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Journal of Atrial Fibrillation

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Stroke Risk Predictor Scoring Systems in Atrial Fibrillation

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Abstract

An effective risk stratification which could help us identify high-risk patients who should take oral anticoagulants (OACs) is the key step for stroke prevention in atrial fibrillation (SPAF). Several scoring systems were available to estimate the risk of stroke in AF, including $CHADS_2$, CHA_2DS_2-VASc, R_2CHADS_2 and ATRIA scores, which were constituted of different clinical risk factors. Recently, several new OACs (NOACs) were demonstrated to be at least as effective as warfarin in stroke prevention and were much safer regarding the risk of intra-cranial hemorrhage. In the era of NOACs, the roles of scoring schemes have shifted to identify patients with a truly low-risk of thromboembolic events, in whom OACs were not recommended. The CHA_2DS_2-VASc score is powerful in selecting "truly low-risk" patients who do not require anticoagulation. Whether the new-emerging scoring systems, R_2CHADS_2 and ATRIA scores, could further improve the stroke prediction in AF deserves a further study.

("SPAF", the same as the initials of a series of studies about aspirin, warfarin and stroke prevention in AF, was used as the abbreviation for "stroke prevention in atrial fibrillation" in this review article.)

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia which is associated with marked morbidity, mortality, and socioeconomic burden.[1-2] AF is an important risk factor of ischemic stroke with a worse prognosis and higher recurrence rate compared to that of non-AF related stroke.[3] Oral anticoagulant (OAC) with vitamin K antagonists (VKAs) could reduce the incidence of stroke by 64% compared to control or placebo, and is much more effective than the use of antiplatelet agents.[4] However, the adverse events resulting from the use of OACs, especially the increased risk of life-threatening bleeding, are important concerns for clinical physicians when managing AF patients. Therefore, an effective risk stratification which could help us identify high-risk patients who should take OACs is the key step for stroke prevention in AF (SPAF).

Scoring Systems For Stratifying Stroke Risk In AF – $CHADS_2$ and CHA_2DS_2-VAScs

The most important point in determining the strategy of SPAF is how to estimate the thromboembolic (TE) risk accurately. Currently, several scoring systems were available for stroke risk stratifications, including $CHADS_2$,[5] CHA_2DS_2-VASc,[6] R_2CHADS_2,[7] and ATRIA[8] scores, which were constituted of different clinical risk factors (Table 1). The Congestive Heart Failure, Hypertension, Age, Diabetes, Stroke/Transient Ischemic Attack (TIA) ($CHADS_2$) scoring system which assigned 1 point each for age > 75 years, hypertension, diabetes mellitus, and heart failure, and 2 points each for a previous stroke or TIA was the most commonly used scheme in stroke risk stratifications for AF patients.[5] $CHADS_2$ score was recommended by the American College of Cardiology (ACC), American Heart Association (AHA), and Canadian Cardiovascular Society to stratify stroke risk and guide the strategy of SPAF.[9-10] Although the $CHADS_2$ score is able to select moderate- and high-risk patients who may get benefits from OAC use, the annual stroke rate was still nearly 2% for patients with a $CHADS_2$ score of 0 (Table 2). Therefore, some patients may be misclassified as "low-risk" and did not receive OAC for stroke prevention. This limitation and flaw of the $CHADS_2$ scheme became more obvious and important in the era of new OACs (NOACs). Although the clinical trials of NOACs, such as dabigatran, rivaroxaban and apixaban, were different from each other about the enrollment criteria and study designs, all these studies demonstrated that NOACs were at least as effective as warfarin in SPAF and were much safer regarding the risk of intra-cranial hemorrhage.[11-13] Therefore, NOACs may lower the threshold for initiating OAC for SPAF considering the net clinical benefit balancing stroke reduction against major bleeding. Based on the viewpoint of the advantages of NOACs, the roles of the stroke scoring

Key Words:
Stroke, $CHADS_2$, CHA_2DS_2-VASc, R_2CHADS_2, ATRIA.

Disclosures:
None.

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Table 1: Stroke risk factors included in each scoring model

Scoring scheme, year	Score range	Age	HTN	DM	CHF	Stroke/TIA	Vascular diseases	Female sex	Renal dysfunction	Proteinuria
$CHADS_2$ (2001)5	0-6	2 points for age >75	+	+	+	+	-	-	-	-
CHA_2DS_2-VASc (2010)6	0-9	2 points for age > 75; 1 point for age 65-74	+	+	+	+	+	+	-	-
R_2CHADS_2 (2012)7	0-8	2 points for age >75	+	+	+	+	-	-	+	-
ATRIA (2013)8	0-12 (for patients without prior stroke); 7-15 (for patients with prior stroke)	Extended range for score assignment (<65, 65-74, 75-84, >85)*	+	+	+	Different roles of score calculation for patients with or without prior stroke	-	+	+	+

* Different roles of score calculation for patients with or without prior stroke
CHF = congestive heart failure, DM = diabetes mellitus, HTN= hypertension, TIA = transient ischemic attack

schemes in risk stratifications may change. Initially, stroke prediction systems were used to identify AF patients at a high risk of stroke, in whom the benefits of use of OACs may preceed the risk of bleeding. However, with more convenient and safer NOACs were available, the role of these schemes has shifted to identify patients with a truly low-risk of TE events, in whom OACs were not recommended.

For this purpose, the Congestive Heart Failure, Hypertension, Age > 75 Years, Diabetes Mellitus, Stroke, Vascular Disease, Age 65 to 74 Years, Sex Category (CHA_2DS_2-VASc) scoring scheme, which extends the $CHADS_2$ scheme by considering additional stroke risk factors (vascular diseases and female gender) was developed.[6] The annual stroke rates were only 0.66% and 1.45% for patients with a CHA_2DS_2-VASc score of 0 and 1, respectively (Table 2). After the CHA_2DS_2-VASc score was proposed in year 2010, several subsequent studies suggested that the CHA_2DS_2-VASc score was most useful in identifying "truly low-risk" patients, and antithrombotic therapy may not be necessary for patients with a CHA_2DS_2-VASc score of 0.[14-17] In the study performed by Taillandier et al. which enrolled a total of 616 AF patients with a CHA_2DS_2-VASc score of 0, an OAC was prescribed on an individual basis in 273 patients (44%), antiplatelet therapy alone in 145 patients (24%), and no antithrombotic therapy in 198 patients (32%).15 They found that the prescription of OACs and/or antiplatelet therapy was not associated with an improved prognosis for stroke/thromboembolism (relative risk = 0.99, 95% condifence interval = 0.25–3.99, p value = 0.99), nor improved survival or net clinical benefit (combination of stroke/thromboembolism, bleeding, and death). More recently, a natiowide cohort study in Taiwan further demonstrated that AF males with a CHA2DS2-VASc score of 0 have a truly low risk for stroke, which was similar to that of non-AF patients (1.6% versus 1.6%, p value = 0.920).[17] Currently, the European Society of Cardiology (ESC) and Asia Pacific Heart Rhythm Society (APHRS) recommended use of the CHA_2DS_2-VASc score to guide the strategy of SPAF.[18-19] The 2012 focus updated ESC guideline suggested that OAC is not necessary for male patients with a CHA_2DS_2-VASc score of 0 and female patients with gender alone as a single risk factor (still a CHA_2DS_2-VASc score of 1) if they fulfill the criteria of "age <65 and lone AF".[18] Otherwise, OACs should be considered for AF patients for stroke prevention.

Table 2: Incidence (per 100 persons-years) of stroke/thromboembolic events in different scoring models

Score	$CHADS_2$5	CHA_2DS_2-VASc (derivation cohort, adjusted for aspirin prescription)6	CHA_2DS_2-VASc (validation cohort)6	R_2CHADS_2 (validation cohort, without warfarin)7	ATRIA8
0	1.9	0	0.66	0.36	0.1
1	2.8	0.7	1.45	1.26	0.4
2	4.0	1.9	2.92	2.21	1.0
3	5.9	4.7	4.28	2.57	0.7
4	8.5	2.3	6.46	3.59	0.6
5	12.5	3.9	9.97	5.32	1.0
6	18.2	4.5	12.52	5.91	1.9
7	-	10.1	13.96	2.77	2.5
8	-	14.2	14.10	7.43	3.9
9	-	100	15.89	-	4.3
10	-	-	-	-	6.4
11	-	-	-	-	6.2
12	-	-	-	-	11.0
13	-	-	-	-	7.5
14	-	-	-	-	16.4
15	-	-	-	-	0

The Role Of Renal Dysfunction In Stroke Risk Prediction – R_2CHADS_2 and ATRIA Scores

Recently, whether renal dysfunction was a risk factor of ischemic stroke in AF patients was a hot issue which generated much attention. In the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study, 676 TE events occurred during the follow up of 33,165 person-years among 10,980 AF patients without use of OACs.[20] Chronic kidney disease was found to increases the risk of TE events in AF independently of other risk factors. Recently, a new risk model, designated the R_2CHADS_2 score, that incorporates the components of the $CHADS_2$ score and awards 2 points for renal dysfunction, was derived from the study subjects enrolled in Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) trial (Table 1).[7,12] After the derivation of the R_2CHADS_2 scheme from ROCKET-AF cohort, it was validated in the cohort of ATRIA study and was demonstrated to be a useful scoring system in predicting stroke or systemic embolism in AF.[7] For patients without taking warfarin in ATRIA cohort, the annual event rate ranged from 0.36% for patients with a R_2CHADS_2 score of 0 to 7.43% for those with a score of 8 (Table 2). Among the derivation cohort (ROCKET-AF cohort), the R_2CHADS_2 scheme could improve net reclassification index by 6.2% compared with CHA_2DS_2-VASc and by 8.2% compared with $CHADS_2$.[7] However, in another recent study performed by Roldán et al. which enrolled 978 AF patients under warfarin treatment in Spain, adding renal dysfunction (1 point if estimated glomerular

filtration rate [eGFR] was 30-60 ml/min, and 2 points if eGFR was < 30 ml/min) to the $CHADS_2$ and CHA_2DS_2-VASc stroke risk scores did not independently add predictive information.[21] Therefore, whether R_2CHADS_2 could be a useful scoring scheme in stroke risk stratifications deserves further studies.

Following the R_2CHADS_2 scheme, another new scoring system, named ATRIA score, which included renal dysfunction (eGFR < 45 ml/min or end-stage renal disease) and proteinuria in the model was derived from the ATRIA cohort consisted of 10,927 patients with non-valvular AF contributing 32,609 person-years off warfarin and 685 TE events (Table 1).[8] Different from $CHADS_2$, CHA_2DS_2-VASc and R2CHADS2 scores, the rules about how to calculate the scores were different for patients with or without prior stroke (Table3). Besides, an extended range of age for score assignment was adopted (<65, 65-74, 75-84, >85) (Table 3). The annual event rate of patients with each ATRIA score was shown in Table 2, and it was collapsed into low (0 to 5 points), moderate (6 points), and high (7 to 15 points) risk categories to fit annualized event rates of <1%, 1% to <2%, and ≥2% per year, respectively. However, it should be noted that the proportion of patients who were categorized as "low risk" was as high as 46.7% which was similar to that stratified by $CHADS_2$ score (49.7%). It may raise a concern that the ATRIA score, like the $CHADS_2$ score, may be not able to identify patients with a truly low-risk of TE events. Besides, the calculation of the ATRIA score was more complicated than other scoring systems and may prohibit its widespread acceptance.

The Potential Roles Of Biomarkers And Imaging Tools

In addition to clinical risk factors included in the scoring models, several biomarkers and parameters derived from imaging tools may also have potential roles in risk stratifications for AF patients (Table 4).[22-30] In the study performed by Roldán et al which enrolled 829 anticoagulated permanent AF patients, high plasma von Willebrand factor (vWF) levels (≥221 IU/dl) were demonstrated to be an independent risk factor for adverse events.[22] In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) substudy, elevations of troponin I and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) are common in patients with AF and independently related to increased risks of stroke and mortality.[23] More recently, Chao et al. enrolled 141 AF patients referred for coronary angiogram and found that a higher level of asymmetric dimethylarginine (ADMA) was a risk factor of adverse events in AF patients, which was independent from the CHA_2DS_2-VASc score.[24]

The individualized left atrial (LA) function and morphology which were assessed by imaging tools, such as transthoracic echocardiogram (TTE) and delayed enhanced magnetic resonance imaging (DE-MRI), may also provide useful information when managing AF patients. Daccarett et al. reported that LA fibrosis detected by DE-MRI was closely associated with $CHADS_2$ score and history of strokes in AF patients.[28] In a multi-center study enrolling 932 AF patients who were planning to undergo catheter ablation, the morphologies of LA appendages were categorized into four types (cactus, chicken wing, windsock, and cauliflower) by computed tomography and MRI.[29] Interestingly, the authors found that patients with chicken wing LA appendage morphology are less likely to have an embolic event even after controlling for comorbidities and $CHADS_2$ score. For AF patients after catheter ablations, the TTE-based measurements of atrial electromechanical intervals, determined as the time interval from the initiation of P wave deflection to the peak of mitral inflow A wave on pulse wave Doppler imaging, were reported to be a useful predictor of TE events independent from the CHA_2DS_2-VASc score.[30] However, how these biomarkers and imaging tools could change the current strategy of SPAF remains unknown and deserves further investigations.

Conclusions:

The newer scoring systems, by incorporating additional risk factors, identify AF patients at risk for stroke who would have been classified as low risk by the $CHADS_2$ score. Since warfarin is difficult to use and associated with a potentially higher risk of bleeding, the $CHADS_2$ scoring system helped identify high risk patients who would benefit most from this risky therapy. Since NOACs are easier to use and associated with a lower risk of intracranial bleeding, the task of the newer scoring systems is to define the risk better, thereby identifying the truly low risk patients in whom these medications should be avoided. In addition to clinical risk schemes, how biomarkers and imaging tools could change the current strategy of SPAF remains unknown and deserves further investigations.

Table 3: Calculation of ATRIA score 8

Risk factors	Patients without prior stroke	Patients with prior stroke
Age		
>85	6	9
75-84	5	7
65-74	3	7
<65	0	8
Female gender	1	1
DM	1	1
CHF	1	1
HTN	1	1
Proteinuria	1	1
eGFR <45 or ESRD		
end-stage renal disease	1	1
Scoring range	0-12	7-15

CHF = congestive heart failure, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HTN= hypertension

Table 4: Biomarkers and parameters derived from imaging tools for risk stratifications in AF*

Biomarkers
Plasma von Willebrand factor (vWF) levels22
Troponin I and NT-proBNP23
Asymmetric dimethylarginine (ADMA)24
High sensitivity cardiac troponin T and interleukin-625
Adiponectin26
D-dimer27
Imaging tools
LA fibrosis detected by DE-MRI28
Chicken wing LA appendage morphology (protective effect)29
Atrial electromechanical interval on TTE30

AF = atrial fibrillation, DE-MRI = delayed enhanced magnetic resonance imaging, LA = left atrium, TTE = transthoracic echocardiogram

*The table was modified from the table by Chao et al. published in Arrhythmia & Electrophysiology Review 2013.31

Acknowledgments

This work was supported in part by grants from the National Science Council (NSC98-2410-H-010-003-MY2), and Taipei Veterans General Hospital (V99C1-140, V99A-153, V100D-002-3, and V101D-001-2).

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