

EDITORIAL COMMENT

Patients With Atrial Fibrillation and a CHA₂DS₂-VASc Score of 1

Are They at Low or High Stroke Risk?*

Menno V. Huisman, MD, PhD



Nonvalvular atrial fibrillation carries a risk for developing ischemic stroke that is lowered by anticoagulant therapy (1). This risk is not uniform and depends on whether a patient has either none or ≥ 1 of the following factors, known as the CHA₂DS₂-VASc stroke risk score: congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category. Both European (2) and U.S. (3) guidelines advocate estimation of a patient's stroke risk by use of the CHA₂DS₂-VASc score for initial risk stratification. The European Society of Cardiology (ESC) guideline recommends oral anticoagulant therapy (OAC) for male patients with a CHA₂DS₂-VASc score ≥ 1 and for female patients with a score ≥ 2 (the latter because this guideline does not classify female sex as a stand-alone risk factor). The U.S. guideline recommends use of OAC at a CHA₂DS₂-VASc stroke risk score ≥ 2 for patients of both sexes.

Decision making for thromboprophylaxis by antithrombotic therapy must balance the risk of stroke against the risk of major bleeding, especially intracranial hemorrhage, which is the most feared complication because it confers a high risk of death and disability. For optimal balancing of stroke and bleeding risk, net clinical benefit has been defined as

the annual rate of ischemic strokes and systemic emboli prevented by OAC minus the rate of intracranial hemorrhages attributable to OAC, multiplied by an impact weight (4,5). A recent Markov decision analysis model suggested that vitamin K antagonists are preferable in patients with a stroke risk $\geq 1.7\%$ per year, whereas treatment with the safer non-vitamin K oral anticoagulants should be considered in patients with a stroke risk $\geq 0.9\%$ per year (6).

Where do we stand in applying the CHA₂DS₂-VASc score in clinical practice and how robust are the data on which the application of CHA₂DS₂-VASc score in the guidelines is currently based? There is little or no doubt of the need for OAC in patients with CHA₂DS₂-VASc scores of ≥ 2 and of the very low-risk status in those with a CHA₂DS₂-VASc score of 0. However, because there are large differences in estimates of stroke risk without antithrombotic treatment, the real focus of debate is in patients with a CHA₂DS₂-VASc score of 1. Thus, studies have shown a 3-fold difference in the annual stroke risk in AF patients with a CHA₂DS₂-VASc score of 1 and no OAC treatment, varying from 0.6% to $>2.0\%$ (7).

SEE PAGE 1385

In this issue of the *Journal*, Lip et al. (8) assessed the stroke event rate in patients with a CHA₂DS₂-VASc score of 0 to 1 in a Danish hospital cohort. They observed a 1-year rate of stroke of 0.49% (intention-to-treat) in patients with a CHA₂DS₂-VASc score of 0 and a score of 1.55% (intention-to-treat) in patients with a CHA₂DS₂-VASc score of 1. These rates are comparable to an earlier analysis from Denmark, in which a rate of 2.01% was seen (9), but much higher than in the original publication validating the CHA₂DS₂-VASc score (10). In that publication, in the 103 patients who participated in the Euro Heart Survey 2006

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

From the Department of Thrombosis and Hemostasis, Leiden University Medical Center Leiden, Leiden, the Netherlands. Dr. Huisman has received research grants from Boehringer Ingelheim and GlaxoSmith-Kline; and has provided lectures and consultations for Bristol-Myers Squibb and Boehringer Ingelheim. The funding source had no role in the preparation of this manuscript.

registry with a CHA₂DS₂-VASC score of 0 and not treated with either OAC or aspirin, the annual thromboembolic rate (defined by ischemic stroke and other thromboembolic events) was 0%. For the 162 patients with a CHA₂DS₂-VASC score of 1, this annual risk was 0.6%. Of note, in the 2010 version of the ESC atrial fibrillation guidelines, a patient with a CHA₂DS₂-VASC score of 1 has a much higher stroke risk of 1.3% (11). This is not a rate derived from an untreated population but a post-hoc calculated stroke risk from analysis of warfarin-treated patients from the 2 SPORTIF (Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation) ximelagatran studies adapted for a presumed lack of effect of warfarin treatment (12). One wonders why the 2010 ESC guidelines incorporated this risk and not the original untreated annual stroke risk of 0.6% from the validation study.

The rate observed in the current study by Lip et al. (8) is also much higher than in a large Swedish cohort recently published in the *Journal* (7). In that study, the annual stroke rate was 0.1% to 0.2% for women with a CHA₂DS₂-VASC score of 1; for men, the ischemic stroke rate was 0.5% according to the Swedish Riks-Stroke and 0.7% according to the Swedish National Patient Register. A closer look at the study of Friberg et al. teaches us important lessons. First, if a wide definition of stroke was used (i.e., if it included hospital discharge diagnoses of stroke, transient ischemic attack, pulmonary embolism, arterial embolism, and stroke not specified as ischemic or hemorrhagic), the annual event rate for men increased by 44% to 1.3%. Second, Friberg et al. investigated the influence of the so-called quarantine period, used to avoid counting strokes that are concomitant with the first index diagnosis of AF, which can lead to spuriously elevated stroke rates. After 4 weeks, event rates stabilized at a level almost one-half as high, as if no quarantine period had been used. How did Lip et al. account for these variations? According to their Online Table w3, the 1-year stroke rates were reduced from 1.46% (continuous treatment) to 1.18% when using only primary discharge diagnoses of ischemic stroke, and it was lowered further to 0.96% with full follow-up. This latter figure is very near the cutoff for starting non-vitamin K oral anticoagulants (6). Because the quarantine period was only 14 days, it is unknown whether the rates would have been even lower, had a longer, more reasonable quarantine period of 4 weeks been used.

The most important drawback of the current studies is that all CHA₂DS₂-VASC validation exercises have been performed by retrospective collection of data in so-called “real-world” registries. It is therefore uncertain on what grounds physicians have selected their patients for treatment with OAC, aspirin, or no treatment. All calculations of CHA₂DS₂-VASC scores in these studies have clearly been performed post-hoc. Ideally, randomized trials should clarify this issue. Importantly, ongoing, large international prospective registries, including GARFIELD (Global Anticoagulant Registry in the FIELD) (13) and GLORIA-AF (Global Registry on Long-Term Oral Antithrombotic Treatment in Patients With Atrial Fibrillation) (14), which are studying the consequences of CHA₂DS₂-VASC risk score estimation with respect to starting “yes or no” with antithrombotic treatment, may yield a more accurate estimate of the stroke risk compared with the retrospective, single-country (e.g., Swedish and Danish) databases that seem to point in opposite directions (7,8).

Thus, although the CHA₂DS₂-VASC score has rightly been introduced into the clinical arena as a useful adjunct to the CHADS₂ score (i.e., congestive heart failure, hypertension [i.e., blood pressure consistently above 140/90 mm Hg, or treated hypertension on medication], age ≥ 75 years, diabetes mellitus [1 point for presence of each], and stroke/transient ischemic attack [2 points]), the current literature demonstrates that the CHA₂DS₂-VASC score has obviously been retrospectively validated in different patient populations, leading to markedly different estimated stroke risks. We are therefore left with uncertainty as to the true stroke rate in untreated patients with a CHA₂DS₂-VASC score of 1. This uncertainty should be incorporated into guidelines, thus enabling clinicians to build it into the decision process when confronted with their next patient presenting with nonvalvular atrial fibrillation. On the basis of current evidence, there is still equipoise as to whether a patient with a CHA₂DS₂-VASC score of 1 carries a low or a high stroke risk.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Menno V. Huisman, Leiden University Medical Center Leiden, Department of Thrombosis and Hemostasis, P.O. Box 9600, 2300 RC, Leiden, the Netherlands. E-mail: m.v.huisman@lumc.nl.

REFERENCES

- Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have non-valvular atrial fibrillation. *Ann Intern Med* 2007;146:857-67.
- Camm AJ, Lip GY, De Caterina R, et al. 2012 Focused update of the ESC guidelines for the

management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation. *Eur Heart J* 2012;33:2719-47.

3. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2014; 64:e1-76.
4. Singer DE, Chang Y, Fang MC, et al. The net clinical benefit of warfarin anticoagulation in atrial fibrillation. *Ann Intern Med* 2009;151: 297-305.
5. Friberg L, Rosenqvist M, Lip GY. Net clinical benefit of warfarin in patients with atrial fibrillation: a report from the Swedish atrial fibrillation cohort study. *Circulation* 2012;125:2298-307.
6. Eckman MH, Singer DE, Rosand J, et al. Moving the tipping point: the decision to anticoagulate patients with atrial fibrillation. *Circ Cardiovasc Qual Outcomes* 2011;4:14-21.
7. Friberg L, Skeppholm M, Terént A. Benefit of anticoagulation unlikely in patients with atrial fibrillation and a CHA₂DS₂-VASC score of 1. *J Am Coll Cardiol* 2015;65:225-32.
8. Lip GYH, Skjøth F, Rasmussen LH, Larsen TB. Oral anticoagulation, aspirin, or no therapy in patients with nonvalvular AF with 0 or 1 stroke risk factor based on the CHA₂DS₂-VASC score. *J Am Coll Cardiol* 2015;65:1385-94.
9. Olesen JB, Lip GY, Hansen ML, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ* 2011;342:d124.
10. Lip GY, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation. *Chest* 2010;137: 263-72.
11. Camm J, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010;31:2369-429.
12. Lip GY, Frison L, Halperin JL, et al. Identifying patients at high risk for stroke despite anticoagulation: a comparison of contemporary stroke risk stratification schemes in an anticoagulated atrial fibrillation cohort. *Stroke* 2010;41:2731-8.
13. Kakkar AK, Mueller I, Bassand JP, et al. International longitudinal registry of patients with atrial fibrillation at risk of stroke: Global Anticoagulant Registry in the FIELD (GARFIELD). *Am Heart J* 2012;163:13-9.e1.
14. Huisman MV, Lip GY, Diener HC, et al. Design and rationale of Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation: a global registry program on long-term oral antithrombotic treatment in patients with atrial fibrillation. *Am Heart J* 2014;167: 329-34.

KEY WORDS anticoagulants, aspirin, vitamin K, warfarin