

How should we treat patients with atrial fibrillation and a CHADS₂ score of 1?

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Warfarin is more effective than aspirin at preventing stroke in atrial fibrillation (AF), but is associated with hemorrhagic events. In patients with a CHADS₂ score of 1, the present guidelines for the management of AF indicate that the choice between oral anticoagulation and aspirin is discretionary, depending on each patient and on the bleeding risk. In *post-hoc* analysis and observational data, oral anticoagulation seemed to be associated with a decreased risk of events in such patients, whereas no such result seems apparent for patients receiving only an antiplatelet agent. We think that such patients should thus be treated with oral anticoagulant whenever possible, unless there is a high risk of a hemorrhagic event.

Randomized trials have demonstrated that, compared with a placebo, adjusted-dose warfarin reduces the incidence of stroke by approximately 60% in patients with AF. By contrast, antiplatelet agents have only demonstrated a reduction of approximately 20% in the incidence of stroke. [1]. Oral anticoagulation with vitamin K antagonists (VKAs) is better at reducing the risk of stroke but is associated with the incidence of serious bleeding [2].

The CHADS₂ score has been used to identify AF patients at low risk of stroke (less than 1–2% per year), for whom the risks and inconvenience of VKAs outweigh their potential benefits [3]. The CHADS₂ score is calculated as one point each for a history of heart failure, a history of hypertension, age over 75 years, diabetes and two points for a prior stroke [3]. It does not apply to patients with a valvular prosthesis or a mitral stenosis for whom an oral anticoagulant is recommended, regardless of the risk-stratification score. In patients with an intermediate risk of stroke, that is, a CHADS₂ score of 1 (2–4% annual rate of stroke), available evidence from clinical trials is inconclusive, and the present American Heart Association (AHA)/American

College of Cardiology (ACC)/European Society of Cardiology (ESC) guidelines for the management of AF still indicate that the choice between VKAs and aspirin in these patients is discretionary, depending on each patient and especially on the bleeding risk [4]. This uncertainty in treatment guidance [4,5] leads to significant differences in the prescription of anticoagulation and antiplatelet therapy among these patients from case-to-case, and is finally subject to physician discretion and patient preference [6–8].

Who are the patients with a CHADS₂ score of 1 & how they are treated in real life?

Patients with a CHADS₂ score of 1 may account for 15–30% of all the patients with AF whether one considers only nonvalvular AF or all AF patients [7,8]. In the series published by Lee, among 1502 patients who were treated for nonvalvular AF, 28% of the patients had a CHADS₂ score of 1. Among 6500 unselected patients with AF seen in our institution, 16% had a CHADS₂ score of 1 and were liable for treatment with an antiplatelet or VKA. Among the four risk factors leading to a CHADS₂ score of 1, criteria were distributed among our patients: 31% were over 75 years old, only 4% had diabetes, 38% had heart failure and 27% had hypertension [8].

The 2006 guidelines from ACC/AHA/ESC certainly helped to define the therapeutic strategy more clearly for many patients with AF. However, while patients with one risk factor for stroke were theoretically likely to be treated by an anticoagulant some years ago, the acceptance in these last guidelines that patients with a CHADS₂ score of 1 may also be treated with aspirin alone probably led some physicians to choose aspirin as a first-line treatment or to switch VKAs to aspirin to avoid long-term monitoring with international normalized-ratio control. In our series of 1012 patients with a CHADS₂



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score of 1, oral anticoagulant was prescribed for 60% of the patients while the 40% remaining patients were either treated with an antiplatelet agent alone or received no antithrombotic treatment at all [8]. Patients with a CHADS₂ score of 1 and who were treated by VKAs are significantly younger and are more often male patients [7,8]. Patients with a CHADS₂ score of 1 with permanent AF are more often treated with VKAs than those with paroxysmal AF [7,8], perhaps as a result of the belief that paroxysmal AF would lead to fewer embolic events, whereas this should not particularly be the case since antithrombotic treatment should not depend on the type of AF [4,9]. In the group of patients not treated with VKAs, they are more likely to have coronary artery disease and, therefore, antiplatelet agents are most frequently prescribed [7,8], a point discussed later in this article. Nevertheless, patients whose only risk factor is their greater age are less often treated with anticoagulant and this points out the reluctance to treat elderly patients with VKAs.

Improving the risk stratification in patients with a CHADS₂ score of 1

The risk of events is variable among the many patients with a CHADS₂ score of 1. The guidelines indicate that there are less validated risk factors of thromboembolic events: female gender, age of 65–74 years, coronary artery disease and thyrotoxicosis [5]. They do not directly affect the antithrombotic strategy based on the moderate risk factors of the CHADS₂ score. However, these weaker risk factors, in addition to a CHADS₂ score of 1, might be considered a '1.5 score' and may lead to the prescription of warfarin rather than aspirin alone.

Hypertension is probably the weaker risk marker in the CHADS₂ score. A history of hypertension in AF is sometimes associated with a low risk of events [8,10,11]. Healey did not find that a history of hypertension was an independent predictor of stroke in the AF Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE-W) [11]. The influence of hypertension on prognosis may have changed over recent years due to more vigorous management of hypertension [12]. In AF patients, a history of hypertension without further precision is probably not enough to accurately assess the risk of stroke if one does not consider the severity of blood-pressure increase, and whether hypertension is treated and/or controlled or not. By contrast, other parameters, such as peripheral arterial disease may be taken into account

for risk stratification. Alternative schemes, other than the CHADS₂ score, have been proposed, such as CHA₂DS₂-VASc, and might help to better determine who are truly 'low-risk' subjects with very low event rates and no need for anticoagulation [13].

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It is worth noting that an important part of events recorded in the follow-up of patients with AF are deaths [8]. In the future, we will perhaps consider the risk stratification of events in these patients differently. Our evidence-based strategy for pharmacological therapy in AF almost only forms around studies performed almost 20 years ago that demonstrate an effective prevention of stroke but not a significant reduction of mortality. Some new medical treatment may effectively decrease mortality in AF [14]. Decreasing the risk of death seems to be the first relevant end point in AF, and decreasing the thromboembolic risk should be considered subsequently [15]. The risk of death is certainly different in a patient aged 45, with controlled hypertension, than in a patient with coronary artery disease who is aged 90, although the risk of stroke is theoretically similar.

Evaluation of the risk of bleeding in patients with a CHADS₂ score of 1

Aspirin monotherapy is not a safer alternative to warfarin in AF, as demonstrated in the Birmingham AF Treatment of the Aged (BAFTA) and the Warfarin Versus Aspirin for Stroke Prevention in Octogenarians with AF (WASPO) trials [16,17]. In the latter trial, 300 mg of aspirin had a worse tolerance than oral anticoagulant in the elderly, with more adverse events. There are currently four published bleeding risk scores, but their major drawback is that they have dissimilar characteristics and scoring systems, which hampers their use for daily clinical practice [18–21]. They take into account risk factors, such as age, gender, comorbidity, malignancy, renal function, falls risk, genetics factors, ethanol abuse or concomitant antiplatelet use. Some bleeding predictor models include fewer variable risk factors compared with others, but may be less

relevant to AF populations since they were built irrespective of the indication for warfarin, or validated in venous thromboembolism [18,19]. Two bleeding risk schemes are based on risk factors drawn from AF populations, but include more variables, and the calculation of bleeding risk is thus complex [20,21]. Clearly, the relationship between stroke and bleeding risk factors, and thromboembolic events and major bleeding now have to be examined prospectively in AF cohorts to establish the best bleeding risk index and finally a unifying consensus on how to treat patients with a CHADS₂ score of 1.

■ Are VKAs more effective than antiplatelet agents in patients with a CHADS₂ score of 1?

There is currently no randomized trial specifically addressing the issue of the best antithrombotic strategy in patients with a CHADS₂ score of 1. However, some *post-hoc* analysis and some observational data may help to compare anticoagulant to antiplatelet agents in this setting.

Some studies have suggested that a vigorous antithrombotic treatment for AF, considered by present guidelines as overtreatment, was less detrimental than undertreatment [22]. This may also be the case in patients with a CHADS₂ score of 1. In a subgroup analysis of the randomized ACTIVE-W study, Healey *et al.* found that, among patients with a CHADS₂ score of 1, patients treated with oral anticoagulant had fewer strokes than those treated with a combination of both clopidogrel and aspirin [11].

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In patients with AF and a CHADS₂ score of 1, we found a lower incidence of stroke and/or death from all causes among patients treated with VKAs as compared with other patients [8]. Prescription of an anticoagulant was associated with a 58% decrease in the rate of death or stroke during follow up. Results remained similar after an adjustment for age and other confounding factors. By contrast, prescription of an antiplatelet agent was not associated with a lower risk of events. Lack of treatment with VKAs was independently and very significantly associated with the occurrence of a greater number of events. These results broadly support those obtained in

their series by Lee *et al.* [7]. The observational method in the two latter analyses [7,8], even after multivariate adjustment, certainly raises a question as to whether some groups were not merely managed better with a possible treatment bias. However, together, these studies suggest that while an antiplatelet strategy probably runs a higher risk of bleeding than an oral anticoagulant strategy, it is also associated with a lower benefit in reducing death and stroke. If one ever chooses to treat patients with an antiplatelet agent, the addition of clopidogrel to aspirin may reduce the risk of major vascular events, especially stroke, but may increase the risk of major hemorrhage [23].

Coronary artery disease associated with AF in patients with a CHADS₂ score of 1

One particular issue in patients with AF and a CHADS₂ score of 1 is the association with coronary artery disease. The importance of platelet-inhibitor drugs in preventing recurrent myocardial ischemia is enhanced in these patients, particularly those undergoing percutaneous coronary intervention [4]. Therefore, they are more likely to be treated in observational series and in real life with an antiplatelet agent than with VKAs alone [7,8]. However, Flaker *et al.* have demonstrated that administering warfarin plus aspirin in patients with AF shows no beneficial effect on vascular events (including coronary events), but does increase bleeding [24]. Aspirin should not be added for an associated stable vascular disease in a patient with AF receiving anticoagulation [25]. In addition, for anticoagulated patients, who present an acute coronary syndrome and/or undergo percutaneous coronary interventions, the most effective antiplatelet agent for the maintenance of coronary and stent patency is certainly clopidogrel. Ambiguity surely remains over optimal antithrombotic management strategies and its duration for patients with AF and a CHADS₂ score of 1 presenting with an acute coronary syndrome and/or undergoing percutaneous coronary intervention/stenting [26,27]. Clinicians need to balance the risk of stroke and thromboembolism against the risk of recurrent cardiac ischemia and/or stent thrombosis, and the risk of bleeding. A recent article comprehensively reviewed the published evidence and established a consensus statement on a ‘best practice’ antithrombotic therapy guideline for the management of antithrombotic therapy in such AF patients [28].

Conclusion

Prescription of an anticoagulant seems to be associated with a decreased risk of events, such as death and/or stroke in patients with AF and a CHADS₂ score of 1. No such result seems clearly apparent for patients receiving only an antiplatelet agent. The American College of Chest Physicians (ACCP) 8 guidelines in 2008 state that for patients with a CHADS₂ score of 1, either warfarin or aspirin may be administered, but with a preference for warfarin. Thus, such patients should be treated with an oral anticoagulant whenever possible. New developments expected from innovative oral direct-thrombin

blockers or oral factor-Xa inhibitors will certainly help to build different and more definitive strategies in the years to come.

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