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THE UTILITY OF THE CHADS$_2$ STROKE RISK SCORING SYSTEM FOR ATRIAL FIBRILLATION PATIENTS

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Atrial fibrillation (AF) is the most common cardiac rhythm disorder in the United States. 2010 figures from the National Heart Lung and Blood Institute (NHLBI) estimate that 2.2 million Americans are living with AF, and this number is expected to double by the year 2020.[1] Some estimates have projected that the number of Americans with AF will be as high as 7.5 million by the year 2050, highlighting the increasing importance of understanding both the etiology and treatment of this disorder.[2]

While AF is often linked to intrinsic cardiac conditions such as sick sinus syndrome, valvular disease and congestive heart failure, there are many other factors which can contribute to an increased risk of developing AF. Nearly two decades ago, the Framingham Heart Study identified a set of additional risk factors for developing AF, which included diabetes and hypertension in both sexes as well as myocardial infarction in men.[3] With national incidences of both hypertension and diabetes on the rise, it is presumable that the diagnosis of AF will also continue to increase in the coming decade.[4,5]

One of the more common—and potentially life-threatening—complications of AF is cardioembolic stroke. Approximately 15% of all strokes in the US are caused by blood clots that form as a direct result of AF. AF-related strokes are also associated with an increase in severity versus non-AF-related strokes. A 1996 study showed that AF-related stroke patients experienced higher mortality rates, more recurrences, graver severity, and poorer post-stroke functional status than patients who suffer strokes not related to AF.[6] An individual with AF carries a five-fold greater risk of stroke than an otherwise healthy person.[7]

The standard of care for several decades has been antiplatelet therapy with low-dose aspirin for lower-risk patients and anticoagulation with warfarin (Coumadin®) if other risk factors are present.[8] However, the large cross-sectional ATRIA study found that many patients with additional risk factors were not being prescribed warfarin, and physician prescribing patterns were not well-defined or consistent.[9] As a result, many researchers sought to develop a validated method for assigning risk to patients and choosing appropriate antithrombotic therapy based on that risk score.

This review will discuss the validity of the CHADS$_2$ scoring system for moderate-risk AF patients, other scoring systems for assessing risk, and information on the treatment options available for AF stroke prevention, including the newer direct thrombin inhibitors and direct factor Xa inhibitors. This review will also discuss the impact of the 2012 CHEST guidelines on the standards of antithrombotic therapy for AF patients.

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Table 1 | Annual Stroke Risk Assuming No Low-Dose Aspirin Usage, Based on Calculation of $CHADS_2$ Score [10,11]

CHADS2 Score	Stroke Risk %	95% CI
0	1.9	1.2-3.0
1	2.8	2.0-3.8
2	4.0	3.1-5.1
3	5.9	4.6-7.3
4	8.5	6.3-11.1
5	12.5	8.2-17.5
6	18.2	10.5-27.4

CI: confidence interval.

The $CHADS_2$ Scoring System

In 2004, several researchers pooled available data on AF stroke risk to develop the $CHADS_2$ score for determining the absolute risk a patient has of suffering a stroke in a given year (**Table 1**).[10,11] This score—an acronym for what the authors deemed to be the stroke risk factors in AF—was heralded as the new standard for identifying patients who would be appropriate candidates for warfarin therapy. The scoring criteria for $CHADS_2$ are contained in **Table 2**.

While the $CHADS_2$ scoring schematic is the most well-known and widely-used system for classifying stroke risk in AF, many questions still exist surrounding its utility, especially in moderate-risk patients. One such question is the age cutoff at which stroke becomes a larger inherent risk. The current $CHADS_2$ scoring system places this risk cutoff at age 75, but other observational studies and meta-analyses have placed the high-risk cutoff as low as age 65.[11,12] The Framingham Heart Study also identified age by decade as an independently-associated risk factor for stroke in AF.[13]

The $CHADS_2$ score primarily employs surrogate clinical markers of stroke risk and does not take into account atrial anatomic abnormalities or other direct contributors to clot formation. For example, the $CHADS_2$ score does not use atrial size in its calculation of stroke risk, yet left atrial enlargement was found to be a significant predictor of stroke in both sexes.[14] Similar predictive evidence exists for other factors such as the visualization of thrombi or atrial stasis on a transesophageal echocardiogram (TEE), left ventricular systolic dysfunction, and atrial hypertrophy.[15,16,17] The $CHADS_2$ score also fails to take female gender into account, which has been shown to be a positive predictor of stroke risk in AF.[18]

Concerns Regarding $CHADS_2$

According to the scale, a $CHADS_2$ score of 2 or more indicates that a patient should receive warfarin or dabigatran (Pradaxa®) therapy, a score of 1 indicates that therapy with either low-dose aspirin, warfarin, or dabigatran is appropriate, and a score of 0 indicates that the patient should receive low-dose aspirin therapy or no antithrombotic therapy.[19] A gray area exists in the scoring system for patients who have moderate stroke risk with a $CHADS_2$ score of 1, creating inconsistencies in prescribing habits among physicians who care for these patients. Other researchers have debated whether such a scoring system is of value for these moderate-risk patients.[20]

The $CHADS_2$ rubric's validity as a diagnostic tool is also occasionally called into question, as the criteria may fail to stratify a large number of patients into the "high risk" or "low risk" categories. In fact, a February 2010 Euro Heart Survey study found that 61.9% of patients were classified as "intermediate risk" by the $CHADS_2$ criteria, providing little guidance in answering the question of whether to initiate treatment with antiplatelet or anticoagulation therapy.[21]

The $CHADS_2$ score uses a risk-to-benefit ratio of risk of thromboembolic event if untreated versus risk of intracranial hemorrhage (ICH) with warfarin treatment to determine at what score to initiate therapy.[22] Although no formal impact analysis of the score's usefulness has been conducted, independent analyses have attempted to determine the annual net benefit of anticoagulation therapy over no treatment at specified baseline $CHADS_2$ scores. From these studies, warfarin appears to have net clinical benefit for patients with a baseline $CHADS_2$ score of 2 or higher, and the value of warfarin is overshadowed by risk of ICH for low risk patients with a score of 0 (**Table 3**). For the large number of patients with a $CHADS_2$ score of 1, there is still no consensus on whether warfarin treatment is worth the potential risk of hemorrhage.[23] This lack of information creates a need for either a better defini-

Table 2 | Risk Factor-based Schema Expressed as a Point-based Scoring System, with the Acronym $CHADS_2$ [10,11]

	Points
Congestive heart failure	1
Hypertension (consistently above 140/90 mmHg and/or treated with medication)	1
Age ≥ 75 years	1
Diabetes mellitus	1
Prior stroke or transient ischemic attack	2

Table 3 | Net Clinical Benefit of Warfarin, Based on Patient's $CHADS_2$ Score at Initiation [23]

CHADS2 Score	Net Clinical Benefit[a] (95% CI)
0	-0.11(-0.44 – 0.20)
1	0.19 (-0.27 – 0.45)
2	0.97 (0.43 – 1.41)
3	2.07 (1.21 – 2.79)
4-6	2.22 (0.58 – 3.75)

[a]Net Clinical Benefit = (TE $rate_{off\ warfarin}$ – TE $rate_{on\ warfarin}$) – **1.5** × (ICH $rate_{on\ warfarin}$ – ICH $rate_{off\ warfarin}$)
ICH = intracranial hemorrhage, TE = thromboembolism

tion of the risk-to-benefit ratio for moderate-risk patients according to the $CHADS_2$ criteria or a new system to classify stroke risk in patients with AF.

Alternative Stroke Scoring Systems

Several scoring schema exist which determine risk factors for stroke in AF. Each employs a slightly different interpretation of low, intermediate, and high risk: the $CHADS_2$ criteria assigns risk based on a numerical score, whereas both the SPAF and AFI schemes assign risk based on the presence or absence of specific patient factors, and no score is calculated.

One of the first AF stroke risk scores created was from the Atrial Fibrillation Investigators (AFI) study. AFI was a multivariate analysis of 5 different randomized trials comprising 1593 AF patients. With this scoring criteria, a patient was considered high risk if they had a history of prior stroke or transient ischemic attack (TIA), hypertension, or diabetes mellitus. Moderate risk included those who were over age 65 but had no other risk factors. Low risk patients were those who did not have any of the aforementioned disease states.[24]

Another early AF stroke risk score was the Stroke Prevention and Atrial Fibrillation (SPAF) schema. This score was determined from a multivariate analysis of a cohort of 854 AF patients treated with aspirin for stroke prevention.[25] In this scoring system, high risk is assigned to women over age 75, systolic blood pressure greater than 160 mmHg in either sex, history of stroke or TIA, and impaired left ventricular function. The moderate risk group consists of patients with hypertension, but a systolic blood pressure less than 160. The low risk group comprised all other AF patients in the cohort.[25,26] Both the SPAF and AFI stroke risk criteria were amalgamated in the creation of the $CHADS_2$ scoring system.[27]

$CHADS_2$ scoring more accurately identifies high-risk patients, as both AFI and SPAF overestimate high risk relative to $CHADS_2$.[27] However, $CHADS_2$ places a wider range of patients in the moderate risk group than either AFI or SPAF, creating the opportunity for inconsistent prescribing among physicians (**Table 4**).

The CHA_2DS_2VASc scoring system was developed in response to this $CHADS_2$ tendency to place a majority of patients at intermediate risk.[28] This refined scoring system builds upon $CHADS_2$ by taking into account stroke risk associated with increasing age, prior vascular disease, and female gender (**Table 5**). The number of points needed to reach intermediate risk (1 point) and high risk (>1 point) remain the same as $CHADS_2$. In a cohort of 1084 patients, the new CHA_2DS_2VASc scoring placed 15.1% of patients in the "intermediate risk" category, compared with $CHADS_2$ placing 61.9% of the same patients in "intermediate risk." [28] However, improved outcomes with the CHA_2DS_2VASc schema have yet to be published.

Pharmacologic Options for Stroke Prevention Based on 2012 CHEST Guidelines

For patients with a $CHADS_2$ score of 2 or more, the 2012 CHEST guidelines continue to suggest oral anticoagulant (OAC) therapy as the most appropriate option.[29] The standard of care has been warfarin therapy, but the newer factor Xa inhibitors and direct thrombin inhibitors are beginning to find a place in the treatment of patients who are unable to maintain goal INR ranges with warfarin. **Table 6** describes the new OACs on the market and in late-stage development along with their pivotal clinical trials.

Table 4 | Validation of Stratification Schemes for Primary Prevention of Stroke in 2014 Participants Prescribed Aspirin [27]

Scheme	Strokes Per 100 Patient-Years, Stratified by Risk		
	Low	Intermediate	High
AFI	0.9 (0.3-2.3; n=235)	1.7 (1.1-2.5; n=781)	3.5 (2.7-4.5; n=998)
SPAF	1.1 (0.7-1.8; n=668)	2.7 (1.8-4.0; n=462)	3.6 (2.7-4.7; n=884)
$CHADS_2$	0.8 (0.4-1.7; n=469)	2.7 (2.2-3.4; n=1322) [a]	5.3 (3.3-8.4; n=223)

Table excludes participants (n=566) who previously suffered a stroke or TIA. Risk rates are calculated from clinical factors alone, thereby excluding echocardiogram results. [a] Intermediate risk is defined as $CHADS_2$ of 1 or 2.

Table 5 | Risk Factor-based Schema Expressed as a Point-based Scoring System, with the Acronym CHA_2DS_2VASc [28]

	Score
Congestive heart failure/Left Ventricular dysfunction	1
Hypertension	1
Age ≥ 75 years	2
Diabetes mellitus	1
Stroke, transient ischemic attack, or thromboembolism	2
Vascular disease (prior myocardial infarction, peripheral artery disease, aortic plaque)	1
Age 65-75 years	1
Sex **c**ategory (ie, female gender)	1

The CHEST 2012 recommendation for patients with a $CHADS_2$ score of 1 is OAC therapy, unless the patient is deemed unsuitable for or chooses not to use OAC for other reasons.[29] For these patients, the guidelines suggest using aspirin dosed between 75mg and 325mg daily with or without clopidogrel.[29] Antiplatelets provide modest prevention of thromboembolic events while incurring a low risk of bleeding events compared to OACs.[34] Studies have been conducted to assess the benefit of adding another antiplatelet such as clopidogrel (Plavix®) to low-dose aspirin therapy in patients with AF, and some of the outcomes have been positive.[35] However, clopidogrel in addition to low-dose aspirin has not been shown to be as efficacious as oral anticoagulation.[36]

For patients with a $CHADS_2$ score of 0, the 2012 CHEST guidelines suggest using no therapy for thrombosis prevention.[29] Recent studies have shown that the risk of ICH with OAC therapy exceeds the benefit of stroke prevention in these patients.[23] Additionally, a meta-analysis showed that the risk of ICH outweighed stroke prevention benefits for both low-dose aspirin and dual aspirin-clopidogrel therapy.[29] For these low-risk AF patients, antithrombotic therapy should only be considered if the patient has significant personal concerns which warrant anticoagulation.[29]

$CHADS_2$ vs. CHA_2DS_2VASc for Intermediate Risk Patients

The $CHADS_2$ score places a large number of patients in an intermediate risk category, complicating the decision of which antithrombotic therapy to initiate.[21] True patient risk for AF-related cardioembolic stroke may be better estimated by employing the CHA_2DS_2VASc scoring system for these intermediate-risk patients with $CHADS_2$ = 1. Since CHA_2DS_2VASc overestimates the risk of AF-related stroke compared to the $CHADS_2$ score, more intermediate-risk patients scored with the CHA_2DS_2VASc schema will reach the high-risk category ($CHA_2DS_2VASc \geq 2$) and be placed on OAC therapy.[28] This overestimation of stroke risk is consistent with the CHEST 2012 recommendation to place most $CHADS_2$ = 1 patients on OAC therapy.[29] Those patients with a CHA_2DS_2VASc = 1 are likely to be true intermediate-risk patients, and may be considered appropriate candidates for dual antiplatelet therapy with clopidogrel and low-dose aspirin, although the 2012 CHEST Guidelines do not recognize the CHA_2DS_2VASc scoring system. It should be noted that dual antiplatelet therapy received a weak recommendation in the 2012 CHEST guidelines (grade 2B) and patients should be evaluated individually for the suitability of this treatment modality.

Summary

Atrial fibrillation is a growing concern for healthcare professionals in the United States. New stroke risk assessment systems are being developed to provide a more accurate evaluation of risk for a thromboembolic event. Innovative therapy options for oral anticoagulation are reaching U.S. markets with the possibility of replacing warfarin as the standard of care. The 2012 CHEST guidelines also make several significant changes to the standards of antithrombotic therapy for low- and intermediate-risk patients. Future efforts should focus on continued reclassification of intermediate stroke risk, as well as development of medications that provide increased stroke prevention benefits along with lower risks of bleeding.

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Table 6 | Summary of Pivotal Clinical Trials for Oral Anticoagulants in Atrial Fibrillation Patients [30,31,32,33]

Drug (Brand®)	Class	Pivotal AF Clinical Trial(s)	Trial Design	Patients (Mean $CHADS_2$ score)	Outcomes	Intervention	Results
Dabigatran (Pradaxa®)	Direct Thrombin Inhibitor	RE-LY[30]	PROBE (open-label WRF, double-blind DAB) N: 18113, duration: 2.0 years	AF + one other VTE risk factor (2.1)	1° efficacy: Stroke or systemic embolism 1° safety: Major bleeding events	Active: DAB 150mg (or 110mg) BID Comparator: WRF	1° efficacy: DAB (150mg): 1.11%/yr WRF: 1.53%/yr HR (95% CI): 0.66 (0.53-0.82)[a] 1° safety: DAB (150mg): 3.11%/yr WRF: 3.36%/yr HR (95% CI): 0.93 (0.81-1.07)[b]
Rivaroxaban (Xarelto®)	Direct Factor Xa Inhibitor	ROCKET-AF[31]	Randomized, double-blind, double dummy, N: 14264, duration: 1.9 years	AF + additional stroke risk factors (3.5)	1° efficacy: Stroke or systemic embolism 1° safety: Major and non-major clinically relevant bleeding events	Active: RIV 20mg (or 15mg) QD Comparator: WRF	1° efficacy: RIV: 1.7%/yr WRF: 2.2%/yr HR (95% CI): 0.79 (0.66-0.96)[c] 1° safety: RIV: 14.9%/yr WRF: 14.5%/yr HR (95% CI): 1.03 (0.96-1.11)[d]
Apixaban (Eliquis®) *(FDA approval expected 2012)*	Direct Factor Xa Inhibitor	AVERROES[32]	Randomized double blind, parallel groups, double dummy, N: 5599, duration: 1.1 years	AF unsuitable for, or previously failed, VKA therapy	1° efficacy: Stroke or systemic embolism 1° safety: Major bleeding events	Active: APX 5mg (or 2.5mg) BID Comparator: ASA 81-324mg QD	1° efficacy: APX: 1.6%/yr ASA: 3.7%/yr HR (95% CI): 0.45 (0.32-0.62)[e] 1° safety: APX: 1.4%/yr ASA: 1.2%/yr HR (95% CI): 1.13 (0.74-1.75)[f]
		ARISTOTLE[33]	Randomized double blind, parallel groups, N = 18201, duration:1.8 years	AF (2.1)	1° efficacy: Stroke or systemic embolism 2° efficacy: All cause mortality 1° safety: Major bleeding events	Active: APX 5mg (or 2.5mg) BID Comparator: WRF	1° efficacy: APX: 1.27%/yr WRF: 1.60%/yr HR (95% CI): 0.79 (0.66-0.95)[g] 2° efficacy: APX: 3.52%/yr WRF: 3.94%/yr HR (95% CI): 0.89 (0.80-0.99)[h] 1° safety: APX: 2.13%/yr WRF: 3.09%/yr HR (95% CI): 0.69 (0.60-0.80)[i]

APX = apixaban, ASA = aspirin, BID = twice daily dosing, QD = once daily dosing, DAB = dabigatran, PROBE = prospective, randomized, open blinded endpoint, VKA = vitamin K antagonists, WRF = dose-adjusted warfarin, yr = year, [a] P < 0.001 for superiority, [b] P = 0.31, [c] P < 0.001 for non-inferiority, [d] P = 0.44, [e] P < 0.001, f P = 0.57, g P < 0.001 for non-inferiority and P = 0.01 for superiority, [h] P = 0.047, [i] P < 0.001

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Clinical Trial Update

Amoxicillin for acute rhinosinusitis: a randomized controlled trial [1]— Although acute bacterial rhinosinusitis (ABRS) is most often a self-limiting disease, 1 in 5 prescriptions for antibiotics in the US are given for the treatment of ARS. Therefore, Garbutt and colleagues developed a randomized controlled trial to determine the incremental effect of amoxicillin (AMX) compared to placebo for adults clinically diagnosed with ABRS.

In 2001 the CDC developed guidelines for the assessment and treatment of adults with ABRS which were used by the researchers to diagnose ABRS.[2] Patients had to have rhinosinusitis symptoms persisting for greater than 7 days, report maxillary pain or tenderness in the face or teeth (especially if unilateral), and purulent nasal secretions. If symptoms persisted for less than 7 days the symptoms had to significantly worsen after initial improvement to be eligible. Patients were excluded if they were allergic to AMX or penicillins, received antibiotics in the previous 4 weeks, had complicated sinusitis, or rated their symptoms as mild or very mild.

Patients that met diagnostic eligibility criteria were randomized to receive a 10-day course of AMX 500 mg given three times daily or placebo; all patients received symptomatic treatments consisting of acetaminophen, guaifenesin, dextromethorphan/guaifenesin, extended-release pseudoephedrine, and saline nasal spray.

The primary outcome was the effect of treatment on disease-specific quality of life at day 3; the authors reported not selecting day 10 for the primary outcome day due to a high rate of spontaneous resolution seen with ABRS. The Sinonasal Outcome Nasal Test-16 (SNOT-16) questionnaire was used to measure the primary outcome; the questionnaire had been previously validated in the setting of ABRS. Questions were answered using a 4-scale (0=no problem to 3=severe problem) and an improvement in symptoms was assessed as the reduction in SNOT-16 scores from baseline, with a difference of 0.5 units selected as the minimally important difference for each question. Patients completed the SNOT-16 at baseline (both in office and via telephone), and then again via telephone on days 3, 7, 10, and 28.

Over 10 primary care clinics in St. Louis, Missouri, 244 patients were screened for eligibility and 166 were randomized: 85 to AMX and 81 to placebo. Overall, 36% were male, 78% were white, and the median age was 32 years; approximately 74% and 33% reported a history of sinus disease and allergic rhinitis, respectively. All patients reported purulent nasal discharge and maxillary pain or tenderness in the face or teeth; 143 (86%) reported symptoms lasting for more than 7 days, and 23 (14%) reported symptoms persisting less than 7 days that had significantly worsened after initial improvement. The most common symptoms reported were facial congestion or fullness (79%), facial pain or pressure (70%), and cough (60%); nasal obstruction was noted in 54%. At baseline, the mean SNOT-16 score (mean score for each question) was 1.71 for the AMX group and 1.70 for the placebo group (p = 0.88).

The reduction in SNOT-16 scores was similar between the AMX and placebo groups at day 3: mean reduction of 0.59 for AMX vs. 0.54 for placebo (p = 0.69). In addition, no difference was noted between groups at day 10: mean difference between groups of 0.01 (p = 0.85). However, at day 7 a significant mean difference between groups of 0.19 (p = 0.02) was noted, favoring AMX. There was no statistically significant difference in patient-reported symptom improvement at day 3 or 10 between groups, but there was a difference noted at day 7 favoring AMX (74% vs. 56%, p = 0.02). Only physician recorded nasal obstructed predicted a benefit from AMX therapy at day 7 (odds ratio, 4.59). No difference was noted between groups in the use of symptomatic treatments. No serious adverse events occurred and the occurrence of events did not differ between groups. Headache (23%) and excessive tiredness (11% with AMX, 21% with placebo) were the most commonly reported events.

Overall, the use of AMX for patients with clinically diagnosed ABRS did not appear to significantly improve symptoms at day 3 vs. placebo. The use of antibiotics in ABRS should be carefully considered for each patient.

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