Published in final edited form as:

Heart Rhythm. 2014 March ; 11(3): 358–359. doi:10.1016/j.hrthm.2013.12.001.

Eastern promises: Additive role of metabolic syndrome for thromboembolic risk stratification in Taiwanese atrial fibrillation patients

Sanjay Dixit, MD, FHRS and Vinay Kini, MD

Cardiovascular Division, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania

The key to prevention of stroke and other thromboembolic (TE) events in atrial fibrillation (AF) patients is effective risk stratification. Several schemes have been developed that use a combination of factors found to be associated with higher occurrence of TE events. Among the various risk stratification schemes, the CHADS₂ (congestive heart failure, hypertension, age ≥ 75 years, diabetes, and prior history of stroke) scoring system is the most popular.¹ Although the simplicity of this scoring system has resulted in its wide adoption, a major criticism has been its inability to consistently identify a truly low-risk group of AF patients.^{2,3} To address this deficit, the CHA₂DS₂-VASc scoring system was developed.⁴ This scheme uses all components of the CHADS₂ system but with greater emphasis on age and includes two additional factors: female sex and vascular disease. Thus, at the present time, using either CHADS₂ or CHA₂DS₂-VASc scoring system, we have some uniformity in our approach to TE risk stratification for AF patients. Nevertheless, the discriminatory power of both these scoring systems is limited (C-statistic <0.7, which implies that the test accounts for a little more than half the attributable risk of events in the population tested).⁵ Models are typically considered reasonable when the C-statistic is >0.7 and strong when C >0.8.⁶ The less than ideal performance of these two scoring systems implies that other important predictive factors of TE risk remain undefined. In pursuit of this hypothesis, in this issue of *Heart Rhythm* Tsai et al⁷ report their observations on the role of metabolic syndrome (MS) for TE risk stratification in Taiwanese AF patients.

The study population comprised 721 subjects diagnosed with AF after 1998 and subsequently followed through 2012. Baseline evaluation and investigative workup for all patients were used to derive their CHADS₂ and CHA₂DS₂-VASc scores as well as an assessment of MS. The latter was based on conventional criteria that included obesity, abnormal lipids (triglycerides and high-density lipoprotein-C), raised blood pressure, and abnormal fasting glucose. The objective of the study was to investigate whether AF patients with MS carry an increased risk of TE events. The investigators also sought to evaluate if the presence of MS offered incremental TE risk stratification over CHADS₂ and CHA₂DS₂-VASc scoring schemes. The mean age of the study population was 64 ± 11 years, and the patients were relatively healthy (hypertension was present in less than half, lipid abnormalities were present in one third, and vascular disease was seen in only 14%). Other

unique features of the population included low obesity rates (mean body mass index $24.8 \pm 4.5 \text{ kg/m}^2$; only 16.2% of subjects had body mass index $>30 \text{ kg/m}^2$), high prevalence of smoking (28.6%), and very low rates of vitamin K antagonist use (only 13.5%). TE events occurred in 84 patients (11.7%), and the majority ($n = 71$) were stroke or transient ischemic attacks. The investigators found that each component of the CHADS₂ scoring system but none of the additional CHA₂DS₂-VASC scoring system components (female sex, age ≥ 65 years, and vascular disease) were independent predictors of TE events. They also found that all components of MS were independent predictors of TE events, and the risk of TE events rose monotonically with increasing number of MS elements. Presence of ≥ 1 MS components also increased TE events within each CHADS₂ risk category (low, intermediate, or high). Based on these observations, the investigators have proposed a new scoring system, CHADS₂-MS, for better risk stratification of TE events, particularly in the CHADS₂ low- and intermediate-risk categories. Although this has not been explicitly stated, the study findings imply that this scoring system will provide the same value in the Taiwanese/Asian populations as the CHA₂DS₂-VASC scoring system has done in the western population, that is, better ability to identify low-risk patients than CHADS₂ alone.

So what can we infer from these findings? The major strength of the study is that it included a homogeneous patient population closely followed for outcomes over a median duration of 10.8 years. However, compared to patient populations from previous studies of stroke prediction in AF, these patients were younger, had fewer comorbidities, were less obese, smoked more, and were undertreated by vitamin K antagonist.^{2,3} Moreover, the patients were exclusively Taiwanese. These demographic differences may underlie some of the study findings. Nevertheless, we need to examine these results more carefully. The CHADS₂ scoring system performed adequately in the study population, and each component of CHADS₂ was an independent predictor of TE risks. However, this was not the case for the CHA₂DS₂-VASC scoring system. Another way to interpret these observations is that although congestive heart failure, hypertension, age ≥ 75 years, diabetes, and prior stroke predicted future occurrence of TE events, age between 65 and 74 years, female sex, and vascular disease did not. The mean age of the study population was 64 ± 11 years, and only one third of the subjects were >75 years. This raises the question whether patient distribution between the two age groups was sufficient to show incremental benefits in risk stratification. With regard to the association between sex and TE risks, a previous study of Taiwanese patients did not show higher stroke rates in female patients with AF.⁸ Likewise, a study of Japanese AF patients showed a higher occurrence of strokes in males compared with females.⁹ Thus, it is possible that the lack of association between female sex and TE events may be unique to Asian AF patients. The inability of vascular disease to predict TE events seen in this study is interesting. In a previous study involving a much larger cohort (7920 subjects), these investigators found that peripheral arterial disease but not coronary artery disease was independently associated with TE events.⁸ The smaller sample size ($n = 721$) of the current study may explain this lack of association. Moreover, the authors have not provided any information on the medical regimen of these patients. It is plausible that the adverse association between vascular disease and TE events may have been mitigated by the undisclosed use of angiotensin-converting enzyme inhibitors and/or statins in some of these subjects. The association between MS and TE events, which was the major observation of

this study, is intriguing because it pertains to the mechanism(s) underlying stroke. Although the majority (~70%) of strokes in AF patients result from cardioembolism, in 30% of these patients the underlying mechanism may be noncardiac.^{3,10} In the latter group, vascular disease (carotid stenosis, aortic plaques, etc.) is most frequently implicated. A major association has been consistently shown between MS and cardiovascular disease across diverse populations.^{3,5,9} How then can we reconcile the observations of the current study, which showed that although individual components of MS predicted TE events, the ultimate manifestation of MS (i.e., cardiovascular disease) did not? A possible explanation for this discrepancy may be that cardiovascular disease was not adequately explored in the study patients. Equally interesting is the lack of association seen between smoking and TE events in this study. The authors do not offer an explanation, but their observations are contrary to previous studies that have shown a strong association between smoking and TE events in AF patients.⁹ Smoking may also underlie the lack of association between female sex and TE events that was seen in this study. Among Asians, smoking is more common in males than females,¹¹ so the adverse impact of female sex on TE events may have been offset by smoking-related TE events in male patients. It also is quite possible that the level of association between different factors and TE events shown in this study reflects the method of regression analysis. The authors used Cox regression to determine independent predictors of TE, but which potentially confounding variables were adjusted for in the final multivariable risk model is unclear. Furthermore, the authors constructed the receiver operating characteristic curves with the derivation cohort (the same cohort that was used to determine whether MS was predictive of TE events). Therefore, the fact that the area under the curve was improved by adding the components of MS to the CHADS₂ score is not entirely surprising. Ideally, a validation cohort is needed to determine whether the CHADS₂-MS score is truly predictive of TE events.^{4,5}

Despite these limitations, the findings of this study are quite interesting. The authors have provided us with intriguing data that challenge some of our current concepts of the mechanisms underlying TE events in AF patients. Whether these observations are unique to Taiwanese AF patients or have more global implications can only be answered by exploring the association between MS and TE events in a wider and more diverse AF population.

References

1. Gage BF, van Walraven C, Pearce L, Hart RG, Koudstaal PJ, Boode BSP, Petersen P. Selecting patients with atrial fibrillation for anticoagulation: risk stratification in patients taking aspirin. *Circulation*. 2004; 110:2287–2292. [PubMed: 15477396]
2. Cripps M, Eikelboom JW, Hart RG, et al. The CHA₂DS₂ VASc identifies those patients with atrial fibrillation and a CHADS₂ score of 1 who are unlikely to benefit from oral anticoagulant therapy. *Eur Heart J*. 2013; 34:170–176. [PubMed: 23018151]
3. Lip GYH, Frison L, Halperin JL, Lane DA. Identifying patients at high risk of stroke despite anticoagulation: a comparison of contemporary stroke risk stratification schemes in an anticoagulated atrial fibrillation cohort. *Stroke*. 2010; 41:2731–2738. [PubMed: 20966417]
4. Lip GYH, Nieuwlaet R, Pisters R, Lane DA, Crijns HJGM. Refining clinical 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; 137:263–272. [PubMed: 19762550]

5. Larsen TB, Lip GYH, Skjoth F, Due KM, Overvad K, Rasmussen LH. Added predictive ability of the CHA₂DS₂VASc risk score for stroke and death in patients with atrial fibrillation: The prospective Danish diet cancer and health cohort study. *Circ Cardiovasc Qual Outcomes*. 2012; 5:335–342. [PubMed: 22534406]
6. Hosmer, DW., Lemeshow, S. *Applied Logistic Regression*. 2. New York: John Wiley and Sons; 2000.
7. Tsai C-T, Chang S-H, Chang S-N, et al. Additive role of metabolic syndrome score to the conventional CHADS₂ score for thromboembolic risk stratification of patients with atrial fibrillation. *Heart Rhythm*. 2014; 11:352–357. [PubMed: 24252289]
8. Lin LY, Lee CH, Yu CC, et al. Risk factors and incidence of ischemic strokes in Taiwanese with nonvalvular atrial fibrillation—a nationwide database analysis. *Atherosclerosis*. 2011; 217:292–295. [PubMed: 21513938]
9. Naganuma M, Shiga T, Sato K, et al. Clinical outcomes in Japanese elderly patients with non-valvular atrial fibrillation taking warfarin: a single center observational study. *Thromb Res*. 2012; 130:21–26. [PubMed: 22137743]
10. Hart RG, Sherman DG, Easton JD, Cairns JA. Prevention of stroke in patients with nonvalvular atrial fibrillation. *Neurology*. 1998; 51:674–681. [PubMed: 9748009]
11. Tsai YW, Tsai TI, Yang CL, Kuo KN. Gender differences in smoking behaviors in an Asian population. *J Womens Health*. 2008; 17:971–978.