CONTEMPORARY REVIEW

Patients with atrial fibrillation and CHA_2DS_2-VASc score 1: "To anticoagulate or not to anticoagulate? That is the question!"

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There is uncertainty regarding the optimal therapy for preventing thromboembolic stroke in patients with atrial fibrillation and CHA_2DS_2-VASc score 1. In fact, no extensive data on this topic are available, and the latest guidelines provide different recommendations. In this article, we examine current results on the use of various antithrombotic agents, including the newer oral anticoagulant agents, in those patients. Several factors must be considered and weighted in this setting and may influence the choice of the antithrombotic approach: the expected incidence of both thromboembolic stroke and bleeding complications as well as their impact in terms of morbidity and mortality, the patient's bleeding risk profile, an accurate, further stratification of the thromboembolic risk beyond the CHA_2DS_2-VASc score, and socioeconomic issues.

KEYWORDS Atrial fibrillation; Warfarin; Novel oral anticoagulant; Bleeding risk: Thromboembolic risk

ABBREVIATIONS ACC = American College of Cardiology; **ACTIVE-W** = Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events; **AF** = atrial fibrillation; **AHA** = American Heart Association; **ARISTOTLE** = Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; **AVERROES** = Apixaban versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin k Antagonist Treatment; **CHA_2DS_2-VASc** = Congestive heart failure, Hypertension, Age $\geq$75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65–74 years, Sex category; **$CHADS_2$** = Congestive heart failure, Hypertension, Age, Diabetes, prior Stroke; **ENGAGE** = Effective Anticoagulation with Factor Xa Next Generation; **ESC** = European Society of Cardiology; **HAS-BLED** = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly ($\geq$65 years), Drugs/alcohol concomitantly; **RE-LY** = Randomized Evaluation of Long-term Anticoagulation Therapy; **ROCKET-AF** = Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation

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Stratification of patients with atrial fibrillation (AF) according to the CHA_2DS_2-VASc score (Congestive heart failure, Hypertension, Age $\geq$75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65–74 years, Sex category) rather than the $CHADS_2$ score (Congestive heart failure, Hypertension, Age, Diabetes, prior Stroke) allows better discrimination of those at low thromboembolic risk. Although the 2 scores have some risk factors in common, our unpublished data show that among AF patients with $CHADS_2$ score 0, 27% have CHA_2DS_2-VASc score 0, 32% CHA_2DS_2-VASc score 1, and approximately 40% CHA_2DS_2-VASc score >1. However, clinical management of AF patients with CHA_2DS_2-VASc 1 is not infrequent. Results from the ARISTOTLE trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) indicated a prevalence of 10% among those patients,[1] and this percentage was more recently confirmed in a large real-world registry.[2] There is uncertainty regarding the optimal antithrombotic therapy in low thromboembolic risk patients with CHA_2DS_2-VASc score 1 because this score has only recently been introduced, and there is no close correlation in the thromboembolic risk of the $CHADS_2$ and CHA_2DS_2-VASc scores. Therefore, no firm conclusion can be derived from historical investigations that compared different antithrombotic approaches according to the $CHADS_2$ score, and only few, albeit increasing, data on the topic are available from more recent studies. This uncertainty remains in light of current guidelines. European Society of Cardiology (ESC) Guidelines indicate that use of warfarin or novel oral anticoagulants in patients with CHA_2DS_2-VASc score 1 should be based on assessment of the risk of bleeding complications and patient preference (class of recommendation IIa, level of evidence A).[3] American College of Cardiology/American Heart Association (ACC/AHA) Guidelines[4] state that no antithrombotic therapy or treatment with an oral anticoagulant or aspirin may be considered (IIb, C).

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Historical data on thromboembolic risk in AF patients with $CHADS_2$ score 0–1

The $CHADS_2$ score, first published in 2001, was derived by combining risk factors from historical studies and tested in a cohort of 1773 patients.[5–7] However, fewer than 10% of patients screened in those investigations were included, and the majority of stroke risk factors were inconsistently defined or not systematically recorded.[8] Current guidelines based on the $CHADS_2$ score recommend initiation of anticoagulant therapy in patients with a score ≥ 1.[9,10] In the first validation cohort, the adjusted stroke rate was 1.9% per year in patients with $CHADS_2$ 0 and 2.8% per year in those with score 1, whereas in the Euro Heart Survey the incidence of stroke was lower (1.4% per year in patients with $CHADS_2$ 0 and 1.9% per year in those with score 1).[5,11] Similar discrepancies were observed in 2 different Japanese cohorts in which ischemic stroke rates ranged from 0.5% to 0.6% per year in patients with $CHADS_2$ 0 and from 0.9% to 2.8% per year in those with score 1.[12,13] The reasons for these apparent differences in the occurrence of stroke remain unclear, but the decade-long differences in the management of coexisting diseases might have a role. Moreover, the risk of patients with $CHADS_2$ 1 could vary depending on the specific conditions (risk factors) composing the score. However, although the $CHADS_2$ score is simple and easy to calculate, its limitations in stroke risk stratification are evident. In fact, many patients classified as "low risk" using the $CHADS_2$ score have stroke rates $>1.0\%$ per year, and a $CHADS_2$ score 0 does not reliably identify AF patients who are "truly at low risk."

Thromboembolic and bleeding risk in AF patients with CHA_2DS_2-VASc score 1

In clinical practice, it is not infrequent that, borrowing the famous monologue of the Shakespeare's tragedy, doctors have this hamletic doubt: "to anticoagulate or not to anticoagulate AF patients with CHA_2DS_2-VASc score 1"? When choosing the appropriate therapeutic approach, it is relevant to balance the degree of ischemic protection provided by antithrombotic therapy with the "iatrogenic" bleeding risk; thus, it appears crucial to first establish the untreated thromboembolic risk in this setting.

A wide range in the incidence of thromboembolic complications without anticoagulant therapy has been reported among AF patients with CHA_2DS_2-VASc 1 (0.2% to 6.6% per year; Table 1).[11,14–25] This variability may be due in part to differences in the design of the various studies: (1) use of a "stricter" vs a "wider" definition of thromboembolic outcome measure (ie, ischemic stroke vs a combined end-point of stroke and systemic embolism vs a composite end-point including stroke, transient ischemic attack, systemic embolism, and pulmonary embolism; (2) different prevalence of female patients without any additional risk factors, who have a low risk of thromboembolic events; (3) variable penetration of concomitant antiplatelet therapy; (4) inclusion or no inclusion of a quarantine period and different durations of quarantine periods; (5) enrollment of patients receiving anticoagulant therapy in some investigations in which the authors subsequently extrapolated the estimated untreated stroke risk; and (6) retrospective validation of the CHA_2DS_2-VASc score in different patient populations (community vs hospitalized). Of note, European registries indicated very low yearly rates of ischemic stroke in AF patients with CHA_2DS_2-VASc 1 without anticoagulant therapy ($\leq 0.7\%$), which led to further concerns regarding indiscriminate unselected use of oral anticoagulation in those patients.[16,21] The latest European registry reported a 1-year stroke rate of 1.55% for CHA_2DS_2-VASc score 1 [male] and score 2 [female], but this incidence was reduced to 0.96% per year when only primary discharge diagnoses of ischemic stroke and full follow-up were used.[17] Conversely, large studies of Asian populations showed that the incidence of this complication may be significantly higher ($\geq 2\%$/year).[19,20,23,24] Similar racial differences were noted in the recent randomized phase III trials on non–vitamin K antagonists oral anticoagulants.[3,4] To date, the reasons for such racial discrepancies are unclear. However, we can speculate that genetic factors in Asian populations may account for the pronounced thromboembolic risk, and the higher prevalence of undiagnosed risk factors (ie, more vascular disease) in the related studies might be hypothesized. Moreover, the power of vascular disease in predicting the risk of stroke in AF patients has been reported to be higher in Asian than European populations (hazard ratio 1.96 vs 1.12–1.22).[16,18,24] Finally, penetration of concomitant antiplatelet therapy was higher in the European investigations, which may have attenuated in part the occurrence of ischemic stroke.

With regard to "on-treatment" bleeding risk in patients with CHA_2DS_2-VASc score 1, randomized data indicated an incidence of major bleeding of 1.2% per year with warfarin and 0.8% per year with apixaban, with annual rates of intracranial bleeding of 0.35% and 0.2%, respectively.[1]

We next examine the available results on different antithrombotic strategies in AF patients with CHA_2DS_2-VASc score 1.

Oral anticoagulant and aspirin therapy

Data from the ARISTOTLE trial showed a 0.53% per year incidence of stroke with warfarin in the patients studied.[1] If we hypothesize that warfarin can reduce the risk of stroke by 64%, the estimated untreated stroke risk should be 1.47% per year.[26] Of note, use of warfarin vs no treatment in patients with CHA_2DS_2-VASc 1 was associated with higher risk of intracranial bleeding but very low rates of the complication (0.14% vs 0.10%) and high number needed to harm (2500).[27]

There is a paucity of data on the comparison of warfarin vs aspirin. In the Stockholm region registry, the rates of ischemic stroke were reduced with warfarin compared to aspirin in AF patients with CHA_2DS_2-VASc 1 (0.3% vs 1.2% per year), with no difference in bleeding risk.[28]