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EDITORIAL

Should All Patients With Atrial Fibrillation Receive an Oral Anticoagulant in the Era of Non-Vitamin K Anticoagulants?*

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KEY WORDS: *atrial fibrillation; anticoagulation; vitamin K anticoagulants; bleeding; non-vitamin K anticoagulants; risk stratification schemes; CHA_2DS_2-VASc score;HAS-BLED score; lone atrial fibrillation*

Abbreviations
AF = atrial fibrillation
INR = international normalized ratio
LAA = left atrial appendage
NOACs = non-vitamin K oral anticoagulants
OAC = oral anticoagulant(s)
TTR = time in therapeutic range
VKAs = vitamin K antagonists

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ABSTRACT

Oral anticoagulants (OAC) decrease the thromboembolic risk of non-valvular atrial fibrillation (AF) at the expense of increased bleeding. Over the years, several risk stratification schemes for both stroke and bleeding risk have been devised, among which lately the respective CHA_2DS_2-VASc and HAS-BLED scores predominate. However, even when the bleeding risk score is high, the guidelines recommend not to withhold OAC at least for patients with high stroke risk, but to attempt to concomitantly modify the conditions contributing to the high bleeding risk. The CHA_2DS_2-VASc score has been considered more reliable than other scores in identifying "truly low-risk" patients who do not require OAC, in whom the risk of bleeding may negate the protective effect of OAC. Some have suggested more complex schemes to better identify very low risk patients, but these schemes may lead to more extensive and costly assessments to decide on a relatively simple question, i.e. the need or not for anticoagulation therapy. In the era of non-vitamin K oral anticoagulants (NOACs), this may not be necessary any more, and a simple recommendation of providing every AF patient with OAC therapy may turn out to be a more practical and realistic approach, as long as these newer agents remain safe and effective.

INTRODUCTION

Oral anticoagulants (OAC) decrease the thromboembolic risk of non-valvular atrial fibrillation (AF) at the expense of increased bleeding.[1] Over the years, several risk stratification schemes for both stroke and bleeding risk have been devised, among which lately the respective CHA_2DS_2-VASc and HAS-BLED scores predominate.[2-8] The general principle is to strike a balance between lower thromboembolic risk with no possible excess in bleeding.[3] Indeed, the data indicate that use of vitamin K antagonists (VKA) has led to a steady decline in ischemic stroke rates over the years in AF patients with either no further increase in the hemorrhagic stroke rate or at least a positive net benefit.[9,10] The advent of non-vitamin K oral anticoagulants (NOACs) may render them a more attractive therapeutic option.[11]

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Initially, the $CHADS_2$ score was introduced and widely promoted for over 10 years as a valuable tool to identify "high-risk" patients, but with very poor ability to discern low-risk patients ($CHADS_2$ score 0), in whom the annual stroke rate was still around 2%, rising as high as 3.2-4.5%/year when substratified by the CHA_2DS_2-VASc score.[12,82] Then, the CHA_2DS_2-VASc score was introduced and proven to be superior to $CHADS_2$ in identifying 'low risk' AF patients.[2,4,5] However, the search for more reliable risk stratification schemes and identification of "truly low-risk" patients has continued in an attempt to identify all possible risk factors causing a high thromboembolic risk;[13-15] to name a few: renal insufficiency, obesity, obstructive sleep apnea, tobacco and ethanol use, ethnicity, genetics, echocardiographic and biochemical or thrombotic parameters, which can also predict adverse thromboembolic events.[6,7,14-17] In essence, though, adopting more complex schemes may lead to more extensive and costly assessments to decide on a relatively simple question about the need for OAC. In the era of NOACs,[11] this may really not be needed, as it is possible for all AF patients to receive OAC therapy, as long as these newer agents further prove their sustained efficacy and safety.

RISK STRATIFICATION SCHEMES

The CHA_2DS_2-VASc score (congestive heart failure; hypertension; age ≥75 years [doubled]; diabetes; previous stroke, transient ischemic attack, or thromboembolism [doubled]; vascular disease; age 65 to 75 years; and sex category)[18] is currently the recommended tool by all guidelines for estimating the risk for thromboembolism in non-valvular AF patients and determining the need for OAC therapy.[19-22] The only risk that is controversial in these guidelines is female gender, which is assigned a CHA_2DS_2-VASc score of 1, but most apply it when females are aged >65 years, while they refer to all patients aged <65 years without co-morbidities regardless of gender as low-risk patients.[23]

In particular, all authorities recommend OAC therapy for CHA_2DS_2-VASc score ≥2 for both genders, while the recommendations for CHA_2DS_2-VASc score of 1 are not consistent. The more recent (2012) ESC guidelines recommend OAC (preferably NOAC) therapy for patients with CHA_2DS_2-VASc score ≥1, when score of 1 is not due to gender.[19] The 2014 American guidelines recommend no antithrombotic therapy or treatment with an OAC or aspirin for such patients,[20] while the 2014 Canadian guidelines consider that women with vascular disease do not qualify for OAC therapy unless they are aged ≥65 or have an additional $CHADS_2$ risk factor.[21] The recommendation for OAC for male patients with a CHA_2DS_2-VASc score of ≥1, also adopted by NICE in 2014 (https://www.nice.org.uk/guidance/cg180), was prompted by compelling evidence from studies showing a high annual stroke risk in AF patients with a CHA_2DS_2-VASc score of 1 and no OAC treatment, ranging from 0.5% to 6.6%/year.[5,24-27] Thus, according to an American study, two-thirds of patients with AF who were previously not recommended for OAC are now recommended under the 2014 American guidelines.[22] Some data indicate that among AF patients with only one additional stroke risk factor (*i.e.* CHA_2DS_2-VASc= 1 in males or 2 in females), the rates of major adverse events may still be high, despite being anticoagulated,[28] attributable to inadequate time in therapeutic INR range (TTR) in warfarin-treated patients. The CHA_2DS_2-VASc score is also predictive of thromboembolism in conjunction with cardioversion for patients even with a single risk factor, if left without OAC.[29]

CHA_2DS_2-VASc 1 in women

Although there is agreement that AF women over 65 years (CHA_2DS_2-VASc score 2) with no additional risk factors have a higher risk than men of similar age (CHA_2DS_2-VASc score 1),[30] the issue of whether younger (<65 years) women with no other risk factors (CHA_2DS_2-VASc score 1) still have a higher risk than men (CHA_2DS_2-VASc score 0 remains controversial. In some studies female patients with no other risk factors have >2-fold higher risk of stroke compared with patients with CHA_2DS_2-VASc score of 0.[31,32] Newly identified AF in apparently healthy women, initially free of any risk factor, appears to portend an unfavorable prognosis if not treated with OAC therapy, as there is no reliable way to identify in advance those who will not subsequently develop cardiovascular risk factors and will thus continue remaining at low risk.[32] Other studies indicate that women <65 years and without other risk factors ("lone atrial fibrillation") have a low risk for stroke similar to men (0.7% vs 0.5%, P=0.09), and thus they may not need OAC, at least when considering VKA therapy.[33] However, the weight of emerging evidence leans towards the fact that women appear to have increased thrombogenicity for a variety of reasons and that this group of patients still remains at higher risk for ischemic events than non-AF female patients.[5,31] This high event rate in females with AF supports the recommendation that thromboprophylaxis is still necessary for patients who have only 1 risk factor (female gender) of the CHA_2DS_2-VASc scoring scheme, preferably with use of a NOAC.[5,31] However, this position has not been adopted yet by current guidelines.

In the 2012 ESC guidelines, female gender alone as a single risk factor (CHA_2DS_2-VASc score of 1) is ascribed a hazard ratio of 1.17 for thromboembolic event and OAC is not recommended if they clearly fulfil the criteria of 'age <65 and lone AF'.[19] The 2014 American guideline for nonvalvular AF and a CHA_2DS_2-VASc score of 1 (not distinguishing men from women) recommends to consider no antithrombotic therapy or treatment with OAC or aspirin (class IIb).[20] Finally, the 2014 Canadian guideline considers female gender associated with low stroke risk.[21]

CHA_2DS_2-VASc 0 (men <65 years with no risk factor)

Male patients aged <65 years with no risk factors may be the only group with a truly low risk not in need for OAC. How-

ever, these data were derived mostly or exclusively from studies utilizing VKAs, hence in the era of NOACs, this may need to be modified. In the initial validation cohort, this group had a thromboembolic risk of 0% at 1 year,[18] but subsequent studies raised it higher at approximately 1%, even up to 2.4%.[2,5,25,34-38]

Among patients with CHA_2DS_2-VASc score of 0, hence very low risk of ischemic stroke, only those with moderately elevated bleeding risk appear to have a net clinical disadvantage from warfarin treatment (ie, 1.7%/year),[39] and this may not prove to be so with NOAC therapy.[39,40] In general, according to 'real world' data, when the risk of bleeding and stroke are both high, NOACs appear to have a greater net clinical benefit compared to VKA.[40,41]

The threshold for initiating OAC treatment has been calculated as a stroke rate of 0.9% per year, based on the balance of ischemic stroke reduction vs intracerebral bleeding with the availability of NOACs.[42] It appears that almost all AF patients with a CHA_2DS_2-VASc score of 1 belong to this category. The question remains whether this also applies to AF patients with a CHA_2DS_2-VASc score of 0.

Several observational studies of 'lone' AF patients (younger patients with no comorbidities), comprising 10-20% of all AF patients, showed that the prognosis of such patients is favourable as long as they stay free of manifest underlying cardiac or other diseases and known clinical stroke risk factors.[43-45] Comorbidities that may emerge subsequent to the initial diagnosis can modulate progression and complications of AF, mainly aging or development of hypertension which do increase thromboembolic risk. Thus, baseline risk stratification score is not reliably predictive of thromboembolism in these patients.[44]

Thus, although "lone" AF patients were initially deemed of good prognosis with regards to thromboembolism and mortality, compared with the general AF population, a more poignant look at some old and emerging new data suggest otherwise.[46-48] Although this entity of "lone" or "idiopathic" AF is currently disputed,[49] it is usually a diagnosis of exclusion. However, conditions that are increasingly recognized over the recent years as associated with AF, such as obesity,[50] sleep apnea,[17] alcohol intake, exercise and sports activity,[51] or genetic factors render this exclusion diagnosis more difficult.[52,53] According to current guidelines, 'lone' AF patients do not need any long-term thromboprophylaxis, but regular clinical re-assessment of stroke risk is required.[19,45]

Other Risk Factors and Scores

In addition to the risk factors included in the CHA_2DS_2-VASc score, investigators have studied several other risk factors and comorbidities documenting their close association with AF risks and complications. Such factors may include obesity, obstructive sleep apnea, impaired renal function, structural left atrial and left atrial appendage (LAA) abnormalities, blood or metabolic abnormalities, tobacco use, and perhaps heavy AF burden or permanent AF.[6,7,13-15,17,50,54-59]

Thus, aiming to improve upon thromboembolic risk prediction, other scores than the CHA_2DS_2-VASc score, have been proposed, such as R_2CHADS_2 and ATRIA, which additionally include renal function, but found inferior to CHA_2DS_2-VASc score.[7,35] although in other comparisons, the R_2CHADS_2 and ATRIA scores seem to perform better that the CHA_2DS_2-VASc score.[54,60,61] However, even in these studies, the low-risk groups (0 score) still had a stroke rate of about 0.40-2.40 per 100 person-years, but not zero, as initially claimed. Of course, there is a debate about the threshold above which a patient should be treated with anticoagulation, whether this should be <1.5% or <1%, etc. However, with the advent of NOACs, this threshold may be lower compared to VKAs.

Increased size of the left atrium has also been considered a risk factor for a complicated course.[62-69] Left atrial fibrosis detected by magnetic resonance imaging has also been proposed as a marker of stroke.[55] Additionally, the morphology of the LAA has been shown to be related to thromboembolic risk. When classified into 4 types (cactus, chicken wing, windsock, and cauliflower) by cardiac imaging, patients with the "chicken wing" LAA morphology have a lower thromboembolic risk, while patients with a "cauliflower" LAA had a higher stroke rate.[15,70]

The types of AF, paroxysmal vs permanent, or the frequency and/or burden of paroxysmal AF, have not been clearly shown to weigh on the decision on the need for OAC therapy. Ischemic stroke is about as common in paroxysmal AF as in permanent AF.[71] However, some studies have indicated that thromboembolic events may be commoner in permanent nonvalvular AF than in paroxysmal AF.[32,72-74] High-burden AF (≥10%) has been associated with progressive left atrial structural remodeling and disease progression ("AF begets AF"),[75] independent of other known factors. This may have some therapeutic implications, indicating that we should monitor our patients with early-onset AF for disease progression using echocardiographic methods, and consider early interventions with ablation[75,76] and/or anticoagulation.

Importantly, despite current guidelines that recognize that high-risk AF patients definitely need OAC, while low-risk patients may not, under- and/or over-treatment still takes place.[77-84] However, it is interesting that even patients at the lowest possible risk profile (CHA_2DS_2VASc-scores=0) are still receiving OAC therapy at rates ranging from 17% to 39%, as if many practicing physicians consider any patient with AF as being at risk for thromboembolic event, and if one includes antithrombotic therapy with antiplatelet agents, these rates reach up to 80% (!), which may only increase in the future with a wider usage of NOACs as a safer, more effective and more convenient antithrombotic therapy.

HEMORRHAGIC RISK AND SCORE

International guidelines recommend that bleeding risk,

usually as determined by the HAS-BLED score, should not be a reason to withhold OAC in AF patients.[19-21] The benefit of stroke reduction conferred by OAC in AF patients outweighs the increased risk of major bleeding, even among those patients with history of prior bleeding.[85] Nevertheless, a high bleeding risk should not deter one from considering OAC but rather urge for potential modification of this risk by addressing correctable or modifiable bleeding risk factors,[86] e.g. by optimizing hypertension therapy ("H"), avoiding non-steroidal anti-inflammatory drugs[87] and limiting concomitant antiplatelet drugs ("D"), and minimizing the lability of INR in patients on VKA ("L"), which could alternatively be managed by preferential use of a NOAC over VKA.[88]

NON-VITAMIN K ANTAGONISTS

The availability of NOACs has transformed the landscape of stroke prevention in AF.[11,89,90] NOACs have a favourable risk-benefit profile, with significant reductions in stroke, intracranial hemorrhage, and mortality, and with similar major bleeding as with VKAs, but increased gastrointestinal (GI) bleeding, at least for some, albeit not all, NOACs.[85] Indeed, in the epoch of VKAs, in an attempt to maintain a balance between ischemic stroke reduction with OAC against increased risk for intracranial hemorrhage, the adopted notion was that low-risk patients, as indentified by the CHA_2DS_2-VASc score, were considered those with thromboembolic rates <1%/year who did not need any OAC therapy.[91,92] However, in the current era of NOACs, one may either commence treatment with a NOAC, especially in new patients, considering it a safer, albeit more expensive, approach, or use better guidance when choosing a VKA agent. Adequate (>70%) individual time in therapeutic range (TTR) of the INR (2.0-3.0) has been associated with low stroke and bleeding risks. A new score has been introduced to help in this decision by assessing the SAMe-TT2R2 score (Sex female, Age <60 years, Medical history with >2 comorbidities, Treatment with interacting drugs, eg, amiodarone, Tobacco use [doubled], Race [doubled]).[28,93] Those patients with a SAMe-TT2R2 score <2 can apparently be managed effectively with a VKA, whereas patients with a SAMe-TT2R2 score >2 can be offered a NOAC. In the future, placing every patient on a NOAC may simplify matters and provide optimal ischemic stroke protection with a very low bleeding risk. For now, one may follow a more individualized approach (Fig. 1). A decision model analysis has suggested

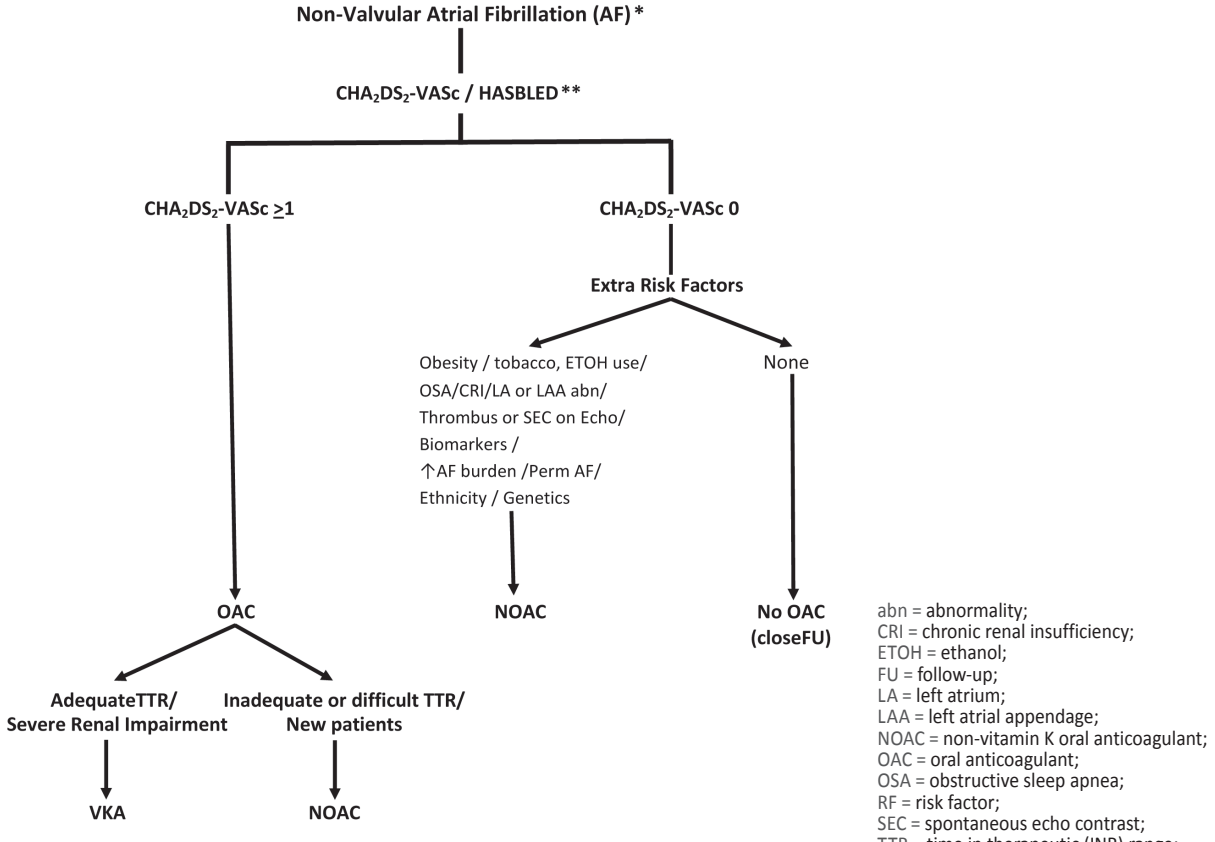

FIGURE 1. Individualized algorithm for oral anticoagulation therapy guidance in patients with non-valvular atrial fibrillation (AF).

that a VKA may be preferable in patients with a stroke risk ≥1.7% per year, whereas treatment with a safer NOAC may be considered in patients with a stroke risk ≥0.9% per year.[42] Recent data indicate that the estimate for the annual risk of ischemic stroke is 1.61% for CHA_2DS_2-VASc score of 1, meeting the threshold for using NOACs (0.9%), but remaining below the threshold for VKA (1.7%).[94] In this analysis, the risk of ischemic stroke was 0.68% for CHA_2DS_2-VASc score of 0 and 2.49% for CHA_2DS_2-VASc score of 2. However, one may argue that the stroke risk rate of ~0.7% for CHA_2DS_2-VASc 0 is still much higher than the risk of intracranial hemorrhage (0.10% to 0.5%) reported in NOAC trials.[95-98]

CONCLUSION

The most feared complication of AF is a multi-fold increase in the risk of ischemic stroke as compared to sinus rhythm, with attendant high fatality or permanent disability, which renders thromboprophylaxis in every AF patient indispensable. NOACs have been proven equivalent or superior to VKAs in the treatment of non-valvular AF, with high thromboembolic protection but with lower intracerebral bleeding rate. This may urge us to generalize their use in most, if not all, patients with nonvalvular AF regardless of their risk stratification score. The accumulated evidence appears compelling that at least those with a CHA_2DS_2-VASc score of ≥1, should receive OAC. For patients with a CHA_2DS_2-VASc score of 0, one may wish to consider additional risk factors beyond those in scores to determine whether there is a need for thromboembolic protection that outweighs the bleeding risk, preferably with use of NOACs, and for now adopt an individualized approach using clinical judgement by taking into account patient's clinical and financial status, options and preferences (Fig. 1).

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