# Towards Ideal Risk Stratification in Atrial Fibrillation

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**To give anticoagulants or not?**

Will the patient develop bleeding complication : haemorrhagic stroke albeit a cardioembolic stroke?

Does the benefit of Stroke prevention outweigh the risk of bleeding?

These are the major questions that haunt a clinician while managing a patient with Atrial fibrillation (AF). Previously AF was a major complication seen with Rheumatic heart disease. Now although the incidence of rheumatic heart disease is declining, the incidence of AF due to non-rheumatic causes is increasing. Cardioembolic stroke is the most dreaded complication of long standing AF. The incidence of stroke in patients with non-valvular AF (i.e. AF not caused by damage to the heart valves) is between two-and-seven fold greater than that in the general population. For patients with AF caused by valvular disease, the risk of stroke is increased 17-fold[1].

The risk of Stroke in AF is dependant on various clinical factors. Stroke risk stratification scores (RSS) incorporate these risk factors to identify patients at different levels of stroke risk. These RSS enable the targeting of oral anticoagulants (OAC) at high-risk patients, who stand to gain the most in terms of stroke risk reduction, and avoidance of their use in low-risk patients, in whom the harms of OAC (increased risk of bleeding) may outweigh their stroke prevention capabilities. Guidelines on the management of AF have used and adapted various RSS for this purpose, and have tailored their therapeutic recommendations around the different risk categories. Current guidelines advocate the use of the CHA2DS2-VASc RSS to assess stroke risk in AF patients, to identify truly low-risk patients (men and women aged <65 years with no risk factors) who may not require antithrombotic therapy, with consideration of OAC for all other patients[2].

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**The 'Ideal' Risk Stratification Score -**

The aim of the original RSS was to identify AF patients at high risk of stroke and target these patients with warfarin. However, with the emergence of additional information on new risk factors and less well-validated risk factors, as well as the development of novel OACs and the accumulation of evidence against the use of aspirin as an effective antithrombotic agent in AF, there has been a 'paradigm shift' in RSS to identify patients at truly low risk of stroke that do not require OAC.

Initial Development of Stroke RSS

The opportunity to identify patients at different levels of stroke risk was first taken in 1994 by the landmark Atrial Fibrillation Investigators (AFI) schema. Derived from a multivariate analysis of pooled data from five early trials of warfarin and aspirin in AF, the AFI schema included previous stroke, age over 65 years, diabetes and hypertension as risk factors for stroke[3].

The Stroke Prevention in AF (SPAF) investigators developed an alternative RSS using data from patients treated with aspirin in the SPAF I and II randomized trials Analyses found that female gender, age over 75 years (these were combined into a single risk factor due to their strong interaction), systolic hypertension (>160 mmHg) and impaired left ventricular (LV) function (recent heart failure or fractional shortening <25%) were independent predictors of stroke in AF. Having any one of these risk factors or a previous thromboembolic event classified patients as high risk, all other patients being considered at low risk of stroke. There was no intermediate risk category[4].

However, these two competing scheme were replaced by $CHADS_2$a point-based RSS. $CHADS_2$

was a far simpler RSS than its predecessors : a score of 1 was assigned to recent congestive heart failure, a history of hypertension, age ≥ 75 years and diabetes, and a score of 2 was given to a previous history of stroke or TIA. CHADS2 provided a score from zero to six, which was subsequently divided into three risk strata : low-risk patients had a score of zero, moderate-risk patients had scores of 1-2, and high-risk patients had scores of 3-6[5]. The CHADS2 risk assessment score does not incorporate a number of documented risk factors for stroke. Therefore, in an effort to improve its predictive value, especially for low-risk patients, the CHA2DS2-VAScscore was developed[6]. This is now preferred over CHADS2 in the latest European 2012 and American 2014 guidelines. CHA2DS2-VASc identifies 'major' risk factors, comprising stroke / transient ischaemic attack / thromboembolism and age ≥ 75 years, and 'clinically relevant non-major' risk factors, comprising congestive heart failure, hypertension, diabetes mellitus, age 65-74 years, female gender and vascular disease.

A number of researchers have validated CHA2DS2-VASc risk stratification score. Tailliander S et al. investigated the rate and risk of adverse events and the impact of antithrombotic management in a community based cohort of AF patients with a CHA(2)DS(2)-VASc score = 0. They observed that prescription of oral anticoagulation and/or antiplatelet therapy was not associated with an improved prognosis for stroke/thromboembolism (relative risk [RR] = 0.99, 95% CI 0.25-3.99, P = 0.99), nor improved survival or net clinical benefit (combination of stroke/thromboembolism, bleeding, and death). Hence they concluded that in a real life cohort study, AF patients with CHA(2)DS(2) VASc score = 0 had a low risk of stroke/thromboembolism that was not significantly different between those taking oral anticoagulation, antiplatelet therapy, or no antithrombotic therapy. This supports current guideline recommendations for no antithrombotic therapy in these "truly low-risk" patients[7].

Potpara et al also tested the predictive ability of the CHA(2)DS(2)-VASc, CHADS(2), and van Walraven risk stratification schemes in a cohort of "lone" AF patients with a 12-year follow-up. The overall rate of ischemic stroke was 0.19 (95% CI : 0.18-0.20) per 100 patient years. In the multivariable analysis, only the CHA(2)DS(2)-VASc score of 0 was significantly related to the absence of stroke (odds ratio 5.1, 95% CI: 1.5-16.8, P=0.008). Only the CHA(2)DS(2)-VASc score had a significant prediction ability (c-statistic 0.72 [0.61-0.84], P=0.031). They concluded that the CHA(2)DS(2)-VASc score reliably identified the "lone" AF patients who were at "truly low risk" for thromboembolism, and was the only tested risk stratification scheme with a significant predictive ability for thromboembolism among lone AF patients[8].

In the current issue Pandharipande MS et al[9] in their study 'Stroke Risk stratification by CHA2DS2-VASc score and short term outcomes in non valvular atrial fibrillation' have evaluated CHA2DS2VASc score in non valvular AF. 104 cases of (45males, 59 females) of atrial fibrillation were screened. Non valvular AF was reported in 64 (61.5%, p<0.05) cases, 7 cases (10.9 %)of non valvular AF had age >75 years, with a mean age of 62.2 years. Hypertension (50, 78.1%) and/or ischaemic heart disease (44, 68.7%) were the common etiologic factors associated with non valvular atrial fibrillation. CHA2DS2VASc score was zero in 3 cases (4.6%), 8 cases (12.5%) had CHA2DS2VASc score as 1, and 53 cases (82.8%) had score 2 or more indicating high stroke risk (p<0.01). At the end of 3 months, total no. of cases with Congestive heart failure was reported be 32 (50%). Cardioembolic stroke was present in 5 (7.8%) cases. Peripheral embolism was documented in 1 case (1.5%). Mortality at the end of 3 months in cases of non valvular AF was reported in 7 cases; 10.9%. Univariate analysis revealed significant association of CHA2DS2VASc score, CHF, stroke, EF<40% and type of AF with mortality. Multivariate regression analysis demonstrated significant association of CHA2DS2VASc score with mortality in non valvular AF (P<O.OO2).

The strength of clinical risk scores is that low risk values (CHADS2 score of 0, CHA2DS2VASc score of 0 to 1) provide very good sensitivity and negative predictive value for stroke, which is helpful for defining thresholds for anticoagulation, but at the cost of poor specificity and overall accuracy[10]. As a result, risk scores provide weak discrimination of stroke risk for some individuals, particularly those with intermediate or high scores[11].

Clinical risk scores can potentially be refined by considering additional indices. A range of biomarkers that reflect pathophysiological processes relevant to AF and stroke also provide independent risk prediction when added to clinical risk scores. These include markers of thrombosis (von Wille brand factor, D-dimer), renal function (creatinine clearance, proteinuria), myocardial necrosis (troponins), and the natriuretic peptides (N-terminal proB-type natriuretic peptide [NT-proBNP], BNP) . Thenatriuretic peptides, which are powerful markers of risk in the setting of heart failure and acute coronary syndromes, are potentially helpful markers in the setting of AF .Secreted from cardiomyocytes, BNP and NT-proBNP levels in plasma reflect left ventricular size, function, and filling pressures, but also renal function, age, and sex, all of which may modify stroke risk in AF[12].

The findings from a large sub study of the ARISTOTLE trial and also the smaller sub study of the RE-LY study indicate that among subjects fully anticoagulated for AF, a single measurement of NT-proBNPprovides powerful prediction of the residual risk of either stroke / SE or of cardiovascular complications. Subjects who are receiving anticoagulation for AF and who have low NT-proBNP levels (<363 ng/l) are at very low risk of stroke/SE or cardiac death regardless of their CHA2DS2VASc score. Conversely, if NT-proBNP levels are high (>1,250 ng/l), the risk of these events is high, even when the CHA2DS2VASc score is < 2. Although guidelines may not endorse routine measurement of NT-proBNP levels, this information may have significant clinical utility, particularly in patients for whom there are concerns about major bleeding or other risks related to anticoagulation[13].

Warfarin has been used since beginning for anticoagulation in AF. It is a potent drug but fortnightly monitoring of INR (International normalized ratio) is essential. Newer oral anticoagulants have been developed to maximize the anticoagulant action, decrease the risk of bleeding and also reduce the need for frequent monitoring of INR. It would be worthwhile to mention direct thrombin inhibitor; Dabigatran. In the RE-LY trial, dabigatran was shown shown to be superior to warfarin in preventing stroke with a reduced risk of life threatening bleeding but a higher risk of GI bleed. Its cardiovascular safety was also doubted. Rivaroxaban an oral factor Xa inhibitor is non inferior to warfarin in stroke prevention with no difference in major bleeding. Also interruption for a period of 28 days risk of thrombotic events is increased. Another major problem with newer OACs is that there is no test to measure the degree of anticoagulation and no reversal agent is available.

Hence the risk scores like CHAD2VaSC score can be used to risk stratify patients with AF and decide about use of anticoagulant drugs, alongwith the cost, patient preferences and expected results.

**References :**

1. Fuster V, Ryden LE, Cannom DS et al. 2011 ACCF / AHA / HRS focused updates incorporated into the ACC / AHA / ESC 2006 guidelines for the management of patients with atrial fibrillation : a report of the American College of Cardiology Foundation / American Heart Association Task Force on Practice Guidelines. Circulation 2011; 123 : e269-e367.
2. Durrant J, Lip GY, Lane DA. Stroke risk stratification scores in atrial fibrillation: current recommendations for clinical practice and future perspectives. Expert Rev Cardiovasc Ther. 2013 Jan; 11 (1) : 77-90. Doi : 10.1586 / erc.12.161.
3. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. Arch. Intern. Med. (1994); 154 : 1449-1457.

4. Stroke Prevention in Atrial Fibrillation Investigators. Risk factors for thromboembolism during aspirin therapy in patients with atrial fibrillation: the Stroke Prevention in Atrial Fibrillation Study. J. Stroke Cerebrovasc. Dis. 1995; (5) : 147-157.
5. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke : results from the National Registry of Atrial Fibrillation. JAMA. 2001; 285 (22), 2864-2870.
6. Lip GYH, Halperin JL. Improving stroke risk stratification in atrial fibrillation. Am J Med 2010; 123 : 484-0488.
7. Taillandier S1, Olesen JB, Clémenty N, Lagrenade I, Babuty D, Lip GY, Fauchier L. Prognosis in patients with atrial fibrillation and CHA2DS2-VASc Score = 0 in a community-based cohort study. J Cardiovasc Electrophysiol. 2012 Jul; 23 (7) : 708-13.
8. Potpara TS1, Polovina MM, Licina MM, Marinkovic JM, Prostran MS, Lip GY. Reliable identification of “truly low” thromboembolic risk in patients initially diagnosed with "lone" atrial fibrillation: the Belgrade atrial fibrillation study. CircArrhythm Electrophysiol. 2012 Apr; 5 (2) : 319-26.
9. Pandharipande MS, Shinde SV, Motlag MD, Nagpure K, Chopde S, Joshi P P, Stroke Risk stratification by CHA2DS2-VASc score and short term outcomes in nonvalvular atrialfibrillation. VJIM Vol 20; Jan, 2016; p7-12.
10. Olesen JB, Lip GY, Hansen ML, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ 2011; 342 : d124.
11. Lip GY. Stroke and bleeding risk assessment in atrial fibrillation : when, how, and why? Eur Heart J 2013; 34 : 10419.
12. Daniels LB, Maisel AS. Natriuretic peptides. J Am CollCardiol 2007; 50 : 235-768.
13. Hijazi Z, Wallentin L, Siegbahn A, Andersson U, et al. N-terminalproB-type natriuretic peptide for risk assessment in patients with atrial fibrillation : insights from the ARISTOTLE trial (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation). J Am CollCardiol 2013; 61 : 227-484.