



## Review

## Stroke prevention in atrial fibrillation: State of the art

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## ABSTRACT

Stroke prevention is the cornerstone of the management of patients with atrial fibrillation (AF). Individual stroke risk stratification is generally the first step of deciding whether oral anticoagulation (OAC) will benefit patients with AF. Given that existing approaches to the prediction of 'high-risk' subjects are of limited value, the initial focus should be the identification of 'low-risk' patients who do not need antithrombotic therapy. For this, the CHA<sub>2</sub>DS<sub>2</sub>-VASc score (congestive heart failure, hypertension, age  $\geq$  75 [2 points], diabetes mellitus, previous stroke/transient ischemic attack [2 points], vascular disease, age 65–74, female sex) performs well in identifying really low-risk patients (score of 0 in males or 1 in females), for whom OAC can be omitted.

The approach to AF management has changed, with the non-vitamin K antagonist oral anticoagulants (NOACs) providing relatively better efficacy, safety and convenience compared with the traditional vitamin K antagonists (VKAs). The latter drugs are performing well, if attention is directed towards good quality anticoagulation control, as reflected by a time in therapeutic range (TTR)  $>$ 70%. Nevertheless, OAC use remains suboptimal especially in some regions, such as Asia and Africa. Long-term adherence and quality of OAC use need to be maintained for better outcomes in patients with AF.

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## 1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia, conferring an increased risk of stroke [1]. AF accounts for 15% of all ischemic strokes and 33% of strokes in the elderly [2]. Stroke events resulting from AF are more severe, associated with high risks of morbidity and mortality than those of non-AF etiologies [3]. Therefore, stroke prevention is an essential part of management for patients with AF.

The approach to stroke prevention for AF merits consideration of three steps. First, recognizing those patients at low risk of stroke for whom oral anticoagulation (OAC) can be omitted; second, choosing the right anticoagulant according to patient clinical profile; and third, optimizing the quality of anticoagulation control, especially if vitamin K antagonist (VKA) (e.g. warfarin) is used, and attention to long-term adherence.

Compared to control or placebo, VKA reduces stroke by 64% and all-cause mortality by 26% [4]. In patients using VKA, quality of anticoagulation control is important, and a TTR  $>$  70% should be maintained to improve outcomes [5]. The introduction of the non-vitamin K antagonist anticoagulants (NOACs), including factor II inhibitor,

dabigatran, factor X inhibitors, rivaroxaban, apixaban and edoxaban, has changed the landscape of stroke prevention in AF patients worldwide, offering relatively improved efficacy, safety and convenience compared with the traditional VKAs [6–12].

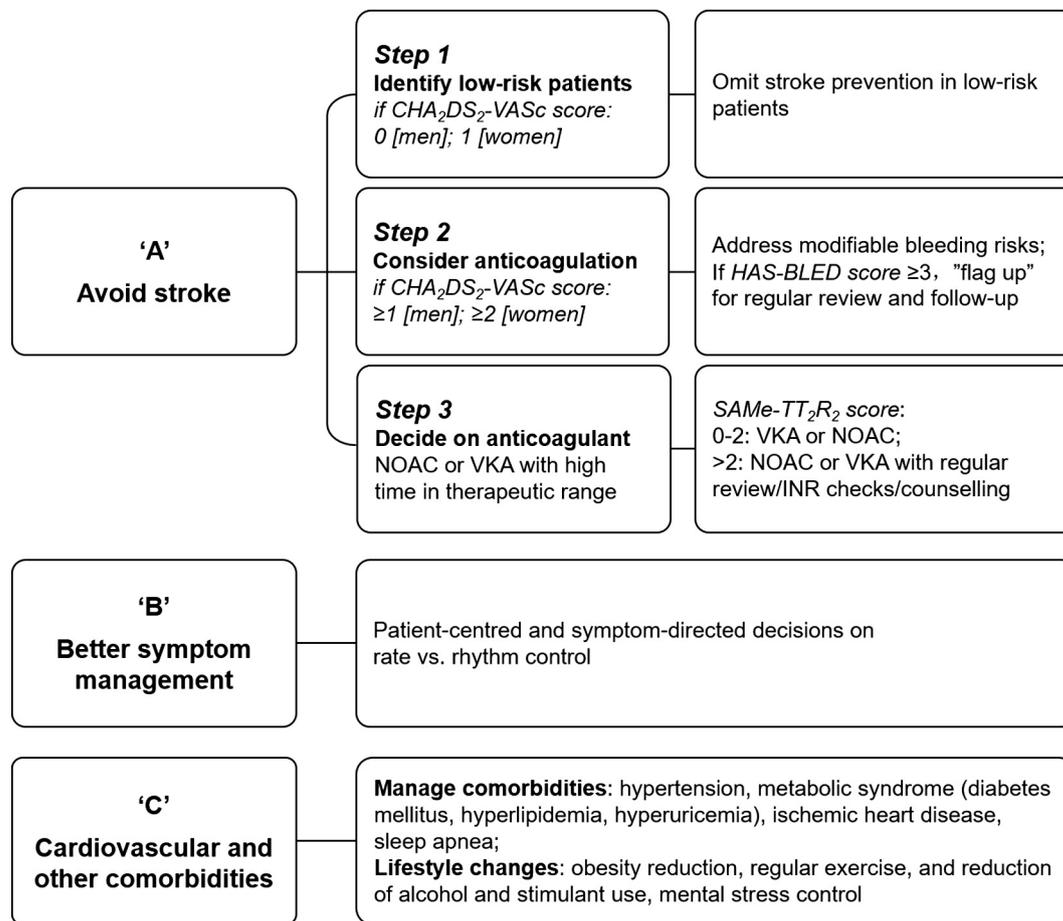
Indeed, all NOACs are associated with a reduced risk for intracranial hemorrhage (ICH), even compared with well-controlled VKAs [13,14]. In addition, NOAC-related bleeding events are less severe, especially for ICH [15]. The use of NOACs is associated with better treatment adherence compared with VKAs [16].

Nevertheless, OAC use remains suboptimal, especially in some regions, such as Asia and Africa. Long-term adherence and quality of OAC use need to be maintained for a better outcome in patients with AF [17]. Significant barriers to OAC use still exist, and fear of bleeding events is the major reason for non-prescription in clinical practice. Indeed, OAC cessation and non-adherence is associated with poor outcomes [18,19]. In general, clinicians have underestimated the benefits and overestimated bleeding risks in OAC use. Of note, aspirin does not reduce the risk of stroke in AF patients, but increases the risk of ICH, leading to a neutral or negative net clinical benefit (NCB) [20].

This narrative review aims to provide an overview of the evidence on stroke prevention for patients with AF. We provide an evidence-based pathway of stroke prevention in AF, signposting risk evaluation, OAC decision-making and anticoagulation quality control, with the

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**Fig. 1.** The “ABC” pathway and “Birmingham 3-step” for AF management and stroke prevention. NOAC = non-vitamin K antagonist anticoagulant; OAC = oral anticoagulant; TTR = time in therapeutic range; VKA = vitamin K antagonist.

aim of providing a simple and holistic approach for stroke prevention and integrated care for patients with AF (Fig. 1).

## 2. Stroke risk stratification and oral anticoagulation decision-making.

Stroke risk stratification is the first step in managing AF patients. The risk of stroke in AF is not homogenous and increases with the presence of more risk factors for stroke. Given that most patients with AF are at risk of stroke, initially ruling out those who are ‘low-risk’ would be a more effective way to direct stroke prevention, following which OAC can be offered to all patients with  $\geq 1$  non-gender stroke risk factors [21].

Patients with low risk of stroke are those with the CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 0 in males or 1 in females [22]. In guidelines, patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 2$  in males or  $\geq 3$  in females are given a strong recommendation for OAC [23], while for patients with a single non-gender stroke risk factor (i.e. CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1 in males or 2 in females), stroke risks may vary with a particular risk factor. Overall, the use of OAC should still be considered given the positive net clinical benefit (NCB) in such ‘medium-risk’ patients [20,24–31]. In general, the tipping point for obtaining an NCB is a stroke threshold of 1.7%/year for VKA, and 0.9% for the NOACs [32].

As mentioned, for a single risk factor with same points, the stroke risk could be different. For example, AF patients at age of 65 and those at 74 have the same assigned 1 point for age, but the stroke risks are clearly different. Patients’ stroke risk is continuous, while a score-based cutoff value is made arbitrary to facilitate simplicity and clinical practicality. Thus, some individualization is needed, for example, for an AF patient at

64 years and borderline hypertension (e.g. 139/80 mm Hg) or a pre-diabetic stage, the increased stroke risk would best trigger OAC indication.

In the real-world setting, the stroke risk of patients with AF is not static. Increasing age, different blood pressure control, status of heart failure and incident risk factors would all contribute to a dynamic change in stroke risk. Thus, a patient without an identified stroke risk factor at baseline may need OAC during follow-up. Baseline risk assessment, even using the CHA<sub>2</sub>DS<sub>2</sub>-VASc score, may not necessarily relate to stroke risk in five or ten years later. For example, Chao et al. studied 31,039 patients from Asia, and found the mean CHA<sub>2</sub>DS<sub>2</sub>-VASc score increased from 1.29 at baseline to 2.31 during follow-up [33]. The change in risk (i.e. ‘delta CHA<sub>2</sub>DS<sub>2</sub>-VASc’) had predictivity for stroke events compared with baseline or follow-up CHA<sub>2</sub>DS<sub>2</sub>-VASc scores [33]. Therefore, regular review and reassessment of stroke risk is recommended in recent guidelines given the dynamic nature of stroke risk [34].

Age  $\geq 65$  is a risk factor for stroke, but this age threshold has been derived from Western populations. Nevertheless, Asian populations have relatively lower age threshold for an increased stroke risk [35]. In a cohort study from Taiwan ( $n = 186,570$ ), for example, patients could be further stratified into 2 subgroups with different stroke risk (>50 years of age: 1.78%/year vs. <50 years of age: 0.53%/year) [35]. Thus, age 50 to 74 years has been proposed with 1 point in the modified CHA<sub>2</sub>DS<sub>2</sub>-VASc score [36].

A recent study using three nationwide registries including 239,671 AF patients demonstrated that sex category (i.e. female sex) in the CHA<sub>2</sub>DS<sub>2</sub>-VASc score is a risk modifier rather than a risk factor [37]. Females exhibit a higher stroke risk with significant interaction with other risk factors, whereby females have a higher risk than males at age  $\geq 65$  or with  $\geq 1$  other risk factors [37].

### 2.1. Beyond clinical risk stratification with established risk scores.

There are several biomarker-based scoring systems proposed to predict stroke and/or systemic embolism (SE) in patients with AF [38–40]. These scoring systems have included biomarkers based on blood tests or cardiac imaging, and have marginally better c-indexes compared with the CHA<sub>2</sub>DS<sub>2</sub>-VASc score. Nevertheless, scoring systems which need laboratory tests would reduce the convenience of a swift stroke risk evaluation in busy clinical settings, and delayed biomarker reading may defer OAC initiation. Also, significant heterogeneity of these biomarkers between populations and laboratory variability may make it difficult to define a cut-off value, especially since many of the studies proposing these biomarker-based scores were from highly selected anticoagulated clinical trial cohorts. Also, using a baseline biomarker level to predict stroke events years later may be unreasonable, given that patients get older and acquire incident risk factors. Second, some biomarkers, such as brain natriuretic peptide, are highly dependent on the patient's clinical situation, e.g. infection, water-sodium retention, etc.

Current risk scores do not consider AF subtypes, i.e., paroxysmal AF, persistent AF, permanent AF, as prior studies show that stroke risk is dependent on underlying risk factors rather than the arrhythmia subtype [21,41–43]. Nevertheless, persistent AF may contribute higher stroke risk compared with paroxysmal AF [44,45]. Indeed, in the non-anticoagulated AF patients, AF pattern was the second strongest predictor after prior stroke or transient ischemic attack (TIA) with an 83% and 44% increased risk for permanent and persistent AF compared with paroxysmal AF [45].

Furthermore, subclinical AF (SCAF) is associated with an increased stroke risk in patients with cardiac implantable electronic device (CIED). For example, in the Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT) trial ( $n = 2580$ ), SCAF duration >24 h was associated with a significant increased risk of subsequent stroke or SE (hazard ratio [HR] 3.24, [1.51–6.95]) [46]. A large analysis from the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE-A) and Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trials suggested a clear gradient of increasing risk of stroke/SE from paroxysmal to persistent to permanent AF, whereby the annualized ischemic stroke rates were 2.1%, 3.0% and 4.2% respectively, with a HR of 1.83 (1.43–2.35) for permanent vs. paroxysmal AF and a HR of 1.44 (1.05–1.98) for persistent vs. paroxysmal AF [45]. However, we are dealing with wide heterogeneity and variability here, as an individual patient may have a short paroxysm during one monitoring period, but get a very long period of AF (or SCAF) in the next monitoring period.

AF occurring transiently with stress (AFOTS) presents frequently in the setting of acute illness, between 4% and 44% [47], and patients with AFOTS have an AF recurrence rate of 42% at 5 years [48]. In one study ( $n = 1409$ ), stroke risk (HR, 1.13 [0.82–1.57]) did not differ between patients with AFOTS and those with incident paroxysmal AF [48]. A large retrospective cohort study ( $n = 48,484$ ) demonstrated that patients with resolved AF had a high risk of stroke/TIA compared with those without AF (relative risk [RR], 1.63 [1.46–1.83]) [49].

### 3. Left atrial appendage occlusion

Evidence on left atrial appendage occlusion (LAAO) in stroke prevention is increasing, and offers an alternative to OAC among patients with contraindications for anticoagulation. Evidence for the use of LAAO comes from the WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation (PROTECT-AF) ( $n = 707$ ) [50] and the Prospective Randomized Evaluation of the WATCHMAN Left Atrial Appendage Closure Device in Patients with Atrial Fibrillation vs. Long-term Warfarin Therapy (PREVAIL)

( $n = 407$ ) [51] trials. In their meta-analysis [52], ischemic stroke/SE rate was numerically higher with LAAO (HR, 1.71;  $p = 0.080$ ), but LAAO was associated with a lower risk of hemorrhagic stroke (HR, 0.20;  $p = 0.002$ ) and similar major bleeding risk (HR, 0.91;  $p = 0.60$ ) [52]. In the PROTECT-AF study, procedural-related adverse events at 7 days after the procedure occurred in 8.7% of patients, including pericardial tamponade requiring intervention in 4.0% [50]. In the Amulet Global Observational Registry ( $n = 1088$ ), major procedural complications occurred in 3.2% of patients, including pericardial effusion or tamponade in 1.2%, vascular complication in 0.9%, periprocedural stroke in 0.2%, and death in 0.2% [53].

Currently, LAAO has a Grade IIb recommendation in the 2016 ESC guideline, and is limited to patients with high risk of bleeding who refuse to take OAC [23]. The performance of LAAO has never been compared against the NOACs in large randomized trials, which may provide more insights considering the safety advantages of NOACs over VKA, especially for ICH. One network meta-analysis indirectly found a trend towards higher rates of ischemic stroke with Watchman compared with NOACs (odds ratio [OR], 2.60 [0.60–13.96]) and a non-significant difference in of hemorrhagic stroke (OR, 0.44 [0.09–2.14]) [54]. In addition, LAAO cannot eliminate the need for antithrombotic therapy, including the peri-procedural anticoagulation and long-term antiplatelet therapy, which may defeat the safety profile of LAAO.

## 4. Unmet needs in oral anticoagulant use

### 4.1. Current trends

Despite the well-documented efficacy and safety of OAC, an unmet OAC use remains common worldwide [55,56]. In the last decade, OAC use remains low (approximately 50%) among AF patients at high-risk of stroke [57]. Generally, OAC use in Western countries is better than in Asia.

In the EurObservational Research Programme-Atrial Fibrillation (EOPR-AF) registry from Europe in 2015 ( $n = 10,000$ ), OAC was used in 79.2% [58]. In the Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) registry including 17,162 patients with AF from Europe, 52.4% of the patients received NOAC, 5.7% received antiplatelet alone and only 4.1% remained untreated [59]. Similarly, the Antithrombotic Treatment Patterns in Patients with Newly Diagnosed Nonvalvular Atrial Fibrillation (GARFIELD-AF) registry involving recently diagnosed AF from 2010 to 2015 ( $n = 39,670$ ) reported an increase in OAC use from 57.4% to 71.1%, and a significant increase of NOACs use from 4.2% to 37.0%, while antiplatelet monotherapy declined from 30.2% to 16.6% [60].

In Asia, suboptimal OAC use is more prevalent. For example, in a survey from China, involving 32 hospitals and 7977 AF patients demonstrated OAC use of 36.5% among those with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 2$  between 2011 and 2014, although this increased from 30.2% to 57.7% [61]. In AF patients from Korea between 2008 and 2015 ( $n = 276,246$ ), OAC use increased from 34.7% to 50.6% and NOAC use accounted for 50% of total OAC use, while aspirin use consistently decreased from 48.2% to 31.5% [62].

### 4.2. Quality of anticoagulation control.

Effective anticoagulation using VKA requires a TTR  $\geq 65$ –70%, but the TTR can be influenced by multiple factors, where the more common ones have been summarized in the SAMeTT<sub>2</sub>R<sub>2</sub> score (sex, age, medical history, treatment of interaction medication, tobacco use, and race)<sup>4</sup> [63]. A patient on VKA with a SAMe-TT<sub>2</sub>R<sub>2</sub> score  $\geq 2$  tends to have suboptimal TTR, who may need more frequent international normalized ratio (INR) checks, education/counseling on optimizing VKA use or switching instead to a NOAC. In general, the patients with AF from Western populations have higher TTR when compared with those from other populations. In the PREvention of thromboembolic events-

European Registry in Atrial Fibrillation (PREFER IN AF) registry, for example, the mean TTR ranged from 70.3% in Spain to 72.5% in the UK and 81.4% in Germany [64,65]. The mean TTR has been reported as higher in Australia (82%) than in Singapore (58%) [66]. In Malaysia, the mean TTR was 65.1% in a professional anticoagulation clinic and only 48.3% in general clinics [67]. In Thailand, the mean TTR ranged from 40.1% to 62.7% in a cohort study with 433 AF patients [68]. In a survey from Saudi Arabia, the mean TTR was 59% [69]. Also, in a cross-sectional study from South Africa, only 48.5% of patients achieved target therapeutic range [70]. In a subanalysis of the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial ( $n = 21,105$ ), the mean TTR was also low (56%) in East Asia [71].

#### 4.3. Off-label reduced dosage of NOACs

Despite the well-established efficacy and safety of NOACs, in everyday practice, clinicians are often more concerned about drug-related bleeding than ischemic stroke/SE, leading to a high rate of inappropriate underdosing of NOACs [72]. Barra et al. demonstrated that 57% of patients who were treated with a reduced dose of rivaroxaban did not meet the explicit dose reduction criteria in the label [73]. In the ORBIT-AF II registry (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation phase II), 9.4% of patients received an inappropriate reduced dose of NOACs, which was associated with increased cardiovascular hospitalization (HR, 1.26 [1.07–1.50]) [74]. In a real-world study including 14,845 AF patients from the U.S., among 13,392 patients without renal indication for dose reduction, 13.3% received inappropriate reduced dose of NOACs; such underdosing was associated with a higher risk of stroke (HR, 4.87 [1.30–18.26]), but a non-significant difference in major bleeding [75]. In this study, patients with age  $\geq 80$  had highest proportion of underdosing (apixaban 48.0%, dabigatran 25.7%, rivaroxaban 35.4%) [75]. Although a few studies showed that even low-dose NOACs had equivalent efficacy and reduced risk of major bleeding (RR, 0.61 [0.40–0.91]) compared to warfarin [76], clinicians should not be encouraged to use off-label dosages of NOACs, unless the presence of certain criteria justifying dose reduction – the evidence suggests that there is little safety advantage but more adverse outcomes result.

### 5. Reversal of anticoagulant activity in urgent medical conditions

Although the bleeding risk is low in NOACs, reversing the anticoagulation activity is important when individuals are suffering from serious bleeding, overdosing or require urgent surgery. In general, some supportive measures could be conducted, including mechanical/surgical management, volume resuscitation, blood transfusion, prothrombic complex concentrates injection, etc. For overdosed patients or those who ingested NOACs within 2 to 4 h, oral activated charcoal may attenuate drug absorption. Hemodialysis is also an optional choice for patient taking dabigatran but not for those taking FXa inhibitors given the latter drugs are highly protein-bound [77].

More important is that specific reversal agents are/coming to available in market, with effectiveness and safety in reversing anticoagulation activity. For example, idarucizumab is a specific antibody that binds all the dabigatran in plasma within minutes [78]. In the Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) study, idarucizumab rapidly (<10 min), durably, and safely reversed the anticoagulant effect of dabigatran [79].

Andexanet alpha is a recombinant modified human factor Xa decoy protein that has been shown to rapidly (within 2–5 min) and completely (>90%) reverse the inhibition of factor Xa [80]. The Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors (ANNEXA) study is an ongoing, multicenter, prospective, open-label, single-group study investigating the role of andexanet in patients with acute major bleeding [81]. On the basis of descriptive

preliminary analysis of this study, an initial bolus and subsequent 2-hour infusion of andexanet substantially reduced anti-factor Xa, with effective hemostasis occurring in 79% [81].

### 6. Special patient subgroups

OAC use in some subgroups of patients, e.g. those with high bleeding risk, renal dysfunction, recent ICH or very elderly patients, can be challenging. Clinicians should fit the right anticoagulants to patient's clinical profile, including those comorbidities such as acute coronary syndrome (ACS), concomitant antiplatelet use, peri-AF ablation procedure, cardioversion, chronic kidney disease (CKD) and elderly patients [14].

#### 6.1. High bleeding risk

When initiating OAC, assessment of bleeding risk is necessary, which should be performed at each medical contact, considering the dynamic risk profile of AF patients who are often elderly with multiple comorbidities. Bleeding assessment can be done using currently available and validated bleeding risk scores, such as the HAS-BLED score (uncontrolled hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile International Normalized Ratio [INR], elderly, drugs/alcohol concomitantly)<sup>7</sup>. The HAS-BLED score is easy for clinical application with similar or better accuracy in predicting major bleeding events compared with other scoring systems which may be more complex and less user-friendly [82–85].

In 'real-world' settings, the individual risk of bleeding is not static. Indeed, among the components of the HAS-BLED score, there are modifiable risk factors, including uncontrolled hypertension, liver/renal function, anemia, labile INR and drugs/alcohol consumption. The changes or management of these risk factors would result in a different status of bleeding risk. Indeed, in a 'real-world' nationwide AF cohort ( $n = 19,566$ ), follow-up HAS-BLED or 'delta HAS-BLED score' was more predictive of major bleeding compared with baseline HAS-BLED score [86].

A high bleeding risk does not eliminate the need for OAC. The HAS-BLED score and other scoring systems were designed to draw attention to modifiable bleeding risk factors [87–89] and to 'flag up' patients with high bleeding risk, for whom more frequent follow-up, monitoring and education are needed [21]. While modifiable bleeding risk factors should be addressed in all patients, relying on this alone is an inferior strategy to an established bleeding risk score to assess bleeding risk [87,90,91].

#### 6.2. Very elderly patients

Evidence for OAC among very elderly patients, such as those over 80 or 90, remains scarce as such patients were under-represented in clinical trials. These patients generally comorbid with multiple risk factors for stroke and bleeding, thus associating with high risks of both events. A meta-analysis ( $n = 8932$ ) show that the benefit of OAC increases with age, and the harm associated with aspirin increases [92]. Such a trend for benefit has also been observed in patients on NOACs [14]. Treatment of elderly patients with edoxaban provided a greater absolute reduction in bleeding events over warfarin compared to young patients [93]. A recent study from an Asian population, including 11,046 AF patients >90 years, showed that warfarin was associated with a lower risk of ischemic stroke and positive NCB [94]. Furthermore, NOACs were associated with a lower risk of ICH compared with the VKA among very elderly AF patients (HR, 0.32 [0.10–0.97]) [94].

#### 6.3. Concomitant coronary artery disease (CAD)

AF commonly coexists with CAD, either as stable CAD or ACS [95]. Thus, combination therapy of anticoagulant and antiplatelet agents is commonly used among patients with AF and CAD, which is associated with increased risk of bleeding (HR, 1.50 [1.23–1.82]) [96]. Among AF

patients experiencing ACS or undergoing percutaneous coronary intervention (PCI), triple therapy (OAC plus dual antiplatelets) should be used for the initial period, followed by OAC plus single antiplatelet drug and after 1 year, OAC alone [97].

The Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Non-valvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention (REDUAL PCI) trial ( $n = 2725$ ) showed lower risk of major or clinically relevant nonmajor bleeding with dabigatran plus P2Y12 receptor inhibitor (110 mg group: HR, 0.52 [0.42–0.63] and 150 mg group: 0.72 [0.58–0.88] and no significant difference in stroke risk (110 mg group: HR, 1.30 [0.63–2.67] and 150 mg groups: 1.09 [0.42–2.83]), when compared with a warfarin-based triple therapy group [98]. In the Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI (PIONEER AF-PCI) trial ( $n = 2124$ ), the rivaroxaban group (rivaroxaban 15 mg once daily plus single antiplatelet group and rivaroxaban 2.5 mg twice daily plus dual antiplatelets group) had lower risk of bleeding (15 mg group: HR, 0.59 [0.47–0.76]; 2.5 mg group: HR, 0.63 [0.50–0.80]), compared with triple therapy with warfarin and similar risks of ischemic stroke (15 mg group: HR, 1.07 [0.39–2.96]; 2.5 mg group: HR, 1.36 [0.52–3.58]) [99].

Recently, the 2018 Joint European Consensus Document on the Management of Antithrombotic Therapy in AF Patients Presenting with ACS and/or Undergoing PCI was published, providing an up-to-date evidence-based guidance on stroke prevention among AF patients with ACS and/or undergoing PCI, which is endorsed by HRS, APHRS, LAHRS and CASSA [100]. Other ongoing trials will provide new evidence. For example, the Apixaban Versus Warfarin in Patients with AF and ACS or PCI study (AUGUSTUS study, NCT02415400) is an open-label,  $2 \times 2$  factorial, randomized, controlled non-inferiority clinical trial to evaluate the safety of apixaban vs. VKA + aspirin vs. aspirin + placebo in patients with AF and ACS [101]. The Edoxaban Treatments vs. Vitamin K Antagonist in Patients with Atrial Fibrillation Undergoing Percutaneous Coronary Intervention (ENTRUST-AF-PCI) study is designed to evaluate the safety and to explore the efficacy of an edoxaban-based antithrombotic regimen vs. a VKA-based antithrombotic regimen in subjects with AF following PCI with stent placement [102].

#### 6.4. Chronic kidney disease

The efficacy and safety of anticoagulation are closely related to renal function, especially for the NOACs. In patients with CKD ( $n = 48,500$ ), warfarin use was associated with a 30% lower risk of stroke/SE and 35% lower risk of death compared with no warfarin use [103]. In subgroup analysis, NOACs showed at least similar efficacy and better safety compared with warfarin in patients with mild or moderate CKD [14]; however, the excretion of the four NOACs also depends on renal function with a degree of renal excretion varying from 27% to 80% [104]. Of note, all the four randomized trials of NOACs excluded patients with creatinine clearance (CrCl)  $< 30$  mL/min ( $< 25$  mL/min for apixaban in the ARISTOTLE trial) [6,105]. Therefore, assessing renal function in AF patients before or during taking NOAC is important to choose/modify the dosage of NOACs [106]. In the major NOAC trials, the assessment approach of renal function was with the Cockcroft-Gault Equation, which is well-validated and recommended in clinical practice to guide the dose of NOACs in CKD [107].

Currently, evidence on the use of NOACs in patients with CrCl  $< 30$  mL/min comes from pharmacological modeling. In Europe, reduced dose rivaroxaban, apixaban and edoxaban are approved for thromboprophylaxis in patients with CrCl 15–29 mL/min not for patients on dialysis. In the USA, the Food and Drug Administration approved the use of reduced-dose of dabigatran (75 mg twice daily) in AF patients with CrCl 15–29 mL/min, and in patients with end-stage renal disease on dialysis, apixaban (5 mg twice daily) [108]. Given

that the CHA<sub>2</sub>DS<sub>2</sub>-VASc score is still a useful scheme to estimate the risk of stroke in AF patient with ESRD undergoing dialysis [109], a careful balancing of risk and benefit of NOACs treatment is possible.

#### 6.5. Peri-procedural AF ablation

Anticoagulation during a peri-procedural period of AF ablation is important given the high inherent risk of stroke in this period. The major debate in this field focuses on several points, namely uninterrupted OAC use, bridging with heparin, OAC interruption/resumption and switching of OAC schemes. Indeed, bridging has been associated with a 4.5-fold increased risk of complications, including major pericardial effusion and major vascular events [110].

In the Role of Coumadin in Prevention Thromboembolism in AF Patients Undergoing Catheter Ablation (COMPARE) trial ( $n = 1584$ ), interrupted anticoagulation significantly increased risk of thromboembolism (4.94% vs. 0.25%,  $p < 0.001$ ) compared with uninterrupted anticoagulation strategy, while major bleeding complications were non-significantly different (0.76% vs. 0.38%,  $p > 0.05$ ), and minor bleeding events were more frequent in the interrupted group (22.0% vs. 4.1%,  $p < 0.001$ ) [111]. These results were confirmed by a meta-analysis including 12 studies and 17,434 patients, demonstrating that uninterrupted OAC was associated with lower risk of stroke/TIA (0.25% vs. 1.21%,  $p = 0.003$ ), stroke (0.08% vs. 0.99%,  $p < 0.001$ ), major bleeding (1.44% vs. 2.03%,  $p = 0.02$ ) and minor bleeding (5.35% vs. 19.6%;  $p < 0.001$ ) events [112]. Of note, NOACs have better safety and similar efficacy among patients receiving AF ablation, compared with the uninterrupted warfarin [10,11,113–115].

#### 6.6. Peri-procedural cardiac electronic devices implantation

One of the most severe complications after CIED implantation is the pocket hematoma. The Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial (BRUISE CONTROL) study, included 668 patients experiencing CIED implantation [116]. In this study, clinically significant hematoma was seen in 16% of the bridging group as compared to 3.5% of uninterrupted warfarin group [116]. Pooled analysis including 11,000 patients also demonstrated a lower risk of pocket hematoma in uninterrupted OAC as compared to those receiving bridging heparin therapy [117]. Considering the increasing usage of NOAC, the BRUISE-CONTROL-2 trial evaluated whether continued versus interrupted NOAC during peri-procedural period would reduce the risk of significant pocket hematoma [118]. The trial was stopped early due to futility, and both strategies had very low rates of device pocket hematoma. Thus, device surgery could be performed safely without interruption of NOACs.

For clinical practice, warfarin could be continued with INR controlling between 2.0 and 3.0. In patients taking NOAC, anticoagulation may be discontinued prior to a planned procedure, and the time of discontinuation depends on the half-life of respective NOAC and patients' renal function. For patients with normal renal function, NOAC should be discontinued at least 24 h preoperatively. For patients with renal dysfunction, a discontinuation for 48–72 h seems reasonable. NOAC resumption is generally recommended within 24–48 h after the procedure.

#### 6.7. Peri-procedural cardioversion

The 2016 ESC guideline recommends anticoagulation for  $\geq 3$  weeks before elective cardioversion and at least 4 weeks thereafter in patients with AF episodes lasting over 48 h or unknown duration, regardless of stroke risk profile and types of cardioversion procedure [23]. The NOACs were non-inferior to warfarin for stroke and bleeding events among AF patients undergoing cardioversion [119–121].

## 6.8. Recent ischemic stroke

Patients experiencing recent ischemic stroke events have a high risk of recurrent ischemic stroke and a tendency for hemorrhagic transformation. A previous meta-analysis demonstrated that immediate anticoagulation did not reduce the risk of stroke recurrence but associated with a higher risk of hemorrhagic transformation [122]. While early OAC resumption seems to reduce recurrent ischemic stroke, but associated with an increased risk of intracranial hemorrhage [123].

As recommended by the 2014 AHA/ASA guidelines, it seems reasonable to initiate OAC within 14 days for most stroke patients with AF, and delay OAC for >14 days in those with high risk for hemorrhagic transformation, including large infarct, uncontrolled hypertension, hemorrhagic tendency and early hemorrhagic transformation showed by brain imaging [124]. Recently, a simple approach was proposed, i.e., the 1–3–6–12 day rule, which suggests that OAC initiation at 1 day after TIA; 3 days after a small, nondisabling infarct; 6 days after moderate stroke; and 12 days after a large infarct [125]; however, these suggestions are not supported by any trial evidence and are based on expert opinion. Given the significantly reduced ICH risk (up to 70%) of NOAC [14], switching from traditional VKA to NOAC for patients experiencing recent stroke may provide better safety, which merits validation in randomized trial.

## 6.9. Recent intracranial hemorrhage

Given the lack of high-quality evidence, the most decision-making processes of OAC resumption are based on observational studies and empirical expert opinion. A large observation study ( $n = 1325$ ) showed a non-significantly increased risk of ICH recurrence in patients restarted with warfarin compared with those without OAC resumption after ICH (HR, 1.31 [0.68–2.50]) [126]. This was also confirmed by a recent meta-analysis which included 5306 patients with ICH [127]. In contrast, OAC resumption is associated with a 51–66% reduced risk of thromboembolism [126,127].

In another large insurance-based study involving 12,917 AF patient with previous ICH, Chao et al. found that the benefits of warfarin use were dependent on individual stroke risk (i.e. CHA<sub>2</sub>DS<sub>2</sub>-VASC score) [128]. In this study, among patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASC score  $\geq 6$ , the number needed to treat for preventing 1 ischemic stroke was lower than the number needed to ham for producing 1 ICH with warfarin use (37 vs. 56); however, in patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASC score  $< 6$ , the number needed to treat was higher than the number needed to harm (63 vs. 53) [128].

The time of OAC resumption after ICH is an important factor for outcomes and it depends on individual. Normally, OAC could be resumed within 2–4 weeks after ICH, but delayed (>4 weeks) resumption should be considered for patients with extremely high risk of bleeding. For example, in patients with brainstem or cerebellar ICH, the timing could be delayed to at least 8–10 weeks after the event [129]. For AF patients with an extremely high CHA<sub>2</sub>DS<sub>2</sub>-VASC score (e.g. >4), an early OAC resumption seems reasonable after confirming the ICH is resolved.

## 7. Patient-centered management

Patient-centered approaches may help optimize management among AF patients, with focus on patient values and preferences [130,131]. A shared decision-making process with patients regarding OAC use may improve anticoagulation management [132]. More recently, improved education and counseling could be reinforced by smart technology, such as apps on smartphones. For example, the pilot mAF App trial, which is the first prospective randomized trial of mobile-health technology in patients with AF, showed that integrating clinical decision support, education and patients-involved management significantly improved drug adherence [133]. Also, a telemonitoring

procedure leads to good adherence and could be improved with additional feedback from patients [134].

## 7.1. Integrated care

AF patients are often elderly with multiple comorbidities, and have a high risk of all-cause mortality and hospitalization. Indeed, nearly 70% of deaths among AF patients are caused by cardiovascular diseases [135], despite high rates of anticoagulation. Most deaths in AF are not related to stroke (which only accounts for about 10%), while 7 in 10 deaths are cardiovascular. Thus, a more integrated management strategy is needed. Such ‘integrated care’ in AF has been associated with a lowered risk of death and hospitalizations [136].

Integrated care can be simplified into the ‘‘Atrial Fibrillation Better care (ABC)’’ pathway, as follows: ‘A’ Avoid stroke with Anticoagulation; ‘B’ Better symptom management, involving patient-centered, symptom-directed decisions on rate or rhythm control; and ‘C’ Cardiovascular and other comorbidity risk management, including attention to lifestyle changes (obesity management, regular exercise, avoiding alcohol, etc.) [137] (Fig. 1). Compliance with this ABC pathway approach has been shown to reduce mortality and other adverse events in anticoagulated patients with AF [138].

## 8. Conclusion

Stroke prevention in patients with AF is the cornerstone of management for this common arrhythmia. Current efforts will still focus on the following: (i) Improving the accuracy of identifying patients at low risk for thromboembolism; (ii) Exploring more effective and safer approaches to avoid stroke, based on a better understanding of the mechanism of stroke events in AF; and (iii) Increasing OAC use and patients’ adherence, especially in many regions of the world, such as Asia, Africa and Middle East. Stroke prevention is merely one component of an integrated managing approach to AF, and attention to symptoms and cardiovascular or comorbidity management should also be emphasized.

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