Formulating a More Comprehensive Stroke-Risk Evaluation Scale

All types of atrial fibrillation (AF)—paroxysmal, persistent, and even subclinical—have been associated with stroke.1-3 In the United States, as many as 6.1 million people have AF and its sequelae. Although AF is observed predominantly in the elderly and its risk increases linearly with age, almost 2% of people younger than 65 years have AF. Atrial fibrillation alone is responsible for more than 750,000 hospitalizations and almost 130,000 deaths each year. Mortality rates associated with AF, including complications such as stroke, have increased in the past few decades.4

The adverse effects of stroke place a burden not only on individual patients but also on our healthcare system. According to findings in a multinational study, the mean cost of stroke management during the initial hospitalization period was nearly $14,000.5 Various stroke-risk scores have been developed to identify those at risk and to aid in prevention. The original scoring system extensively used in the U.S., CHADS2, was superseded by CHA2DS2-VASc, which incorporates additional risk factors for predicting stroke risk.6 The latest scoring system, ATRIA, is even more comprehensive.7 Table I highlights differences between the 3 scoring systems.

Additional factors considered in ATRIA (Table II) include renal dysfunction (estimated glomerular filtration rate <45 mL/min or end-stage renal disease) and proteinuria. Unlike CHADS2 and CHA2DS2-VASc, ATRIA incorporates the finding that history of stroke independently increases the risk of future events. An extended age range for assigning scores (<65, 65–74, 75–84, and >85 yr) accounts for the increase in stroke risk with age. Table III shows the annual rate of stroke incidence with use of different scores.7

On the basis of C-index and net reclassification improvement (NRI), indices used to compare models and quantify improvements, ATRIA is relatively more effective than are CHA2DS2-VASc and CHADS2. For ATRIA, C=0.708 (range, 0.704–0.713); for CHA2DS2-VASc, C=0.694 (range, 0.690–0.700); and for CHADS2, C=0.690 (range, 0.685–0.695). The NRI for ATRIA was 0.16 (range, 0.14–0.17) in comparison with CHADS2, and 0.21 (range, 0.20–0.23) in comparison with CHA2DS2-VASc. Both C-index and NRI indicate improvement in accuracy when ATRIA is used.8 The efficacy of ATRIA notwithstanding, CHA2DS2-VASc is easier to calculate at bedside and remains more popular.

Female patients older than 65 years are assigned a CHA2DS2-VASc score of 2 and qualify for anticoagulant therapy, despite their low risk of stroke according to European guidelines.9 Female patients <65 years of age are scored 1 and are eligible for antiplatelet therapy. Antiplatelet and anticoagulant therapy in an inappropriate patient can cause bleeding, so a stroke score must be specific enough to reveal actual risk without increasing the potential for severe complications. Accordingly, investigators are now considering additional evidence from echocardiography, magnetic resonance imaging (MRI), sleep studies, and biomarkers (Table IV).10-18

Cryptogenic Stroke

Because of failure to identify AF or other causes, up to 40% of ischemic strokes are classified as cryptogenic. Atrial fibrillation is found in only a few such cases, even after 3 years of monitoring events.19,20 Thus, other factors might augment thrombogenicity in the absence of AF. We have shown that complex left atrial (LA) morphology may be an independent risk factor for stroke in the absence of AF.12 Left atrial ap-
pendage (LAA) morphology is broadly classified into simple (chicken wing) and complex—the latter including all the other types, such as chicken wing with pectinated walls, and cauliflower (multiple branches). In a retrospective case-controlled study of patients with and without ischemic stroke, those with complex LAA morphology had higher odds of ischemic stroke (OR=5; 95% CI, 1.05–23.73; P=0.043).11

### TABLE I. Risk Factors for Stroke Included in the Scoring Models

| Risk Factor                  | CHADS₂ (2001) | CHA₂DS₂-VASc (2010) | ATRIA (2013)         |
|------------------------------|---------------|----------------------|----------------------|
| Score range                  | 0–6           | 0–9                  | 0–12 (pts without prior stroke); 7–15 (pts with prior stroke) |
| Age (yr)                     | >75 = 2 points| >75 = 2 points; 65–74 = 1 point | Extended range (<65, 65–74, 75–84, and >85) |
| Hypertension                 | Yes           | Yes                  | Yes                  |
| Diabetes mellitus            | Yes           | Yes                  | Yes                  |
| CHF                          | Yes           | Yes                  | Yes                  |
| Prior stroke or TIA          | Yes           | Yes                  | Higher scores for pts with prior stroke |
| Vascular disease             | No            | Yes                  | No                   |
| Female                       | No            | Yes                  | Yes                  |
| Renal dysfunction            | No            | No                   | Yes                  |
| Proteinuria                  | No            | No                   | Yes                  |

CHF = congestive heart failure; pts = patients; TIA = transient ischemic attack

### TABLE II. ATRIA Score Calculation

| Risk Factors                  | No Prior Stroke | Prior Stroke |
|------------------------------|-----------------|--------------|
| Age (yr)                     |                 |              |
| <65                          | 0               | 8            |
| 65–74                        | 3               | 7            |
| 75–84                        | 5               | 7            |
| ≥85                          | 6               | 9            |
| Female                       | 1               | 1            |
| Hypertension                 | 1               | 1            |
| Diabetes mellitus            | 1               | 1            |
| Congestive heart failure     | 1               | 1            |
| Proteinuria                  | 1               | 1            |
| eGFR <45 mL/min or ESRD      | 1               | 1            |
| Range                        | 0–12            | 7–15         |

eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease

Diastolic Dysfunction

Ventricular diastolic dysfunction is also implicated in ischemic stroke. It is widely accepted that the LA undergoes adverse remodeling in response to increased pressure, against which it needs to pump blood in cases of diastolic dysfunction. Diastolic dysfunction increases the chance of AF by altering LA morphology.24 It is increasingly evident that, in aberrant diastiology, the rheologic properties of blood are altered, making it more thrombogenic.25 In a small group of patients, diastolic dysfunction greater than grade II (on echocardiography) was an independent risk factor for cardioembolic stroke.12 Other investigators have reached similar conclusions.26

Left Atrial Fibrosis

Left atrial structural changes are accompanied by functional changes. Increased LA size leads to LA functional deterioration. Left atrial dilation is the indication that LA remodeling has occurred, and this eventually leads to AF.27 Idiopathic dilated cardiomyopathy has been
strongly associated with LA thrombi on the basis of transthoracic echocardiographic findings. Patients with AF and prior stroke tend to have more extensive LA fibrosis on delayed-enhancement MRI. Investigating LA structure and function can be valuable in evaluating stroke risk.

Biomarkers
Evidence indicates that investigating biomarkers alone or in combination can assist in predicting risk of cardioembolic events and ischemic stroke. Patients without heart failure who have elevated plasma levels of the N-terminal fragment of B-type natriuretic peptide (NT-proBNP) are 5 times more likely to have a transient ischemic attack or stroke than are those with lower levels. Elevated plasma BNP was significantly associated with higher post-stroke mortality rates than were lower levels (OR=2.3; 95% CI, 1.32–4.01; P=0.003). Similarly, patients with higher levels of cardiac troponin I are more likely to develop thromboembolism than are those with lower levels. Infammmation is significantly associated with AF. Among patients monitored for a mean duration of 6.9 ± 1.6 years, those with elevated C-reactive protein levels had a 33% greater likelihood of future AF events.

Summary
Existing stroke scores, including those derived from ATRIA, can lead to over- or underestimating actual stroke risk in different cohorts of patients. This mandates the use of newer methods to formulate a more robust scoring system. Left atrial appendage morphology, MRI-determined LA fibrosis, and heart failure with preserved ejection fraction (not congestive heart failure, as is considered in the “heart failure” category of the CHA2DS2-VASc score) may need consideration in stroke risk, as may biomarkers for heart failure and infarction. It is crucial to devise a new, improved scoring system that incorporates all determinants of thromboembolism that lead to stroke while ensuring that low-risk patients are spared from being prescribed an anticoagulant.

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