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Viewpoint

Stroke prevention in recent guidelines for the management of patients with atrial fibrillation: An appraisal

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Abstract

Formal guidelines play an important role in disseminating the best available evidence knowledge and are expected to provide simple and practical recommendations for the most optimal management of patients with various conditions. Such guidelines have important implications for many disease states, which thereby could be more professionally managed in everyday clinical practice by clinicians with divergent educational backgrounds, and also more easily implemented in wards or outpatient clinics eliminating inequalities in health care management.

In this brief Viewpoint, we provide an appraisal on the recommendations pertinent to the prevention of atrial fibrillation-related stroke or systemic thromboembolism, as provided in recently published guidelines for the management of this arrhythmia.

Introduction

Prevention of stroke is central to the optimal management of patients with atrial fibrillation (AF). Oral anticoagulant therapy (OAC) using well-controlled vitamin K antagonists (VKAs) or non-VKA oral anticoagulants(NOACs) effectively reduces stroke and all-cause mortality in atrial fibrillation patients, but the treatment benefit must be balanced against the risk of OAC-related major bleeding. Worldwide, the VKAs remain the most widely used OAC, although the NOACs use is increasing rapidly[1].

Formal ATRIAL FIBRILLATION guidelines play an important role in disseminating the state-of-the-art knowledge and are expected to provide simple practical guidance for atrial fibrillation management, which could be easily applied in clinical practice by clinicians with diverse educational backgrounds and various clinical commitments. Figure 1 provides an overview of several contemporary guideline treatment algorithms with recommendations for thromboprophylaxis in patients with atrial fibrillation[2]. In 2014, guidelines from the AHA/ACC/HRS and National Institute for Health and Care Excellence (NICE) were published[3, 4], while in 2016, a focussed update from the Canadian Cardiovascular Society (CCS)[5] and new European Society of Cardiology (ESC) guidelines[6] were published. The last Asia-Pacific Heart Rhythm Society[7] and American College of Chest Physicians (ACCP)[8] guidelines on antithrombotic therapy in atrial fibrillation were published in 2012-2013, and new versions are pending.

In this brief Viewpoint, we provide an appraisal of the recommendations pertinent to the prevention of atrial fibrillation -related stroke or systemic thromboembolism, as provided in more recently published guidelines for the management of patients with atrial fibrillation.

Stroke and bleeding risk assessment

Most of the contemporary international guidelines on atrial fibrillation management published since 2013 recommend the CHA_2DS_2-VASc score for stroke risk assessment in atrial fibrillation.

In line with the 2012 ESC Atrial Fibrillation Guidelines focused update[9], the use of the CHA_2DS_2-VASc score is a Class I, Level of evidence A recommendation in the new 2016 ESC Guidelines[6].

The CHA_2DS_2-VASc score, which has been validated in numerous different atrial fibrillation cohorts, provides a good balance of predictive ability and practicality and has often out-performed other stroke risk assessment tools in the reliable identification of 'truly low risk' patients, who need no antithrombotic therapy due to low annual stroke rates of <1%[10, 11]. Like many clinical factor-based risk scores in the atrial fibrillation or non- atrial fibrillation setting, CHA_2DS_2-VASc only has a modest predictive value for identifying the 'high risk' patients who subsequently develop events. As would be expected, for each point of the CHA_2DS_2-VASc score there would be a wide range of reported event rates, given that this would be dependent on population studied (trial vs 'real-world'), clinical setting (hospitalised vs community cohorts), ethnicity, etc[12, 13].

The predictive value of clinical risk scores can always be improved by the addition of biomarkers ('biological markers', whether blood, urine or imaging based). In the light of recent sub-studies from the landmark NOAC trials (describing the role of various blood biomarkers in the prediction of stroke, bleeding or death in anticoagulated patients)[14-16], the 2016 ESC Guidelines recommend that 'biomarkers such as high-sensitive troponin or natriuretic peptide may be considered to further refine stroke and bleeding risk' (Class IIb, Level B). This is a weak recommendation for a number of reasons. First, these findings were derived mostly from the already anticoagulated cohorts, and it is unclear whether they could be extrapolated to non-anticoagulated patients, a substantially different population which includes many lower-risk patients for whom the decision to use an OAC is yet to be made. Second, a large body of evidence shows the association of various biomarkers of thrombogenesis, inflammation, myocardial damage, impaired cardiac function, oxidative stress, renal failure, etc. (e.g., von Willebrand factor, D-dimer, C-reactive protein, cardiac troponins, glomerular filtration rate, etc.) with increased risk of stroke in atrial fibrillation patients, and it is not clear why high-sensitive troponin or natriuretic peptide should be preferred[17]. The particular biomarker cut-off values relevant for stroke or bleeding risk evaluation are unknown, notwithstanding the inter-

assay variability in measuring the biomarker levels, cost issues and patient variability (some have a diurnal pattern and can be influenced by co-morbidities such as renal impairment). Many of these biomarkers not only predict stroke or bleeding, but death, myocardial infarction and heart failure – and may confuse clinicians who may try to balance the various outcomes. Finally, the use of biomarkers needs to be tempered by cost, as well as loss of simplicity and practicality for everyday use.

The introduction of biomarkers to refine stroke risk stratification, albeit statistically improving on clinical scores, may result in delayed or postponed OAC initiation while waiting for test results with the risks inherent to the treatment omission. Nevertheless, the new recommendation to consider biomarkers for stroke and bleeding risk assessment indicates future development possibilities for improved risk prediction, especially for those at the 'borderline' threshold for OAC.

OAC-related bleeding risk

The assessment of OAC-related bleeding risk is not a new concept but has been subject to considerable misuse and misinterpretation[18]. The 2016 ESC Guidelines provide guidance to practitioners, but focus on listing the modifiable, partly modifiable, non-modifiable and biomarker-related bleeding risk factors, rather than recommending a specific bleeding risk score, of which there are now many[19-23], including the HAS-BLED score which was recommended in earlier ESC guidelines[9 19]. The modifiable bleeding risk factors, to which our attention is drawn are all factors listed in the HAS-BLED score.

The HAS-BLED score[19] has been well-validated in various atrial fibrillation cohorts, including patients treated with NOACs or a combination of OAC and antiplatelet drugs. The HAS-BLED score enables a simple identification of increased bleeding risk (i.e., score ≥3 points) and 'flags up' the patient potentially at risk of bleeding for more careful review and follow-up. Importantly, HAS-BLED draws attention to the reversible bleeding risk factors (summarised in Table 12 of the 2016 ESC guidelines) i.e. uncontrolled hypertension, labile International Normalized Ratio (INR), concomitant aspirin or non-steroidal anti-inflammatory drugs, excess alcohol, renal or liver function, or bleeding predisposition[24].

Several other bleeding risk scores are mostly less-well validated than HAS-BLED, and many would significantly under-perform in predicting VKA-related bleeding events by not considering the quality of anticoagulation control (i.e. labile INR) as a bleeding risk factor[25].

The reason for removing reference to a specific bleeding risk score and to focus on the modifiable bleeding risk factors in the 2016 ESC guidelines is related to the a misconception that specifying a particular bleeding risk score leads clinicians to use a high score value as a reason to withhold OAC[18], which is an inappropriate use of bleeding scores. The use of a formal score should focus the physician's attention towards provision of adequate education, management of modifiable risk factors, and perhaps implementation of modern adherence tools, such as electronic alerts, etc.[18]. The outline of bleeding risk factors in the new guidelines is very useful but could easily have been added to the more common bleeding risk assessment using the HAS-BLED score. Indeed, the new guidelines recommend that bleeding risk scores should be considered in atrial fibrillation patients on OAC to identify modifiable risk factors for major bleeding (Class IIa, Level B), but do not refer to a specific bleeding risk score, which may confuse clinicians.

Nevertheless, we welcome the 2016 ESC Guidelines note that 'a high bleeding risk score should generally not result in withholding OAC.'. This may be particularly important in atrial fibrillation patients with an acute coronary syndrome or percutaneous coronary intervention, in whom the choice of optimal treatment regimen (i.e., a combination of OAC and antiplatelet therapy for a variable time period) highly depends on the estimated thrombotic and bleeding risks.

Bleeding management whilst on OAC is highlighted in the new ESC guidelines, especially since we are entering an era of reversal agents and specific antidotes to the NOACs, with idarucizumab already being available for dabigatran[26].

Stroke prevention strategies

The new 2016 ESC Guidelines fully acknowledge that aspirin has no role in the prevention of atrial fibrillation-related stroke or systemic thromboembolism[27] (Class III recommendation).

The 2012 ESC Guidelines focused update[9] recommended a simple and effective stepwise approach to stroke prevention – first, identify patients at truly low risk of stroke who do not need any antithrombotic therapy (that is, males with CHA_2DS_2-VASc=0 and females with CHA_2DS_2-VASc=1) and next, consider OAC use in *all* other atrial fibrillation patients without absolute/strong contraindications to OAC (that is, in patients with a CHA_2DS_2-VASc score of ≥1, excluding female gender as the only risk factor). The new 2016 guidelines, however, re-introduce the categorisation into the low, intermediate and high stroke risk strata.

Whilst stating that male patients with a CHA_2DS_2-VASc score of 0 and female patients with a CHA_2DS_2-VASc score of 1 do not need any antithrombotic therapy and that patients at high risk of stroke (that is, male patients with a CHA_2DS_2-VASc score of ≥2 and female patients with a CHA_2DS_2-VASc score of ≥3) should be recommended OAC (Figure 1 and 2), the new ESC Guidelines increase the size of the 'intermediate' risk stratum of patients with a single CHA_2DS_2-VASc risk factor (that is, with a CHA_2DS_2-VASc score of 1 [males] or 2 [females], Figure 2) and state that in such patients OAC 'should be considered' (Class IIa, Level B), cautioning that such approach should prevent the overtreatment (i.e., OAC overuse) in atrial fibrillation patients. However, the new ESC Guidelines do not provide explicit guidance how to 'consider' OAC use in the 'intermediate' stroke risk patients, and the approach with divergent CHA_2DS_2-VASc scores for males and females leads to gender-specific recommendation statements with an inherent risk for under-treatment of female patients.

To inform decision-making pertinent to atrial fibrillation patients with a single additional stroke risk factor, the 2016 ESC Guideline Task Force commendably commissioned a systematic review of observational studies reporting the annual stroke rates in such non-anticoagulated patients[28]. The stroke rates in those studies were highly heterogeneous and sometimes low[10, 12, 13, 29]. A recent meta-analysis[30] found that the annual stroke risk in the CHA_2DS_2-VASc score 1 category is sufficiently high to prescribe a NOAC but not warfarin; however, the CHA_2DS_2-VASc score 1 data in the meta-analysis included low-risk females with score 1 who should not receive antithrombotic therapy, while the treatment threshold for well-managed warfarin with high-quality anticoagulation control would probably approach that of NOACs[31].

Older guidelines have previously given a strong recommendation for OAC for atrial fibrillation patients with 1 $CHADS_2$ stroke risk factor[8] (notably, $CHADS_2$ and CHA_2DS_2VASc scores share 4 stroke risk factors scoring 1 point). There are no randomised trials specifically in patients with CHA_2DS_2-VASc 1; however, trials such as RELY, ARISTOTLE, SPORTIF (all of which compared NOACs vs warfarin), AVERROES and ACTIVE (both compared OAC to antiplatelet drugs) have all included patients with a single stroke risk factor resembling CHA_2DS_2-VASc score components, where subgroup analyses show evidence of benefit of NOAC vs warfarin[32, 33], or OAC vs non-anticoagulation[34, 35]. An ancillary analysis from the SPORTIF trials showed that high time in therapeutic range (TTR) amongst warfarin users was associated with low event rates, suggesting that the treatment threshold for warfarin could be comparable to that seen for NOACs[31].

With a single stroke risk factor, it is only common sense that not all risk factors carry equal weight, and reported event rates would differ by study setting, population and ethnicity. The most robust study (not considered by the guidelines)[10, 29], larger than other European atrial fibrillation cohorts altogether (n=177,966), reported event rates according to the selected outcome criteria and specific CHA_2DS_2-VASc score levels[36], showing how stroke rates vary with different methodological approaches, especially in patients with a single additional stroke risk factor.

Methodological differences in the definition of cohorts 'off OAC treatment' would significantly influence the reported stroke rates, most relevant to a CHA_2DS_2-VASc score of 0 and 1. For example, two Swedish studies[37] [38] cited in the guidelines reported that patients with a CHA_2DS_2-VASc score of 1 would not benefit from OAC, but these studies excluded all patients who during follow-up had initiated OAC treatment, thus 'conditioning on the future' and biasing outcomes towards lower event rates by excluding the higher-risk subjects who would have been started on OAC during follow-up.

Simple stroke risk scores such as CHA_2DS_2-VASc are designed to be reductionist, and help dichotomise (and simplify) decision-making. Thus, once the individual stroke risk has been established to be above the threshold for OAC use, what difference would it make if the score

was 2 or 9, or the patient's risk was 2 or7% per year? OAC should be the default treatment at any stroke risk level exceeding the treatment threshold, excluding 'truly low-risk' AF patients (see the Birmingham '3-step' algorithm, Figure 1).

This simplified concept of considering OAC use in all atrial fibrillation patients with ≥1 additional stroke risk factors (excluding female sex as the only risk factor) leads to improved adherence to guidelines with better outcomes in daily practice and is cost-effective[4, 39]. Modelling analyses show that adoption of the CHA_2DS_2-VASc-based approach and NOAC use would result in an annual reduction of >60000 strokes, deaths and bleeding events in Europe alone[40].

Hence, patients with atrial fibrillation and a single additional stroke risk factor should generally not be denied OAC on the grounds of a misperception that their risk of stroke is insufficiently high to justify OAC use. In comparison to no therapy or aspirin, the use of OAC (well-controlled VKA or NOACs) in such patients has been associated with a positive net clinical benefit, with significant reduction in stroke, systemic embolism or death and no increase in major bleeding relative to aspirin [41, 42].

Choosing between NOACs and VKAs in daily practice

Compared to VKAs, NOACs have the advantage of greater safety (significantly lower risk of haemorrhagic stroke or other intracranial haemorrhage, critical site or life-threatening/fatal bleeding) and more convenient use (fixed dosing without the need for routine laboratory control of anticoagulation intensity, but requiring strict adherence to treatment), and are at least as effective as VKAs in stroke prevention in atrial fibrillation patients.

However, VKAs are still widely used for the prevention of atrial fibrillation -related stroke, mostly due to the cost and reimbursement issues, and for patients whose adherence to therapy is uncertain. The quality of the management of VKA therapy has generally improved, particularly in Europe.

The 2016 ESC Atrial Fibrillation Guidelines commendably prefer NOACs (dabigatran, rivaroxaban, apixaban or edoxaban) over VKAs when starting OAC in the NOAC-eligible patients (Class I, Level A), but do not make such a strong preference for NOACs in patients already taking VKA, even if the TTR is not well controlled or if the patient prefers NOACs in the absence of NOACs-specific contraindications (Figure 1 and 2) - the recommendation is only Class IIb, i.e may be switched. However, patients with poorly controlled INRs despite good adherence and compliance have a higher bleeding risk and should be (Class I recommendation) switched to a NOAC associated with a lower bleeding risk. The preference to NOACs is a welcomed development, especially since the randomised trial data are clearly supported and augmented by large observational cohorts comparing various NOACs to warfarin, with evident consistency of effectiveness and safety[43].

The new guidelines do not provide a cut-off TTR value for the good quality of VKA anticoagulation, instead stating that TTR 'should be kept as high as possible' (Class I, Level A) and providing no formal guidance to clinicians how to assess the quality of the management of VKA therapy.

The outcomes of VKA therapy strongly depend on the quality of anticoagulation, as measured by the individual patient's TTR. Low TTR values (<65%) are associated with increased rates of stroke and major bleeding, and serious adverse events are particularly common during the inception period, in the first months of OAC use[44]. Since the anticoagulation control in a VKA user can be influenced by a long list of clinical parameters, genetic testing before initiation of VKA therapy is not recommended (Class III).

For those clinicians and patients who for any reason would prefer VKA as the initial OAC treatment, the SAMe-TT_2R_2 score provides a simple way to identify patients who would do well on VKAs in advance, avoiding potentially deleterious initial months of 'trial of VKA treatment'. OAC-naive atrial fibrillation patients with a good TTR (SAMe-TT_2R_2 0-2) are likely to do well on VKAs,, whilst those with SAMe-TT_2R_2 >2 are less likely to achieve a good TTR and may instead be prescribed a NOAC[45]. The SAMe-TT_2R_2 score has been validated in various atrial fibrillation cohorts and is predictive not only of the anticoagulation control quality with VKAs, but also of

all-cause mortality or a composite endpoint of thromboembolic events, major bleeding and mortality[46]. The SAMe-TT_2R_2 is easily calculated assigning 1 point each to female sex, age of <60 years, history of ≥2 co-morbidities or treatment with drugs interacting with VKAs (e.g., amiodarone) and 2 points each to tobacco use and non-Caucasian ethnicity. Although the 2016 ESC guidelines briefly mention the SAMe-TT_2R_2 score, there is no formal recommendation on its use, because the score has not been tested in randomised trials.

The 2016 ESC guidelines recommend (Class IIa) a specific NOAC in preference to other NOACs for patients at increased risk for gastrointestinal bleeding. Such recommendation is based on the randomised trials, post-market studies and meta-analysis, although the head-to-head comparisons between the NOACs are lacking. The recommendation may also imply that the lower doses of rivaroxaban, edoxaban or dabigatran could be preferred for these patients. However, little information is available about the efficacy of rivaroxaban 15mg once daily[47], and the low dose regimen of edoxaban was less efficacious than warfarin[48]. Divergent results from the various trials emphasise the different patient populations as reflected by different bleeding rates in their VKA arms, different CHA_2DS_2-VASc scores, variable definitions of major bleeds etc., all of which could have influenced the results, and makes head-to-head comparisons questionable.

Specific considerations

The 2016 ESC guidelines have comprehensive sections on the optimal management of atrial fibrillation patients presenting with an acute stroke or intracranial haemorrhage (reflecting the collaboration with the European Association for Cardiothoracic Surgery and the European Stroke Association) or patients with an acute coronary syndrome or percutaneous coronary intervention/stenting (with recommendations broadly consistent with the recent European consensus document[49]). Clearly, complex atrial fibrillation patients need a multidisciplinary approach and carefully integrated care, which is a welcomed new recommendation (Class IIa) made in the guidelines[41, 42, 50].

Patient education and their values and preferences are an increasingly important feature in the guidelines[51]. This is relevant since OAC discontinuation (affecting 20-50% of patients in the first year of OAC treatment) is an important problem. The 2016 ESC guidelines provide important novel guidance in this emerging field.

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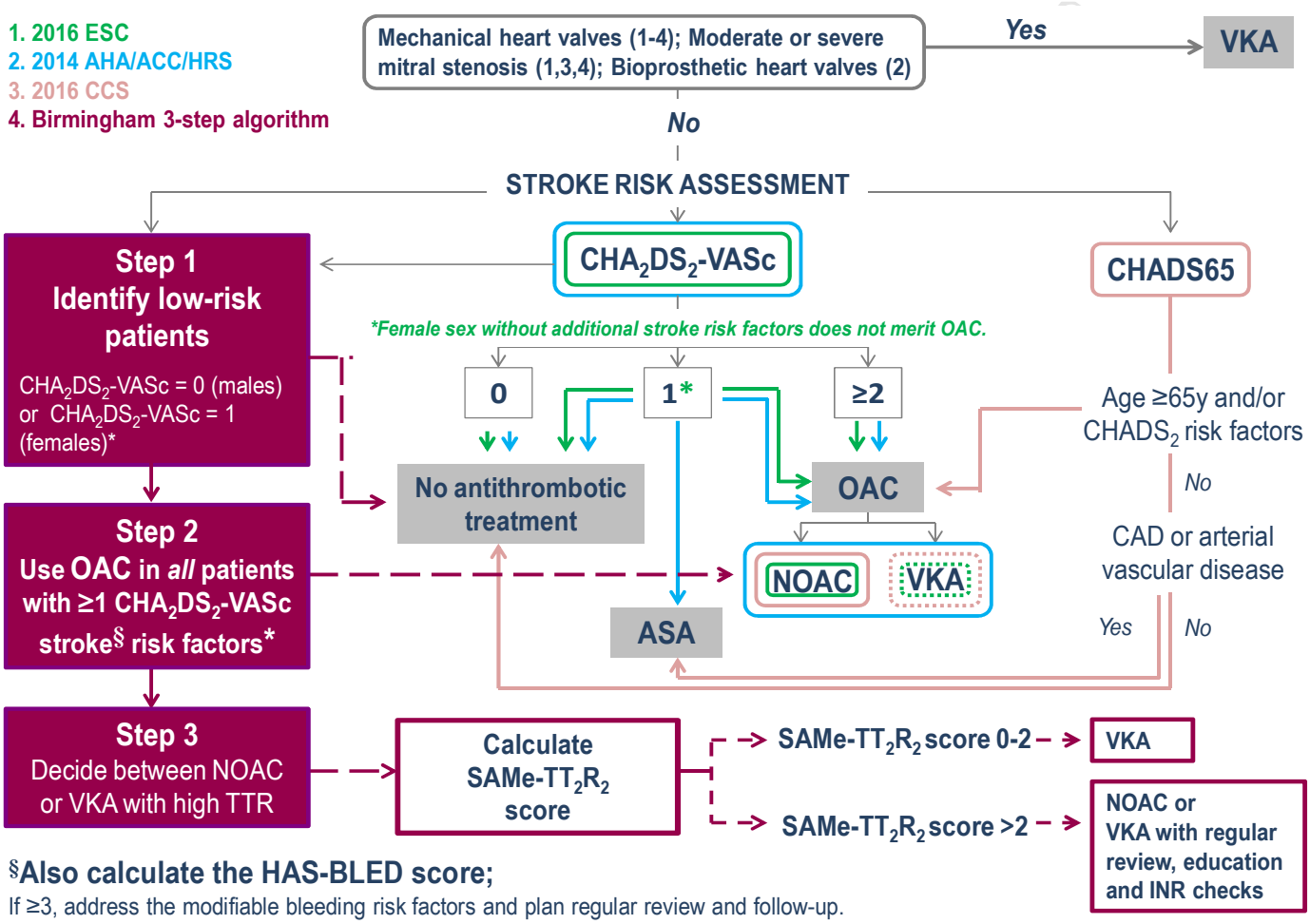
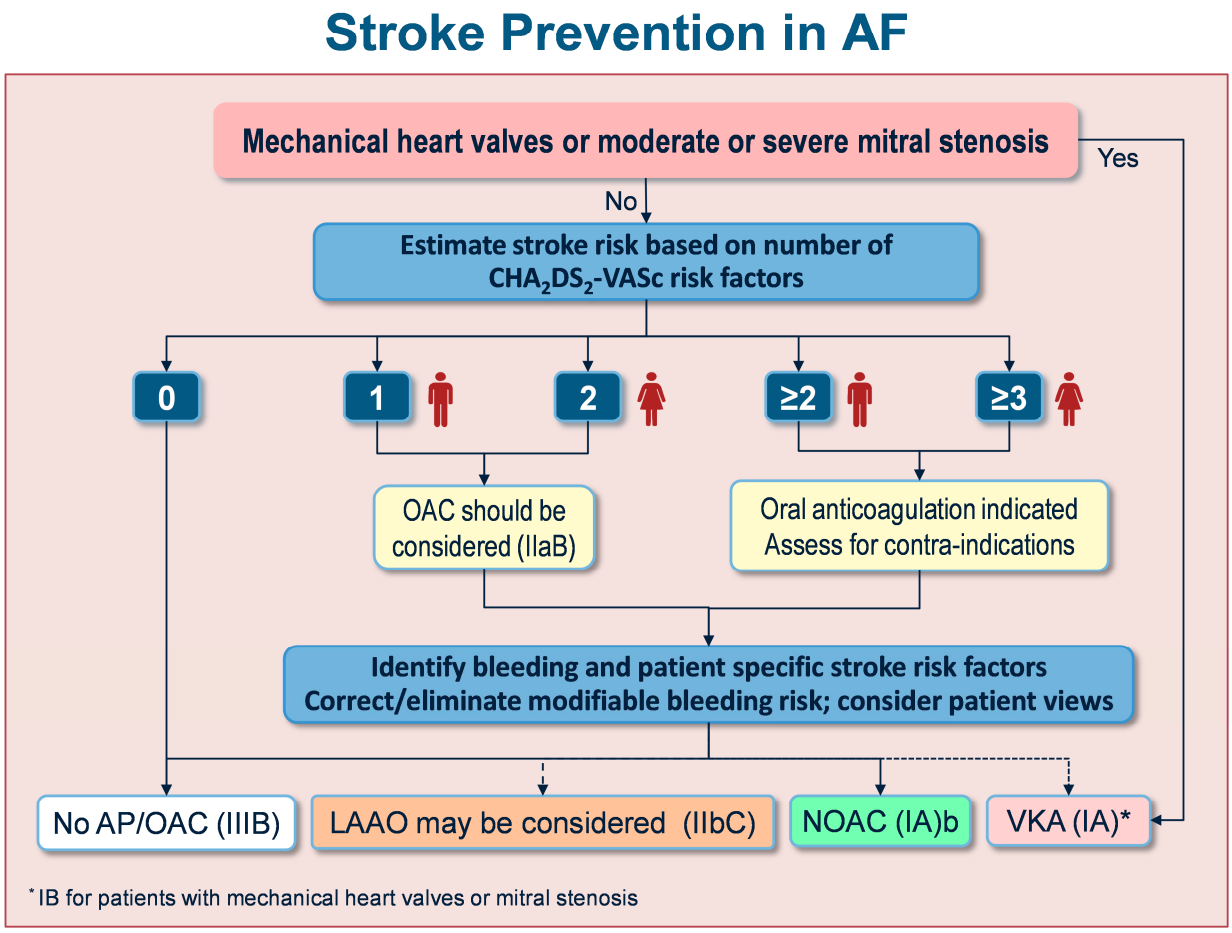
Figure 1. An overview of guideline algorithms for thromboprophylaxis in patients with atrial fibrillation (adapted from Lip et al [2])



ESC: European Society of Cardiology; AHA/ACC/HRS: American Heart Association/ American College of Cardiology/Heart Rhythm Society; CCS: Canadian Cardiology Society; VKA: Vitamin K antagonist; OAC: Oral Anticoagulant; NOAC: Non-VKA Oral Anticoagulant; ASA: Acetyl-Salicylic-Acid; CAD: Coronary Artery Disease; TTR: Time in Therapeutic Range; INR: International Normalized Ratio.

Figure 2. The 2016 European Society of Cardiology Guideline Recommendation on thromboprophylaxis in atrial fibrillation (adapted from the original document).



AF: Atrial Fibrillation; OAC: Oral Anticoagulant Therapy; AP: Antiplatelet Drugs; LAAO: Left Atrial Appendage Occlusion; NOAC: Non-vitamin K Oral Anticoagulant; VKA: Vitamin K Antagonist.

CLINICAL SIGNIFICANCE

- Formal guidelines play an important role in disseminating the state-of-the-art knowledge and are expected to provide simple practical guidance for atrial fibrillation management, which could be easily applied in clinical practice by clinicians with diverse educational backgrounds and various clinical commitments.
- We provide an appraisal on the recommendations pertinent to the prevention of atrial fibrillation-related stroke or systemic thromboembolism, as provided in recently published guidelines for the management of this arrhythmia.