

Risk stratification schemes for stroke in atrial fibrillation: the predictive factors still undefined

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Atrial fibrillation (AF) is the most common sustained cardiac rhythm disorder, which is associated with a substantial risk of mortality, morbidity, stroke, and thromboembolic complications.^{1,2} A substantial evidence base is in favor of anticoagulation with oral anticoagulants, which reduce the risk of stroke in AF population by two-thirds.^{1,3} Not all patients with AF seem to be equal in terms of thromboembolic risk; therefore, not all of them will benefit from anticoagulant treatment. The crucial role in the prevention of AF-related stroke is effective risk stratification. Although several schemes have been developed, the currently available models have limited discriminatory power.

Various clinical features are associated with a higher risk of stroke, and some of them have been used to develop different risk scores proposed in the last decade. Numerous risk factors have been derived from the analyses of non-warfarin users in clinical trials, registries, or health care facilities. Although none of the existing 5 risk schemes such as the Atrial Fibrillation Investigators, Stroke Prevention in Atrial Fibrillation, CHADS₂ (congestive heart failure, hypertension, age ≥ 75 years, diabetes, and prior stroke or transient ischemic attack), Framingham score, and the 7th American College of Chest Physicians Guidelines, seems to be superior to others, the various guidelines recommend using the CHADS₂ score for the initial assessment of stroke risk.⁴

Further analyses and the use of the above schemes in clinical practice allowed to identify new risk factors for stroke and led to the reevaluation of the existing risk stratification scores. Based on the previous analyses and experience, the CHA₂DS₂-VASc scheme was proposed, complemented with the new risk factors such as age of 65–75 years, vascular disease, and sex (female), as a tool with better positive and negative predictive

values for the identification of AF subjects at low risk of stroke.^{5,6}

So far, a number of guidelines have focused on a categorical approach to stroke prevention, with a focus on identifying patients at moderate or high risk for oral anticoagulation. Currently, it is recommended to use CHADS₂ or CHA₂DS₂-VASc scores to initially identify patients with nonvalvular AF at low risk of stroke who do not require antithrombotic treatment. However, the recommended scores do not incorporate all possible factors associated with a high thromboembolic risk. Factors such as impaired renal function, obstructive sleep apnea, and echocardiographic, biochemical, or coagulation parameters can also predict adverse thromboembolic events.

In the current issue of the *Polish Archives of Internal Medicine (Pol Arch Med Wewn)*, Sikorska et al⁷ reports their post hoc analysis of the population of patients with nonvalvular AF scheduled for pulmonary vein isolation. The authors attempted to reassess the predisposing factors for left atrial appendage (LAA) clot formation, including those not included in the CHA₂DS₂-VASc score.⁷ Analyzing the results of preprocedural transesophageal echocardiography, the authors revealed an LAA thrombus or dense echo contrast in 10% of the patients despite routine anticoagulation. Diabetes, age above 65 years, persistent AF, and renal dysfunction with an estimated glomerular filtration rate (eGFR) of less than 60 ml/min/1.73 m² were predictors of an LAA thrombus. In a multivariate analysis, the only significant predictors of LAA clot formation were persistent AF and renal dysfunction with an eGFR of less than 60 ml/min/1.73 m². None of the studied patients with a CHA₂DS₂-VASc of 1 or less, eGFR of 60 ml/min/1.73 m² or higher, and paroxysmal AF had an LAA thrombus. The greatest area under the curve (AUC = 0.845) was achieved for

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Received: December 14, 2015.

Accepted: December 14, 2015.

Conflict of interest: none declared.

Pol Arch Med Wewn. 2015;

125 (12): 889-890

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the CHA₂DS₂-VASC-AFR score (adding 1 point for persistent AF and 1 point for renal impairment). However, the difference between the AUC for the “new” and standard schemes was not statistically significant ($P = 0.062$). These observations are largely consistent with some previous analyses.⁸⁻¹⁰ However, other previously identified risk factors, such as congestive heart failure, left ventricular dysfunction, or hypertension, were not independent predictors promoting LAA clot formation in the study population. The study by Sikorska et al⁷ is particularly valuable because the authors refined the risk stratification scheme based not only on episodes of ischemic events but also on the direct visualization of a thrombus or dense echo contrast in the LAA. However, AF leads to a hypercoagulable state favoring clot formation in each part of the circulatory system, even the distant and peripheral ones, and embolization of the left atrium or the LAA, which plays a crucial role in the development of ischemic stroke in patients with AF.

Renal dysfunction as an independent predictor of embolic complications in patients with nonvalvular AF was also identified and evaluated by Piccini et al¹¹ in the ROCKET-AF population, and its significance was further assessed in the ATRIA cohort. The authors proposed the R₂CHADS₂ scheme in which renal insufficiency with creatinine clearance of less than 60 ml/min/1.73 m² was assigned 2 points, a power equivalent to that of previous stroke or transient ischemic attack.¹¹ Renal impairment has been known as a predictor of poor prognosis in AF population not only due to the higher risk of stroke but also to a higher mortality rate in individuals with acute coronary syndrome and a history of arrhythmia.^{12,13}

Although the assessment of stroke risk factors in patients treated with oral anticoagulants has many limitations and the stroke prediction models generally perform better in subjects not receiving the treatment, the R₂CHADS₂ score was able to properly identify the risk of stroke in patients in the ATRIA cohort who received and did not receive warfarin. Sikorska et al⁷ also revealed the value of their own risk stratification scheme in anticoagulated AF patients scheduled for ablation.

Impaired renal function contributes to an increased risk of stroke through procoagulant state and inflammation but also leads to a higher bleeding rate during anticoagulant therapy. Of the various proposed bleeding risk scores, renal dysfunction was also considered as an independent bleeding risk factor in the HEMORRH₂AGES, HAS-BLED, and the most recent ORBIT-AF scores, which have been developed and validated in AF populations.¹⁴

In conclusion, the current risk stratification system requires further studies to develop such scores that would allow a simple and reliable identification of individuals at risk of stroke and bleeding events. For a better understanding and more convenient application, antithrombotic risk stratification systems should be based on a

combination of various biochemical, echocardiographic, and clinical risk factors that go beyond the CHA₂DS₂-VASC and the available bleeding scores. Although useful in some cases, the presented parameters should perhaps be used to further refine the initial identification of patients at low risk, following which effective stroke prevention could be offered to those with 1 or more additional risk factors for stroke. Renal impairment should be strongly reconsidered as an independent risk factor for stroke in stratification tools used for the evaluation of AF patients.

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