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Formulating a More Comprehensive Stroke-Risk Evaluation Scale

Indranill Basu Ray, MD, FACP
Sumit K. Shah, MD, MPH

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From: *CHI St. Vincent's Infirmary (Dr. Basu Ray); and W.P. Rockefeller Cancer Institute (Dr. Shah), University of Arkansas for Medical Sciences; Little Rock, Arkansas 72205*

Address for reprints: *Indranill Basu Ray, MD, St. Francis Hospital, 5959 Park Ave., Memphis, TN 38119*

E-mail: *ibasuray@yahoo.com*

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 The original scoring system extensively used in the U.S., $CHADS_2$, was superseded by CHA_2DS_2-VASc, which incorporates additional risk factors for predicting stroke risk.[6] The latest scoring system, ATRIA, is even more comprehensive.[7]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 $CHADS_2$ and CHA_2DS_2-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 CHA_2DS_2-VASc and $CHADS_2$. For ATRIA, C=0.708 (range, 0.704–0.713); for CHA_2DS_2-VASc, C=0.694 (range, 0.690–0.700); and for $CHADS_2$, C=0.690 (range, 0.685–0.695). The NRI for ATRIA was 0.16 (range, 0.14–0.17) in comparison with $CHADS_2$, and 0.21 (range, 0.20–0.23) in comparison with CHA_2DS_2-VASc. Both C-index and NRI indicate improvement in accuracy when ATRIA is used.[8] The efficacy of ATRIA notwithstanding, CHA_2DS_2-VASc is easier to calculate at bedside and remains more popular.

Female patients older than 65 years are assigned a CHA_2DS_2-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-

TABLE I. Risk Factors for Stroke Included in the Scoring Models[7]

Risk Factor	$CHADS_2$ (2001)	CHA_2DS_2-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[7]

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

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]

Left Atrial Appendage Morphology

The presence of more lobes in complex LAA morphology is an independent cause of blood stasis and thrombus formation.[21] The LAA emptying velocity, volume, and number of lobes are significantly associated with risk of thromboembolism and stroke.[22] In addition, LAA flow velocity has been implicated in cardioembolic events and ischemic stroke. Patients with low flow velocity were significantly associated with non-chicken wing morphology (OR=9.664; 95% CI, 1.075–86.9; P=0.0429) and with higher plasma B-type natriuretic peptide (BNP) levels (OR=1.012 for every 1-pg/mL rise in BNP; 95% CI, 1.001–1.022; P=0.035). Patients with non-chicken wing morphology, low flow velocity, and higher plasma BNP levels were more likely to have an ischemic stroke.[23]

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 diastology, 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

TABLE III. Incidence* of Stroke and Thromboembolic Events in the Scoring Models[7]

Score	$CHADS_2$	CHA_2DS_2-VASc	ATRIA
0	1.9	0.66	0.1
1	2.8	1.45	0.4
2	4	2.92	1
3	5.9	4.28	0.7
4	8.5	6.46	0.6
5	12.5	9.37	1
6	18.2	12.52	1.9
7	—	13.96	2.5
8	—	14.1	3.9
9	—	15.89	4.3
10	—	—	6.4
11	—	—	6.2
12	—	—	11
13	—	—	7.5
14	—	—	16.4
15	—	—	0

*per 100 person-years

TABLE IV. Imaging Findings and Biomarkers in Atrial Fibrillation Risk Stratification

Imaging Findings
Complex left atrial appendage morphology[11]
Diastolic dysfunction[12]
Left atrial fibrosis on delayed-enhancement MRI[13]
Dilated cardiomyopathy on TEE[14]
Biomarkers
N-terminal proBNP[15] and BNP[16]
Cardiac troponin I[17]
C-reactive protein[18]

BNP = B-type natriuretic peptide; MRI = magnetic resonance imaging; TEE = transesophageal echocardiography

strongly associated with LA thrombi on the basis of transthoracic echocardiographic findings.[14] 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.[13]

Biomarkers

Evidence indicates that investigating biomarkers alone or in combination can assist in predicting risk of cardioembolic events and ischemic stroke.[28] 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.[15] 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).[16] Similarly, patients with higher levels of cardiac troponin I are more likely to develop thromboembolism than are those with lower levels.[17] Inflammation 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.[18]

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 CHA_2DS_2-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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References

1. Healey JS. The winding path towards rationale anti-thrombotic therapy to prevent stroke in patients with atrial fibrillation. Eur Heart J 2018;39(6):474-6.
2. Renoux C, Patenaude V, Suissa S. Incidence, mortality, and sex differences of non-valvular atrial fibrillation: a population-based study. J Am Heart Assoc 2014;3(6):e001402.
3. Brambatti M, Connolly SJ, Gold MR, Morillo CA, Capucci A, Muto C, et al. Temporal relationship between subclinical atrial fibrillation and embolic events. Circulation 2014;129(21):2094-9.
4. Centers for Disease Control and Prevention. Atrial fibrillation fact sheet. Available from: https://www.cdc.gov/dhdsp/data_statistics/fact_sheets/fs_atrial_fibrillation.htm [revised 2017 Aug 22].
5. Caro JJ, Huybrechts KF, Duchesne I. Management patterns and costs of acute ischemic stroke: an international study. For the Stroke Economic Analysis Group. Stroke 2000;31(3):582-90.

6. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182,678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. Eur Heart J 2012;33(12):1500-10.
7. Chao TF, Chen SA. Stroke risk predictor scoring systems in atrial fibrillation. J Atr Fibrillation 2014;6(5):998.
8. Aspberg S, Chang Y, Atterman A, Bottai M, Go AS, Singer DE. Comparison of the ATRIA, CHADS2, and CHA2DS2-VASc stroke risk scores in predicting ischaemic stroke in a large Swedish cohort of patients with atrial fibrillation. Eur Heart J 2016;37(42):3203-10.
9. Lip GY. Can we predict stroke in atrial fibrillation? Clin Cardiol 2012;35 Suppl 1:21-7.
10. Szymanski FM, Lip GY, Filipiak KJ, Platek AE, Hrynkiewicz-Szymanska A, Opolski G. Stroke risk factors beyond the CHA2DS2-VASc score: can we improve our identification of "high stroke risk" patients with atrial fibrillation? Am J Cardiol 2015;116(11):1781-8.
11. Basu-Ray I, Schwing G, Novak J, Monlezun D, Boja H, Deere B, et al. Complex left atrial appendage morphology increases risk of cryptogenic ischemic stroke [abstract]. Circulation 2016;134:A18983. Available from: http://circ.ahajournals.org/content/134/Suppl_1/A18983.
12. Basu-Ray I, Schwing G, Middour T, Monlezun D, Allencherril J, Martin-Schild S, et al. Heart failure with preserved ejection fraction is associated with cardioembolic stroke independent of history of atrial fibrillation [abstract]. Eur Heart J 2017;38(Suppl 1):902. Available from: https://academic.oup.com/eurheartj/article/38/suppl_1/ehx504.P4365/4090407.
13. Daccarett M, Badger TJ, Akoum N, Burgon NS, Mahnkopf C, Vergara G, et al. Association of left atrial fibrosis detected by delayed-enhancement magnetic resonance imaging and the risk of stroke in patients with atrial fibrillation. J Am Coll Cardiol 2011;57(7):831-8.
14. Vigna C, Russo A, De Rito V, Perna G, Villella A, Testa M, et al. Frequency of left atrial thrombi by transesophageal echocardiography in idiopathic and in ischemic dilated cardiomyopathy. Am J Cardiol 1992;70(18):1500-1.
15. Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Omland T, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. N Engl J Med 2004;350(7):655-63.
16. Garcia-Berrocoso T, Giralt D, Bustamante A, Etgen T, Jensen JK, Sharma JC, et al. B-type natriuretic peptides and mortality after stroke: a systematic review and meta-analysis. Neurology 2013;81(23):1976-85.
17. Providencia R, Paiva L, Faustino A, Botelho A, Trigo J, Casalta-Lopes J, et al. Cardiac troponin I: prothrombotic risk marker in non-valvular atrial fibrillation. Int J Cardiol 2013;167(3):877-82.
18. Aviles RJ, Martin DO, Apperson-Hansen C, Houghtaling PL, Rautaharju P, Kronmal RA, et al. Inflammation as a risk factor for atrial fibrillation. Circulation 2003;108(24):3006-10.
19. Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, et al. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med 2014;370(26):2478-86.
20. Yaghi S, Song C, Gray WA, Furie KL, Elkind MS, Kamel H. Left atrial appendage function and stroke risk. Stroke 2015;46(21):3554-9.
21. Korhonen M, Muuronen A, Arponen O, Mustonen P, Hedman M, Jakala P, et al. Left atrial appendage morphology in patients with suspected cardiogenic stroke without known atrial fibrillation. PLoS One 2015;10(3):e0118822.
22. Yamamoto M, Seo Y, Kawamatsu N, Sato K, Sugano A, Machino-Ohtsuka T, et al. Complex left atrial appendage morphology and left atrial appendage thrombus formation in patients with atrial fibrillation. Circ Cardiovasc Imaging 2014;7(2):337-43.
23. Kishima H, Mine T, Ashida K, Sugahara M, Kodani T, Masuyama T. Does left atrial appendage morphology influence left atrial appendage flow velocity? Circ J 2015;79(8):1706-11.
24. Tiwari S, Schirmer H, Jacobsen BK, Hopstock LA, Nyrnes A, Heggelund G, et al. Association between diastolic dysfunction and future atrial fibrillation in the Tromsø Study from 1994 to 2010. Heart 2015;101(16):1302-8.
25. Lee JM, Shim J, Uhm JS, Kim YJ, Lee HJ, Pak HN, et al. Impact of increased orifice size and decreased flow velocity of left atrial appendage on stroke in nonvalvular atrial fibrillation. Am J Cardiol 2014;113(6):963-9.
26. Seo JY, Lee KB, Lee JG, Kim JS, Roh H, Ahn MY, et al. Implication of left ventricular diastolic dysfunction in cryptogenic ischemic stroke. Stroke 2014;45(9):2757-61.
27. Casaclang-Verzosa G, Gersh BJ, Tsang TS. Structural and functional remodeling of the left atrium: clinical and therapeutic implications for atrial fibrillation. J Am Coll Cardiol 2008;51(1):1-11.
28. Montaner J, Perea-Gainza M, Delgado P, Ribo M, Chacon P, Rosell A, et al. Etiologic diagnosis of ischemic stroke subtypes with plasma biomarkers. Stroke 2008;39(8):2280-7.