

Atrial Fibrillation: Stroke and bleeding Risk Assessment

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Abstract

Atrial fibrillation increases with increased elderly population and it increases the risk of thromboembolism that may lead to stroke. Both CHADS2 and CHA2DS2 VAS scores are widely used to assess the stroke risk according to current international guidelines. The accuracy of both scores in predicting stroke risk is only modest. Some important clinical risk factors are missing of those scores such as chronic kidney disease, Body Mass Index BMI, echocardiographic abnormalities and other biomarkers. Assessment of bleeding risk using HEMORR2HAGES, HAS-BLED, and ATRIA scores are discussed in detail.

Keywords: Atrial fibrillation; Stroke; Bleeding; Risk assessment

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice [1, 2]. It is associated with significant increase in morbidity and mortality notably stroke and thromboembolic complications [2-4].

There is a recent enthusiasm in the stroke risk and bleeding risk stratification trying to balance the potential cost/benefit ratio for optimum decision of thromboprophylaxis of AF patients, especially in the era of the novel antithrombotic therapy, such as the oral direct thrombin inhibitors (e.g. dabigatran) and oral factor Xa inhibitors (e.g. rivaroxaban, apixaban) [5].

AF and stroke epidemiology

AF is the most common sustained tachyarrhythmia [1, 2], with estimated prevalence in the developed world is 1.5-2% of the general population [6]. Recently, Friberg and Bergfeldt found the prevalence of AF in the Swedish population at least 2.9% not including the silent AF [7]. Moreover, Go and his colleagues found, in the Atria study, that the prevalence of AF is 1% in all age groups, and it increases with age, reaching 4% in people aging 60 years or more and 9% of people aging 80 years or more [8]. Hypertension, diabetes mellitus, old age, heart failure, and hyperthyroidism were reported as risk factors for developing atrial fibrillation [1]. AF is associated with significant morbidity and mortality, and is an independent risk factor for stroke, increasing the

risk about four times [2, 3]. Moreover, it significantly increased the cost of stroke hospitalizations [4]. Recently, Sussman et al, in November 2013, found that AF increased the health-related cost of ischemic stroke, hemorrhagic stroke, and transient ischemic attacks by 20%[9]. It was found that AF-associated stroke is more severe than stroke without AF [4]. Interestingly, AF is found to be independently associated with increased risk of myocardial infarction in women (HR=2.2) and blacks (HR=2.5) [10].

Although most patients with AF are identified because they have symptoms, many patients with AF are asymptomatic in fact, it is sometimes first diagnosed when patients present with complications as heart failure, thromboembolism or stroke [11,12]. In a recent meta-analysis of six prospective cohort studies of 18558 general population, it was found that 3165 of them have developed AF during 22 years of follow-up. Baseline serum adiponectin was significantly associated with increased risk of first AF HR: 1.17, 95% CI 1.08- 1.27 P<0.001.

Asymptomatic versus symptomatic atrial fibrillation and stroke

Asymptomatic attacks of AF are more frequent than symptomatic ones amongst patients with paroxysmal AF. Page and his colleagues found that asymptomatic AF occurs 12-fold more frequently than symptomatic attacks [13]. It was found that even short episodes of asymptomatic AF carry a risk for stroke, these data found in the studies

used Holter ECGs and the studies used implanted devices [14,15]. The AFFIRM investigators studied 481 asymptomatic patients with AF based on ambulatory ECG. They found that their patients have significantly more cerebrovascular attacks but with less adverse cardiac events [16].

Hohnloser et al found in the ACTIVE W trial that paroxysmal AF carries similar risk of stroke and thromboembolism to sustained AF under treatment [17]. There is strong relationship between AF burden and thromboembolism. Capucci et al studied 725 patients with an implanted dual chamber pacemaker due to brady-tachy syndrome. They followed them up for two years and found that patients with AF longer than one day (detected by the pacemaker device) were independently associated with 3-fold increase of embolic events [18]. Similar findings were reported by Glotzer and colleagues, in the TRENDS study. This study was a prospective and observational study recruiting patients with pacemakers or defibrillators that detect atrial tachycardia/ fibrillation burden. During a mean follow-up of 1.4 years, they found that patients with high atrial tachycardia/fibrillation burden have about double the annual thromboembolic risk (including transient ischemic attacks). This was a trend not reaching the statistical significance ($P=0.06$) [19]. Moreover, Healy et al studied, in the ASSERT trial, 2582 hypertensive patients without prior AF, in whom a pacemaker or defibrillator had been implanted. They found that device-detected subclinical atrial tachyarrhythmias occurred in 261 (about 10%) patients, and the risk of stroke and systemic embolism increased more than two times (hazard ratio, 2.49; 95% CI, 1.28 to 4.85; $P=0.007$) [15].

Assessing stroke risk in AF

The CHADS₂ score is a clinical prediction score for estimating the risk of stroke in patients with non-rheumatic AF that has been widely used due to its simplicity and ease. It was emerged by combing the AF Investigators and SPAF-1 risk schemes [20]. It includes Congestive heart failure (CHF), hypertension, age of 75 years or more, (diabetes mellitus) DM, and prior stroke or TIA. Each condition has been given one point, except prior stroke or TIA has been given 2 points (see table 1) [1, 20]. The annual stroke risk increases from 1.9% for the minimum score of zero to 18.2% for the maximum score of 6 (see table 3) [20].

Clinical Parameter		Points
C	Congestive heart failure (any history)	1
H	Hypertension (prior history)	1
A	Age ≥ 75 years	1
D	Diabetes mellitus	1
S ₂	Prior Stroke or TIA (most experts include systemic embolism)	2

Table 1: Criteria of CHADS₂ score

Based on its original validation study, it categorizes a score of 0 as low risk, 1-2 as moderate/intermediate risk and >3 as high risk [20]. Nonetheless, current guidelines have changed the previous categories by defining high risk as a CHADS₂ score > 2 [6]. It has become the standard score described and recommended in the 2006 American

College of Cardiology/American Heart Association/Heart Rhythm Society guidelines for the management atrial fibrillation [1]. Welles et al., the Heart and Soul Study, studied 916 sinus rhythm patients (by baseline electrocardiogram) with stable coronary artery disease and do not receive anticoagulation. They studied the prognostic performance of the CHADS₂ score in the coronary artery disease patients without atrial fibrillation. They found that the event rate in the sinus rhythm with the CHADS₂ high score (5-6) was comparable to the AF published event rate of the intermediate CHADS₂ score (1-2). But, it is not known that this group of patients will benefit from stroke prevention strategies or screening of silent AF or not [21].

Although, the CHADS₂ score has become widely used, there are many concerns. First, it does not include common stroke risk factors in atrial fibrillation as, female gender, and vascular disease [22-24]. Secondly, studies found that 30-50% of AF have CHADS₂ score=1, and the risk of bleeding and the risk of stroke is similar in this subset of patients. Therefore, the recommendation was to use either aspirin or oral anticoagulation. This resulted in a large proportion of AF patients without clear thromboprophylaxis policy [20, 25]. To complement the CHADS₂ score by inclusion of additional stroke risk factors as age 65-74 years, female gender, and vascular disease, the CHA₂DS₂-VaS score has been emerged [26], and recommended by the ESC guidelines [6].

The CHA₂DS₂-VaS score or Birmingham Schema is a refinement of CHADS₂ score and extends the latter by including additional common stroke risk factors. The maximum CHA₂DS₂-VaS score is 9, but it places 2 risk factors (age more than 75 years, and previous stroke and/or TIA) as major risk factors by allocating 2 points for each (see table 2). The other risk factors are allocated one point for each, they are (systolic heart failure, hypertension, diabetes, age 65-74 years, vascular disease and female gender), with total scores ranging from 0 to 9 [26].

Condition		Points
C	Congestive heart failure	1
H	Hypertension	1
A ₂	Age = or > 75 years	2
D	Diabetes Mellitus	1
S ₂	Stroke	2
V	Vascular disease	1
A	Age 65-74 years	1
Sc	Sex category (female)	1

Table 2: CHA₂DS₂-VaSc score

Congestive heart failure is the first criterion of the acronym the CHA₂DS₂-VaS score [26], while, history of heart failure is not considered a risk factor for stroke. Nevertheless, decompensated heart failure requiring hospitalization (regardless of ejection fraction) is a stroke risk factor [27, 28]. It was found that moderate to severe LV systolic

dysfunction as an independent risk factor of stroke non-valvular AF cohorts [27, 29, 30]. Therefore, in patients with moderate to severe LV systolic dysfunction the relative risk of stroke is 2.5 (1.5 to 4.4), $p < 0.001$ [31]. Whereas, the odds ratio for stroke for abnormal LV ejection fraction is 1.8 (1.2 to 2.7), $p = 0.003$ [32]. Other less important risk factors, as obesity and chronic lung disease were not found to be independent stroke risk factors on multivariate analysis [33]. Moreover, thyroid disease (or of current hyperthyroidism), in contrary to the older and conflicting data, was not an independent stroke risk factor the Swedish Atrial Fibrillation cohort study [33].

The CHA2DS2-VaS score has been validated by several studies as the Euro Heart survey on AF [26], data base from UK General Practice Research Database [34], and hospitalized patients in Denmark [35]. Moreover, Olesen and his colleagues studied more than 47 thousands patients with chads2 (score 0-1). From this apparently low to moderate risk patient for stroke by the CHADS2 score, the patients were further categorized according to the CHA2DS2-VaS score. They found that about 15.8% of their studied population was the CHA2DS2-VaS score of 0, 21.2% were the CHA2DS2-VaS score of 1, 30.1% were the CHA2DS2-VaS score of 2, 29.8% were the CHA2DS2-VaS score of 3, and 3.1% were the CHA2DS2-VaS score of 4. The stroke/thromboembolism risk increases with increasing the CHA2DS2-VaS score. The previously labeled low-risk patients by the CHADS2 score are not truly low-risk by the CHA2DS2-VaS score [36]. It is well known, nowadays, that the CHA2DS2-VaS score is better than the CHADS2 score in identifying the true low risk patients [33]. Thus, the CHA2DS2-VaS score improves the predictive value of CHADS2 score and refines the stroke risk assessment of the low risk patients of CHADS2 [36]. Furthermore, both scores performance was modest in assessing stroke risk may be because several other important clinical risk factors are not included such as renal dysfunction, the exact type of AF (persistent vs paroxysmal) m BMI, Echocardiographic abnormalities and novel blood biomarkers.

Lone AF

The term lone AF was introduced by Evans and Swann in 1953 [37]. Currently, lone atrial fibrillation is considered when clinical and echocardiographic evidence of cardiovascular or pulmonary disease has been excluded. Also, conditions as hypertension, diabetes mellitus, thyrotoxicosis, recent cardiothoracic or abdominal surgery, and acute infections should be ruled out [38]. Patients, who are below 65 years of age and have lone AF, have significantly low stroke rates. Therefore, female patients with gender alone as a risk factor is considered low risk patient for stroke if they have fulfilled the 2 criteria of age below 65 and lone AF, although they still have CHA2DS2-VaS score of 1 [36, 39]. Thus, the 2012 ESC focused update on AF strongly recommends meticulously identifying 'truly low-risk' patients with AF (as age below 65 years of age and lone AF), who do not need any antithrombotic treatment [6].

Annual Stroke Risk (Percent / Year)		
Score	CHADS ₂ Score [1, 20]	CHA2DS2-VaSc score [6, 26]

0	1.9	0
1	2.8	1.3
2	4.0	2.2
3	5.9	3.2
4	8.5	4
5	12.5	6.7
6	18.2	9.8
7		9.6
8		6.7
9		15.2

Recommendations for Antithrombotic Treatment

The CHA2DS2-VaS score of 0 is considered low risk, and no antithrombotic therapy is recommended [6, 28]. The CHA2DS2-VaS score = 1 'intermediate risk' [28] recommend antithrombotic therapy with oral anticoagulation or antiplatelet therapy, but preferably oral anticoagulation [6]. Patients, at the intermediate risk category, should be treated with anticoagulation rather aspirin, because under treatment is more harmful than overtreatment. Nevertheless, patient preference should be considered [40, 41]. Moreover, according to the BAFTA trial, there was no difference in major bleeding between aspirin (75 mg daily) and oral anticoagulant warfarin (target INR 2-3) in an AF elderly population [42]. The CHA2DS2-VaS score > 2 'high risk category' recommends oral anticoagulation [6, 28].

Bleeding Risk Assessment

The approach to thromboprophylaxis of AF needs balancing the benefits of the anticoagulation against the risk of bleeding. The most feared bleeding complications is intracranial cranial haemorrhage (ICH). Thus, bleeding risk assessment remains a corner stone in management of AF anticoagulation policy. Hughes and his colleagues who developed the NICE (the National Institute for Clinical Excellence in the United Kingdom) guidelines reported that the risk factors for bleeding due to anticoagulation in patients with AF were "advanced age, uncontrolled hypertension, history of myocardial infarction or ischemic heart disease, cerebrovascular disease, anaemia or a history of bleeding, and the concomitant use of other drugs such as antiplatelet agents" [43]. Factors as controlled hypertension, diabetes and gender are not significant bleeding risk factors in the AF patients [44].

There are 3 scores for anticoagulation-related bleeding risk have

been validated in the AF patients. They are HEMORR2HAGES, HAS-BLED, and ATRIA scores. The first one is HEMORR2HAGES score that includes “hepatic or renal disease, ethanol abuse, malignancy, older (age ≥ 75 years), reduced platelet count or function, Re-bleeding risk, hypertension (uncontrolled), anaemia, genetic factors, excessive fall risk, and stroke”. Each risk factor has been allocated 1 point, except that prior bleeding has been allocated 2 points [45]. The second score is the ATRIA score “Anticoagulation and Risk factors In Atrial fibrillation”. It includes anaemia, severe renal disease, age ≥ 75 years, any prior haemorrhage diagnosis, and diagnosed hypertension [46]. The third one is the HAS-BLED score that has been emerged and recommended to be used by the recent (ESC and Canadian) guidelines. It includes “hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (e.g. age ≥ 65 , frailty, etc.), drugs/alcohol concomitantly” [47]. It has been validated by several studies in different patient population [33] [47-49]. The difference between the HAS-BLED score from the ATRIA score is that it has a better predictive value, and includes factors that can be managed to reduce the risk of bleeding [50, 51]. It has been found to be well correlated with the risk of ICH [33]. For any given HAS-BLED score, it was found that the rate of major bleeding and ICH was similar between those patients on aspirin and those on warfarin [33]. The ESC guidelines recommend assessing the bleeding risk routinely for all patients with AF, this gives the clinician an objective assessment of the risk. The risk assessment should not be used merely to exclude patients from OAC, but assesses the risk to be able to balance the risk benefit ratio of anticoagulation decision in AF patients. Patients with a HAS-BLED score ≥ 3 should be treated with caution with regular checks when appropriate, moreover, all the potentially correctable risk factors should be managed: as uncontrolled hypertension, labile INR, use of non-steroidal anti-inflammatory drugs (NSAIDs) [6].

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