bleeds, may be devastating when they do occur (3). The decision for OAC should therefore be based on a careful assessment of both stroke risk and bleeding risk. Clinical scores for bleeding risk estimation are much less well validated than stroke risk scales and the estimation of bleeding risk is rendered difficult as many of the known factors that increase bleeding risk overlap with stroke risk factors, and many factors that increase bleeding risk are transient, such as variable INR values, operations, vascular procedures, and drug-drug or food-drug interactions.

This is an executive summary of a Consensus Document from the European Heart Rhythm Association (EHRA), endorsed by the European Society of Cardiology (ESC) Working Group on Thrombosis, where we comprehensively review the published evidence and propose a consensus on bleeding risk assessments in AF patients. The full document has been published in Europace (10) and includes systematic reviews of the evidence/data pertaining to bleeding risk in AF patients.

2. Systematic review of evidence/data

2.1 Epidemiology and size of the problem of bleeding risk in AF

OAC therapy greatly reduces the risk of stroke in AF and the clinical dilemma faced by physicians and patients is anticoagulant-related haemorrhage, which increases with age. The reported rate of intracranial haemorrhage has increased markedly with expanded use of anticoagulants in older adults, often with AF as the primary indication (11). Perceived bleeding risk and older age are potent negative predictors of receiving warfarin and partly explain the reported low rates of warfarin use in clinical practice (12, 13). The risk of both haemorrhage (and stroke) are highest when AF is newly diagnosed and during the initiation of anticoagulant medication (14). One recent randomised trial did not suggest that OAC naïve status conferred a disadvantage in relation to efficacy and bleeding endpoints (15).

Reported rates of major bleeding among individuals with AF taking oral VKA vary widely ranging from 1.3% to 7.2% per year (16–35) (Table 1). These disparate rates reflect the wide variability in patient characteristics studied and the methodology employed. The early trials in AF that established the efficacy of warfarin excluded almost 90% of individuals screened (16). Trial participants may be selected, based on a lower bleeding risk profile and higher likelihood of adherence. Thus, bleeding rates reported from randomised trials will often be lower than in clinical practice.

More recent randomised controlled trials designed to evaluate the safety and efficacy of new anti-thrombotic agents have tried to include substantial numbers of patients without prior exposure to anticoagulation since these individuals are at high risk for bleeding and thromboembolism (15).

Observational studies are also subject to selection bias and methodological differences. The proportion of patients within the defined AF population taking warfarin should be recorded, which reflects individual physician judgment of VKA candidacy or eligibility which is often subjective. However, prospective registries that require written informed consent for participation are less likely to enrol the more acutely ill, medically complex, or frail individuals, and may underestimate the bleeding that occurs in routine care. Indeed, rates reported from these studies are lower than rates of haemorrhage on warfarin from recent studies (15, 22–24) that have enrolled older individuals and more first-time takers of warfarin (warfarin naïve) (36, 37).

Available data suggest that strokes in AF patients are more severe than other types of stroke, and more often result in permanent disability or death than in non-AF stroke (38). Given the severity of these presumably ischaemic strokes, determination of a bleeding risk threshold that would justify withholding anticoagulant therapy is difficult. One recent real-world analysis using nationwide cohort data reported that there was a negative net clinical benefit balancing ischaemic stroke against intracranial haemorrhage (ICH) for warfarin treatment, only in ‘truly low risk’ patients with AF (39); of note, the net clinical benefit was more positive in patients at high bleeding risk, and the absolute benefit in reducing stroke with warfarin would outweigh the small increase in ICH with warfarin.

2.2 Definitions of bleeding

The incidence of bleeding with OAC varies widely in published studies, reflecting differences in study design, patient populations and quality of monitoring. There are also diverse classifications of bleeding events (major, life-threatening and minor) adopted in each study. For example, many differences are found in the various definitions for the decrease in haemoglobin (Hb) level required for a bleed to be considered as ‘major’ (40).

Heterogeneous definitions are frequently observed in the trials assessing the benefits of anti-thrombotic drugs in acute coronary syndromes (ACS), with the TIMI (Thrombolysis in Myocardial Infarction) and GUSTO being the two bleeding definitions most commonly used in trials on ACS (41–51). Different definitions are also used in studies on patients with other clinical conditions (25, 27, 33, 46, 52–58) (see Suppl. Table 1 available online at www.thrombosis-online.com). The Academic Research Consortium has
defined bleeding clinical endpoints in coronary stent trials, as shown in |Suppl. Table 1c (available online at www.thrombosis-online.com) (43).

Most studies focusing on bleeding events in AF patients have used broadly similar definitions for major bleeding, including the following: fatal, bleeding requiring hospitalisation or transfusion of ≥2 units of packed red blood cells, or bleeding with involvement of a critical site (i.e. intracranial, retroperitoneal, intraspinal, intraocular, pericardial, or atraumatic intra-articular haemorrhage) (44, 45).

The subcommittee on control of anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis (ISTH) proposed a definition of bleeding complications in non-surgical patients which was recently revisited (46). Most of the contemporary AF studies have been performed according to this standardised definition. Even the ISTH definition suffers from the inclusion of a wide range of events with variable clinical relevance to the patient, ranging from death or severely life threatening events to 'laboratory indices of bleeding' (2 g/dl Hb drop).

How to interpret major bleeding rates in clinical practice

Clearly, there is a need to record major bleeds in order to assess the safety of a new antithrombotic therapy. However, many of the events that are counted as major bleeds in large trials are clinically less significant: In addition to life-threatening bleeds, events that cause permanent organ damage, and bleeds requiring acute intervention or operation to stabilise the patient, major bleeds also comprise asymptomatic Hb drop of 2 or 3 g/dl combined with a small access site or nasal bleed.

For decision making in clinical practice, it may therefore be helpful to distinguish major bleeding events into clinically relevant major bleeds and clinically less relevant major bleeds. The former would include life-threatening events, symptomatic intracerebral bleeds and other bleeding events resulting in permanent organ damage, and bleeds that require an acute operation to stabilise the patients. Clinically less relevant major bleeds would be less acute events, e.g. an asymptomatic Hb drop associated and bleeding events that result in a temporary cessation of antithrombotic therapy.
2.3 Prognostic implications of bleeding

Despite the varying clinical impact of different subtypes of “major” bleeds, major bleeding events are associated with a greater risk of death for up to one year compared with non-bleeders, at least in patients with ACS.

The adverse prognosis of patients with bleeding events may stem from the critical location of blood loss (intracranial, pericardial, haemothorax) or to the development of haemorrhagic shock, but also from the negative impact of transfusions and from the frequent discontinuation of antithrombotic therapy, with the ensuing enhanced risk of thromboembolic events. In the short term, reduced tissue oxygenation through declining Hb concentrations, increased cardiac work, haemodynamic compromise, and activation of sympathetic, vasoconstrictive and prothrombotic mechanisms may all contribute to adverse outcomes (Table 2).

There may also be unfavourable cluster of baseline characteristics, typical of “high risk” patients; indeed, patients with bleeding events are older and with more comorbidities (e.g. renal failure, hypertension, history of prior bleed or stroke) compared to non-bleeders (59). Not surprisingly, the baseline features of patients who bleed largely overlap with those of individuals at high risk of thromboembolic events, thereby denoting a general condition of vascular frailty. Intracranial and spontaneous bleeds carry worse prognosis than procedure-related or extracranial bleeds (59).

2.4 Established bleeding risk factors

Important determinants of bleeding risk include intensity of anticoagulation, management modality and patient characteristics (Table 3). Drug compliance and maintenance of a therapeutic INR range are other considerations.

| Table 2: Factors by which bleeding may negatively impact short- and long-term outcome. |
|---------------------------------|-------------------------------------------------|
| **Short, mid and long term prognosis** | **Short and mid term prognosis** |
| Accumulation of risk factors for cardiovascular events in patients with bleeding events | Critical location, e.g. intracranial, pericardial, haemothorax |
| | Impaired tissue perfusion, e.g. by hypotension, shock, hypoxemia |
| | Withdrawal of antithrombotic agents, with resultant increased risk of ischaemic complications |
| | Activation of sympathetic, vasoconstrictive and prothrombotic mechanisms |
| | Increased cardiac work through increased heart rate and output |
| | Negative impact of transfusions, especially of older blood |
| | Prolonged hospitalisation and bed rest, with increased risk of venous thromboembolism |

**Age**

Older age, in the majority of studies, has been shown to increase the risk of major haemorrhage. Elderly patients have a two-fold increased risk of bleeding (36), and the relative risk of ICH was 2.5 (95% confidence interval [CI] 2.3–9.4) at age >85 years compared to patients 70–74 years old (37). In the AFFIRM trial (Atrial Fibrillation Follow-up Investigation of Rhythm Management), the risk of major bleeding increased by approximately 5% per year of age (18).

**INR range**

The most important risk factor for haemorrhage is the intensity of the anticoagulant effect (Table 3) (37). Studies indicate that with a target INR of >3.0 the incidence of major bleeding is twice as high as in studies with a target INR of 2.0–3.0, at least in some patient groups (52, 60). In patients with prosthetic heart valves, a lower INR target range resulted in a lower frequency of major bleeding and ICH (61). One retrospective analysis of outpatients using warfarin who presented with ICH found that the risk of ICH doubled for each 1 unit increment of the INR (62). Not only the target INR but also the actual individual INR is strongly associated with the risk of bleeding (63).

Anticoagulation control is an important consideration. Among individuals randomised to warfarin in the SPORTIF (Stroke Prevention Using an Oral Direct Thrombin Inhibitor in Atrial Fibrillation) trials, those with Time spent in the therapeutic range (TTR) less than 60% experienced higher rates of major haemorrhage compared to those with TTR greater than 75%, 3.85%/year versus 1.58%/year, p<0.01 (64). A similar trend was found in the ACTIVE W (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events) (65).

Structured and well-organised management in specialised anticoagulation clinics, results in higher proportions of patients in the therapeutic target range (66). Point-of-care testing as well as patient self-management did not improve TTR compared with conventional care in one recent large trial (67). Careful INR monitoring by experienced personnel, e.g. in anticoagulation clinics, results in similar rates of bleeding and thrombosis as self-monitoring (66, 68).

**Genetic factors affecting VKA metabolism and their antithrombotic effect**

Genetic factors have been identified that may affect the risk of bleeding. Common polymorphisms in the cytochrome (CYP) P450 2C9 gene were found to be associated with slow metabolism of VIKAs and (possibly) a higher risk of bleeding (69). Other genetic factors that may influence the requirement of VKA are variants in the vitamin K epoxide reductase complex subunit 1 gene (VKORC1) (70).

Indeed, the combined analysis of VKORC1, CYP2C9 SNPs, and age may account for more than 50% of the individual variability in the warfarin maintenance dosage, and based on this, prediction...
models of warfarin maintenance dosage taking into account these individual parameters have been developed (71). Nonetheless, the clinical relevance of these genetic polymorphisms is still controversial.

Comorbidities including uncontrolled hypertension, hepatic and renal insufficiency

History of bleeding and anaemia are risk factors for subsequent bleeding, being part of various bleeding risk prediction models (see later in the manuscript).

Prior stroke is a potent risk factor for thromboembolic stroke in AF, but it is also a risk factor for ICH. Systolic blood pressure of 140 mmHg or greater has been shown to increase the risk of both haemorrhagic and ischaemic stroke among patients with AF (44, 45, 72). A case-control study in 1,986 patients on VKA showed that renal impairment and hepatic disease each independently more than doubled the risk of bleeding (73). These associations were confirmed in the AFFIRM study, in which hepatic or renal disease conferred a twofold increase in risk (hazard ratio, 1.93; 95% CI, 1.27–2.93); these investigators also found heart failure and diabetes to increase bleeding risk, with hazard ratios of 1.43 and 1.44, respectively (18). However, diabetes has been a less consistent risk factor for bleeding in other overviews (44, 45).

Concomitant medications

The use of concomitant medications, especially antiplatelet drugs, may increase bleeding. Two meta-analyses, comprising 6 trials with a total of 3,874 patients and 10 trials with a total of 5,938 patients, found a relative risk of major bleeding when VKA were combined with aspirin of 2.4 (95% CI 1.2–4.8) and 2.5 (95% CI 1.7–3.7), respectively (74, 75). One nationwide cohort study confirmed the high risk of upper gastro-intestinal bleeding in patients using VKA in combination with aspirin and/or clopidogrel (76, 77). Non-steroidal anti-inflammatory agents (NSAIDs) and alcohol abuse are also associated with an enhanced risk of gastro-intestinal bleeding. The combined use of VKA and NSAID may result in bleeding as compared to the general population (77–79). This risk is not significantly lower when using selective inhibitors of cyclooxygenase (COX)-2 (78, 79).

The patient’s frailty is an important consideration, and biological age rather than calendar age is perhaps a better associate of bleeding risk. Falls may be overstated as a risk factor for bleeding, and based on a Markov decision analysis model, a patient with AF would need to fall 295 times per year for the benefits of stroke prevention with warfarin to be outweighed by the risk of ICH (80).

Implications for clinical practice

Trial data for bleeding may not be representative of the ‘real world’ situation. In the six pivotal trials that demonstrated the superiority of warfarin over placebo in the prevention of thromboembolic complications in patients with AF, 28,787 patients were screened but only 12.6% of these patients were included in the study (81). As many patients were not included in the clinical trials may have a major impact on the external validity of these trials, in particular regarding safety (81).

Recent trials of stroke prevention in AF have reported rates of major haemorrhage of 3%/year among patients randomised to warfarin (20, 22). Bleeding rates have not differed markedly between open and double-blind trials (81). Rates as high as 7% have been reported in the first year of warfarin therapy among unscreened patients with AF in routine practice, especially in the elderly (28). Indeed, warfarin-naïve patients may carry a higher risk for severe bleeding events than other patients.

Systematic reviews (44, 45) have concluded that the following patient characteristics had supporting evidence for being risk factors for anticoagulation-related bleeding complications in AF patients: advanced age, uncontrolled hypertension, history of myocardial infarction or ischaemic heart disease, cerebrovascular disease, anaemia or a history of bleeding, and the concomitant use of other drugs such as antiplatelet agents. The presence of diabetes mellitus, controlled hypertension and gender were not identified as significant risk factors.

Appreciation of bleeding risk factors will help to inform decision making and will also identify higher risk patients for whom management strategies to mitigate bleeding risk should be implemented, for example, by correcting reversible risk factors for bleeding (e.g. uncontrolled blood pressure).

Table 3: Factors affecting bleeding risk when using oral anticoagulant therapy.

<table>
<thead>
<tr>
<th>Intensity of anticoagulation</th>
<th>Management modality</th>
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<tbody>
<tr>
<td>Patient characteristics</td>
<td></td>
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<tr>
<td>age</td>
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<tr>
<td>genetics (may also be assessed by the INR response in the initial period of VKA therapy initiation)</td>
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<tr>
<td>prior stroke</td>
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<tr>
<td>history of bleeding</td>
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<tr>
<td>anaemia</td>
<td></td>
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<tr>
<td>co-morbidity (hypertension, renal insufficiency, liver disease)</td>
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<tr>
<td>Use of concomitant medication or alcohol</td>
<td></td>
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<tr>
<td>antiplatelet agents</td>
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<tr>
<td>NSAIDs</td>
<td></td>
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<tr>
<td>medication that affects the intensity of anticoagulation</td>
<td></td>
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<tr>
<td>alcohol abuse</td>
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2.6 Bleeding risk stratification and current published bleeding risk schema

Several distinctive clinical prediction rules have been proposed for assessment of the individual risk for bleeding during OAC in patients with AF, based on combination of treatment- and person-associated factors, which may help physicians evaluate the individual risk/benefit ratio of antithrombotic therapy. The characteristics of the available clinical prediction rules specifically addressing AF patients are reported in Table 4 (27, 56, 57, 82, 83).

The modified Outpatient Bleeding Risk Index (mOBRI) (27) has been prospectively derived and validated in patients with different indications for OAC, including AF patients. Another strength of the mOBRI schema was the blinded assessment of bleeding (27). In addition, the settings of anticoagulation control were the primary care physician (27) or a pharmacist-run anticoagulation clinic (55), demonstrating derivation and validation in 'real-life' AF patients.

Whilst all of the clinical prediction rules include age as a risk factor for bleeding, different schemes employ a different cut-off. In the mOBRI (27), age ≥65 years scores one point. Given the advanced age of most AF patients, the majority of the evaluated patients would be attributed at least to the intermediate-risk classification (1–2 points) using the mOBRI, that in the validation cohort (27) was associated with an incidence of major bleeding of 5%, 8% and 12% after three, 12 and 48 months of treatment, respectively. In the independent validation of the mOBRI among elderly AF patients by Aspinall et al. (55), the mOBRI discriminated significantly (p<0.001) between those in the intermediate- and high-risk categories for major bleeding.

The remaining prediction schemas have a retrospective design, based on the review of data from the National Registry of Atrial Fibrillation (56), the same Registry plus Medicare data (57), the Euro Heart Survey cohort (82) and the Anticoagulation and Risk factors in Atrial fibrillation (ATRIA) study (83). The retrospective design of these schemes would be a limitation of their validity since a potential loss of patients with complications in early phase of treatment cannot be excluded.

The HEMORR\_HAGES score (56) considers age >75 years as a condition at risk, also includes factors, such as CYP2C9 single nucleotide polymorphism, that is rarely investigated, while important factors, such as antiplatelet treatment or other co-medication are not included. The rate of patients at high risk of bleeding was 12.0%. The cumulative incidence of major bleeding by risk category in the validation cohort was 2.1%, 5.0% and 8.8% patient-years in the low, intermediate and high risk categories, respectively. The schema by Shireman et al. (57) incorporates eight risk factors for bleeding, including female gender and an antiplatelet treatment, as well as age. There was a relatively short (90 days) follow-up period and the rate of patients at a high risk was very low (3.4%). This schema requires a complex mathematical calculation to derive the individual patient bleeding risk score, thereby limiting its applicability. In general, some important factors related to bleeding risk, such as poor quality anticoagulation control and the presence of NSAID as concomitant medication (44, 45), have not been included in some of the aforementioned schemas. Reliable ascertainment of aspirin therapy given its non-prescription status is problematic. Moreover, no blinded outcome assessment was conducted and no indication of the setting of anticoagulation control was provided in either the HEMORR\_HAGES (56) or Shireman (57) studies.

More recently a new clinical prediction rule for bleeding risk evaluation in AF patients, HAS-BLED, has been proposed by Pisters et al. (82). The HAS-BLED score demonstrated a good predictive accuracy in the overall cohort (c-statistic 0.72), but performed particularly well in predicting bleeding risk when only antiplatelet therapy (c-statistic 0.91), or no antithrombotic therapy at all (c-statistic 0.85) were used. In the SPORTIF III and V cohorts, the HAS-BLED score was a modest predictor of bleeding events among warfarin-naïve patients at baseline (c-statistic 0.66) and in patients receiving warfarin plus aspirin (c-statistic 0.60) [84]. The HAS-BLED score has also been validated in a large ‘real world’ nationwide cohort study, with c-statistics nearing 0.8 indicating good predictive value for the HAS-BLED score (85), and has been incorporated into the 2010 ESC guidelines for the management of AF (2) and the Canadian guidelines (86). The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) score (83) was derived from a cohort of prevalent warfarin users with AF who were randomly divided into a split-sample derivation and validation cohort, and led to a weighted score (which contains elements of the HAS-BLED score) that gives 3 points for anaemia (Hb <13 g/dl in men and <12 g/dl in women), 3 points for severe renal disease (defined as glomerular filtration rate <30 ml/min or dialysis dependent), 2 points for age ≥75 and 1 point each for prior bleeding and hypertension. Thus, this score essentially includes similar components as other scores discussed above, but assigns a weight to the various risk factors (thus, making it more complicated). The c-statistic for the continuous risk score was 0.74, but on collapsing points into a three-category risk index, the annual major haemorrhage rate was 0.8% in the low risk group (0–3 points), 2.6% in medium risk (4 points), and 5.8% in high risk (5–10 points). Limitations are the non-inclusion within the score of uncontrolled blood pressure or concomitant medications (e.g. antiplatelet drugs and NSAID) known to increase bleeding risk with warfarin and its derivation from a selected cohort of prevalent warfarin users.

In summary, the available published bleeding risk prediction rules demonstrate wide differences in the risk factors comprising each schema. Despite the limitations of the available bleeding risk schema, they do offer a starting point for physicians to consider bleeding when initiating and/or continuing long-term oral anticoagulation in AF patients, and this Task Force recommends use of the HAS-BLED score, in keeping with international guideline recommendations (2, 86).
### Table 4: Published bleeding risk prediction schemas for patients with atrial fibrillation.

<table>
<thead>
<tr>
<th>Schema, acronym, author</th>
<th>Ref.</th>
<th>Population</th>
<th>Definition of major bleeding Event adjudication</th>
<th>Calculation of risk score</th>
<th>Bleeding risk classification n (%) patients in each risk category</th>
<th>Major bleeding events by risk category in validation cohort, n (%)</th>
<th>Validated in other cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOBRi Beyth 1998</td>
<td>27</td>
<td>a Prospective inception cohort b Derivation- n=556, 61 (14); 46.6% Validation-n=264, 60 (16); 47.3% c Derivation- Post-op cardiac surgery, mitral valve disease, AF, stroke, TIA, PE, DVT, or other thromboembolism Validation- VTE &amp; cardiac surgery d 4 years</td>
<td>Overt bleeding that resulted in the loss of ≥2.0 units in ≤7 days, or was otherwise life-threatening Blinded event adjudication, unaware of bleeding risk factors</td>
<td>Age ≥65 years, previous stroke, GI bleed in last two weeks, ≥1 of the following comorbidities [recent MI, haematocrit &lt;30%, creatinine &gt;1.5 mg/dl, or diabetes mellitus] with 1 point for presence of each risk factor and 0 if absent</td>
<td>Low: 0 Intermediate: 1–2 High: ≥3 Derivation</td>
<td>Low: 0 Intermediate: 80 (30.3) Validation Intermediate: 166 (62.9) High: 18 (6.8)</td>
<td>Cumulative incidence of major bleeding (95% CI) at 3/12/48 months Low: 1 (0–4)/3 (0–8) Intermediate: 5 (1–8)/8 (3–12) High: 6 (0–17)/30 (0–62)/53 (11–97)</td>
</tr>
<tr>
<td>HEMORRHAGES Gage 2006</td>
<td>56</td>
<td>a Prospective inception cohort b Derivation- n=2971, 80.2 (t); 43% AF c 3,138 pt-years Bleeding risk factors for schema identified by adaptation of 3 existing bleeding risk schema [mOBRi, SBRPS, plus bleeding risk factors identified in literature [Beyth et al, 2002 [27]]</td>
<td>ICD-9-CM codes for major bleeds except those unrelated to antithrombotic therapy †</td>
<td>Hepatic or renal disease, Ethanol abuse, Malignancy, Older (aged &gt;75), Reduced platelet count, Uncontrolled bleeding risk, , uncontrolled Hypertension, Anaemia, Genetic factors (CYP 2C9 single nucleotide polymorphisms), Excessive fall risk, Previous Stroke/TIA, 1 point for each risk factor present, &amp; 2 points for previous bleed</td>
<td>Low: 0–1 Intermediate: 2–3 High: ≥4 Among those on warfarin (n=1604) Low: 717 (44.7%) Intermediate: 694 (43.3%) High: 193 (12.0%)</td>
<td>Low: 15 (2.1%) Intermediate: 35 (5.0%) High: 17 (8.8%)</td>
<td></td>
</tr>
<tr>
<td>Shireman 2006</td>
<td>57</td>
<td>a Retrospective chart review of NRAF cohort b Derivation- n=19 875, ≥65 years; 47.5% Validation- n=6511, ≥65 years; 46.9% AF c 3 months</td>
<td>Hospitalisation within 90 days of hospital discharge following index AF for GI haemorrhage (diagnosis-related group code 174 or 175) or intracranial haemorrhage (ICD-9 430–432) †</td>
<td>[0.49 x age ≥70] + [0.32 x female gender] + [0.58 x remote bleed] + [0.62 x recent bleed] + [0.71 x alcohol/drug abuse] + [0.27 x diabetes] + [0.86 x anaemia] + [0.32 x antplatelet] with 1 point for the presence of each condition and 0 if absent</td>
<td>Low: ≤1.07 Intermediate: &gt;1.07 to &lt;2.19 High: ≥2.19 Low: 3889 (59.7%) Intermediate: 2400 (36.9%) High: 222 (3.4%)</td>
<td>Low: 35 (0.9%) Intermediate: 48 (2.0%) High: 12 (5.4%)</td>
<td></td>
</tr>
<tr>
<td>HAS-BLED Pisters 2010</td>
<td>82</td>
<td>a Retrospective analysis of Euro Heart Survey cohort b Derivation- n=3978 Validation- n=3071, 66.8 (12.8); 59% male AF patients d 12 months Bleeding risk factors drawn from Euro Heart Survey cohort and ‘historic’ bleeding risk factors (OAC, alcohol use &amp; hypertension)</td>
<td>Requiring hospitalisation &amp;/or causing drop of Hb ≥2g/l, need for blood transfusion that was not a haemorrhagic stroke †</td>
<td>Hypertension (uncontrolled SBP &gt;160 mm Hg), Abnormal renal &amp;/or liver function, Stroke, Bleeding history, Labile INR, Elderly (age ≥65 years), Drugs (antiplatelets/NSAIDS)/concomitant alcohol (≥8units/week), with 1 point for the presence of each risk factor [maximum of 9 points]</td>
<td>Low: 0–1 Intermediate: 2 High: ≥3 Low: 2084 (67.9%) Intermediate: 744 (24.2%) High: 243 (7.9%)</td>
<td>Low: 22 (1.1%) Intermediate: 14 (1.9%) High: 12 (4.9%)</td>
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</table>
2.7 Patient values and preferences

Patients' beliefs about their health, the medications and healthcare they receive are important determinants of whether or not they accept recommended treatments and adhere to therapy. Patients often have perceptions about VKA, including the inconvenience of dosing adjustments, the need for daily medication and regular blood tests to monitor INR levels, reduction/abstinence from alcohol, dietary restrictions, the risk of minor and major bleeding, and under-appreciation or lack of knowledge regarding the risk of stroke which may influence their acceptance of warfarin and their ability to maintain good INR control (87–89). On the other hand, patients may feel protected by taking VKA. Thus, patients' preferences and their beliefs about their health are fundamental in determining whether anticoagulant treatment, particularly with warfarin, is adopted in the first place and maintained long-term. Changes in health-care policy emphasise the need to achieve, and benefits of, patient involvement in the management of their own health (90) and incorporation of patients' preferences for anti-thrombotic therapy should be considered in the decision-making process.

To date, various studies have examined patient preferences for antithrombotic therapy in AF patients (91–101) and in patients at high risk of developing AF (102–106), although one study has yet to report its results (106) [►Suppl. Table 2 available online at www.thrombosis-online.com]. A variety of decision aids, such as audio-booklets, decision boards and interactive videos/computer programs have been designed to enable patients to participate in the decision-making process with regard to their antithrombotic therapy, to ensure that treatment choices are consistent with their personal preferences, values, and beliefs. These decision aids provide written, visual and verbal information on the likelihood of clinically important outcomes, such as stroke and major haemorrhage associated with antithrombotic therapy, present the treatment options (currently warfarin, aspirin, or no antithrombotic therapy), and ask patients to indicate their treatment choice (for full details, see full version of this document [10]).

Patients appear to trade off the risks associated with antithrombotic treatment in order to avoid death (105, 107). Overall, these studies appear to suggest that patients place greater emphasis on avoidance of stroke and are willing to accept a higher risk of bleeding to achieve this, although this may represent a lack of patient understanding of the disability associated with major bleeding, particularly ICH. However, it is hard to draw firm conclusions from the available studies as the sample sizes are often small, typically ≤100 patients, and there is significant heterogeneity between the studies (methods employed to elicit preferences, patients' education, risks employed; inclusion of AF patients and those without AF etc.).

Further studies need to elicit patient preferences for antithrombotic treatment in warfarin-naïve AF patients, with and without previous stroke, to remove these potential biases. In addition, perceptions of risk can be altered by the way in which information is presented. There is also tremendous disparity in perceptions of the impact of warfarin therapy on the lives of AF patients which may influence the acceptance of such therapy, with many physicians...
tending to underestimate the level of patient’s satisfaction (108), whereas most patients report that warfarin did not precipitate any significant changes in their day-to-day lives other than minor inconveniences (such as regular blood tests, adjusting warfarin dose, and dietary restrictions) which they are willing to accept.

In summary, patients’ preferences for antithrombotic treatment are largely influenced by the type and format of information provided to the patient by the care provider, their level of education and understanding of the consequences of such treatment, and their previous experiences of antithrombotic therapy. Stroke is the most feared complication which patients wish to avoid (described as a ‘fate worse than death’) but bleeding risk with treatment attenuates the proportion of patients willing to take antithrombotic therapy. Patients need clear, simple, and individualised information on their need for antithrombotic therapy and the potential complications.

2.8 Special situations with additional bleeding risk considerations

Various situations can have important bleeding risk considerations in patients with AF, for example, ablation, devices (implantable cardioverter defibrillator [ICDs], pacemakers), percutaneous coronary interventions (PCI)/stenting, surgical procedures/bridging, etc – for full details, please see full version of this document (10).

Ablation

Catheter ablation carries a small but relevant risk of severe bleeding, associated with vascular access – often with relatively large diameter sheaths - and peri-interventional anticoagulation, increasing when ablation is performed in the left atrium or left ventricle. Interestingly, bleeding events do not appear to be related to peri-procedural antithrombotic therapy (aspirin, VKA, or other). Indeed, bleeding events during or shortly after catheter ablation procedures are largely due to mechanical factors such as vascular access, transseptal puncture, and the ablation lesions themselves. Catheter ablation for AF combines the difficulties related to bleeding (from transseptal puncture, requirement for anticoagulation in many patients) and stroke risk (left atrial lesions, long periods with foreign material in the left atrium, often long endocardial lesions in already diseased atria). The stroke and transient ischaemic attack (TIA) rate is approximately 1% in recent surveys, while bleeding events occur at around 1% for cardiac tamponade and 1–2% for access site bleeds (109, 110). To avoid bleeding complications and to allow rapid adaptation of antithrombotic regimens, a consensus document from EHRA in 2008 recommended stopping warfarin 4–5 days before the ablation procedure and bridging with heparin (110). More recently, uninterrupted OAC is a potential alternative to strategies that use bridging with heparin or low-molecular-weight heparin (LMWH) (111, 112). In summary, recent data suggest that continuation of OAC during catheter ablation procedures for AF may be safe with respect to bleeding events, and help to prevent peri-procedural strokes.

Most guidelines recommend continued anticoagulant therapy for 2–3 months following an AF ablation in all patients regardless of stroke risk factors (2). The optimal duration of this therapy has not been clearly established. Owing to the risk of relapse, the EHRA and ESC guidelines recommend that anticoagulation should be continued long-term as per original indication in subjects with stroke risk factors (2, 113). This is in line with current recommendations for AF and with the observation that AF tends to recur in many patients, including late recurrences in patients after AF ablation.

Peri-devices (ICDs, pacemakers)

It may be necessary to interrupt oral anticoagulant therapy for elective implantation or replacement of a pacemaker or an ICD, although smaller procedures can often be performed without interrupting anticoagulation. In patients with mechanical prosthetic heart valves, it may be appropriate to substitute unfractionated heparin (UFH) or LMWH to prevent thrombosis (114). In patients with AF who do not have mechanical valves, however, based on extrapolation from the annual rate of thromboembolism in patients with non-valvular AF, it was the consensus of the Task Force for the 2010 ESC guidelines that anticoagulation may be interrupted temporarily for procedures that carry a risk of bleeding, such as ICD or pacemaker implantation, without substituting heparin (2). In high-risk patients (particularly those with prior stroke, TIA, or systemic embolism), UFH or LMWH may be administered. In the 2008 ACCP guidelines (114), bridging is “suggested” for patients with CHADS2 score of 3 or 4 (considered at moderate risk of thromboembolism after interruption of antithrombotic therapy) and “recommmended” for those with CHADS2 score of 5 or 6 (considered at high risk, i.e., >10% risk per year). It is possible that such operations can in part be performed without interruption of anticoagulation, as for vascular procedures.

In a systematic review of the literature including eight studies on the perioperative management of anticoagulation in patients having implantation of a pacemaker or ICD, a strategy involving bridging anticoagulation with therapeutic-dose heparin was associated with an incidence of pocket haematoma of 12–20%, while a strategy involving perioperative continuation of a coumarin was associated with an incidence of pocket bleeding of 2–7% (115). The incidence of thromboembolic events was 0–1%, irrespective of the perioperative anticoagulation strategy used. In a prospective randomised study including patients with high risk of thromboembolic events in whom 80% had AF, implant of devices while maintaining OAC was as safe as bridging with heparin infusion and allowed a significant reduction of in-hospital stay (116). When drainage systems are used, device implantation appears to be safe and performed without significantly increased risk of clinically relevant haematoma.

Thus, it has been recommended that for such implantations treatment be interrupted pre-operatively and replaced by heparin only if needed (2). If that is not feasible and implantation must be
performed under anticoagulant (whether maintaining OAC or bridging with heparin) and/or antiplatelet therapy (see section Patients with ACS and/or requiring PCI/stents), the procedure should be carried out by an experienced operator who will pay close attention to haemostasis.

ACS and coronary angiography/intervention

Several factors associated with coronary angiography or PCI bear an increased bleeding risk in AF patients with a need for oral anticoagulation (for a detailed review see [117]). These include: “triple therapy” using an oral anticoagulant and dual platelet inhibition, most often aspirin and clopidogrel; factors prolonging the duration of combined antithrombotic therapy [e.g. use of drug-eluting stents (DES)]; oral anticoagulation, when compared to non-anticoagulated patients; additional use of a GPIIb/IIIa inhibitor (GPI, e.g. in bailout situations in elective patients or in very high-risk ACS patients); left main or three-vessel disease; older age (e.g. >75 years); female gender; smoking; chronic kidney disease; and high INR value (> 2.6).

Some measures have been undertaken to reduce this increased bleeding risk: radial instead of femoral access was associated with less access site bleeding events in “all-comers” (118, 119). The use of femoral closure devices, although believed to reduce bleeding risk compared to manual compression, was not associated with reduced bleeding events (120).

Due to lack of prospective randomised investigations in this field, a group of European and North American experts recently published recommendations (117, 121), which in the majority are level C, i.e. largely based on expert opinion. The recommendations can be summarised as follows: (i) avoid the use of DES for patients who require triple antithrombotic therapy; (ii) when OAC is given in combination with clopidogrel and/or low-dose aspirin, the intensity must be carefully regulated, with a target INR of 2.0–2.5; and (iii) in case of combined antithrombotic strategies, gastric protection is recommended at least for the duration of combination therapy (122).

2.9 Managing bleeding complications

Management of bleeding consists of measures to preserve adequate circulation, local control (e.g. endoscopic treatment or surgical haemostasis), and proper transfusion procedures. If serious bleeding occurs in a VKA user it may be necessary to reverse the anticoagulant effect of the agent. When interrupting the administration of VKA important differences in the half-lives of the various agents (9 hours for acenocoumarol, 36–42 hours for warfarin, and 90 hours for phenprocoumon, respectively) need to be taken into account (123). There is debate over the best management strategy when a patient on VKA bleeds, given the competing concern for thromboembolic risk. Adequacy of haemostasis and duration of VKA interruption would vary with different patient scenarios (123).

The most straightforward intervention to counteract the effect of VKA is the administration of vitamin K (124–126). There is some debate on the need for vitamin K in the management of a patient with a very high INR but no signs of bleeding. A recent randomised controlled trial did not find any difference in bleeding or other complications in non-bleeding patients with INR values of 4.5 to 10 that were treated with vitamin K or placebo (127, 128). In patients with clinically significant bleeding, administration of vitamin K is crucial to reverse the anticoagulant effect of VKA. Vitamin K can be given orally and intravenously, but the parenteral route has the advantage of a more rapid onset of the treatment (128). After the administration of intravenous vitamin K, the INR will start to drop within 2 hours and will be completely normalised within 12–16 hours (127–129). After oral administration it will take up to 24 hours to normalise the INR. Intramuscular injections of vitamin K should be avoided in patients who are anticoagulated and subcutaneous administration of vitamin K results in a less predictable bioavailability.

When the INR is below 7, a dose range of 2.5–5 mg vitamin K has been advocated, whereas a dose of 5 to 10 mg may be required to correct higher INR. Higher doses of vitamin K are equally effective but may lead to VKA resistance for more than a week, which may hamper long-term management (129).

In case of very serious or even life-threatening bleeding, immediate correction of the INR is essential and can be achieved by the administration of vitamin K-dependent coagulation factors. Theoretically, these factors are present in fresh frozen plasma; however, the amount of plasma that is required to correct the INR is very large, carries the risk of fluid overload, and will probably take hours to administer (130). Therefore, prothrombin complex concentrates (PCCs), most of which containing all vitamin K-dependent coagulation factors, are more useful, and individualised dosing regimens based on INR at presentation and body weight are more effective (131–133). The risk of disseminated intravascular coagulation (DIC) due to traces of activated coagulation factors in PCCs comes from older literature and modern PCCs are not associated with precipitating DIC (134).

3. Left atrial appendage closure

A substantial number of patients eligible for OAC will suffer bleeding complications that may be potentially life-threatening. Patients at high risk of embolic stroke, but with contraindications for OAC are in a need of an alternative strategy that is not associated with long-term bleeding risk. This is particularly true for those after an ICH.

Surgical closure of the left atrial appendage (LAA) has been practiced, and indeed, current guidelines suggest obliteration of the LAA during mitral valve surgery (135). Currently, excision of the LAA at the time of mitral valve surgery is recommended for reduction of future stroke risk. Exclusion of the LAA during coronary artery bypass graft surgery has also been proposed, but with suboptimal results (136).
A reasonable alternative may be exclusion of the LAA cavity from the circulation, using either surgical or percutaneous catheter-based procedures (137). The WATCHMAN Left Atrial Appendage System for Embolic PROTECTION in Patients With Atrial Fibrillation (PROTECT AF) study was designed to demonstrate safety, efficacy, and non-inferiority of the WATCHMAN device against chronic warfarin therapy in patients with non-valvular AF who are eligible for long-term OAC (138). An important risk of serious procedural complications was observed (e.g. pericardial tamponade) perhaps related to a learning curve of device implantation. This risk appears to taper a bit with increased operator experience (139). Other devices, such as the AMPLATZER double-disk transseptal occluder, are in development. The available data base is not yet sufficient to define the degree of long-term stroke prevention conferred by this technique.

4. A brief perspective on newer anticoagulants

At the time of writing of this summary, the direct thrombin inhibitor dabigatran is approved for clinical use in the US and in Canada, as well as in Europe. The pharmacokinetics of the drug and its apparent safety compared to warfarin render dabigatran a potentially attractive therapeutic option in patients in need for anticoagulation and at risk for bleeding.
At the lower dose tested (110 mg bid) the rate of intracerebral bleeding events was higher in the VKA group in the RELY trial than in the dabigatran group (22). At the higher tested dose (150 mg bid), dabigatran prevented ischaemic strokes more effectively than VKA. Practical approaches to the management of patients on dabigatran have recently been published, as a consensus document of the Italian Federation of Thrombosis Centers (FCSA) (140).

New data on the efficacy and safety of the oral factor Xa inhibitors, rivaroxaban and apixaban, in comparison to warfarin for stroke prevention in AF, as well as information on their clinical pharmacology, are also available (23, 24, 141–143).

In addition to these long-term benefits, the shorter half-life of direct thrombin or factor Xa antagonists compared to VKA suggests that the management of bleeding complications and the anti-thrombotic regimen during operations and invasive procedures could become simpler with those substances than with VKA (144). A remaining concern would still be the lack of a specific antidote for these new drugs. One recent small trial in 12 healthy subjects found that the use of PCC 50 IU/kg (Cofact) immediately and completely reverses the anticoagulant effect seen with rivaroxaban (as measured by prothrombin time, endogenous thrombin potential) but had no influence on the anticoagulant effect of dabigatran (increased the activated partial thromboplastin time, ecarin clotting time (ECT), and thrombin time ) at the PCC dose used in this study (145). Finally, the use of dabigatran peri-ablation appears safe, with no evidence of thromboembolism and bleeding, in one small reported series (146).

Conflict of interest
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