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REVIEW ARTICLE

Stroke risk stratification in atrial fibrillation: a review of common risk factors

Oreoluwa Oladiran[a] and Ifeanyi Nwosu[b]

[a]Department of Internal Medicine, Reading Hospital, Tower health system, West Reading, PA, USA; [b]Department of Internal Medicine, Leighton Hospital NHS Trust, Crewe, Cheshire, UK

ABSTRACT

Atrial Fibrillation (AF) has become a major global health concern being the most common sustained arrhythmia in clinical practice. Risk factors for AF include congestive heart failure, hypertension, increasing age and diabetes. Many of these factors also increase the risk for thromboembolism and ischemic stroke in AF patients. Great efforts have been made from the latter part of the 20th century towards developing an ideal stroke risk stratification tool in AF with the aim of reducing the incidence of stroke in AF patients and the limiting unnecessary use of thromboprophylaxis. The thromboembolic risks posed by AF with valvular heart disease are an important subgroup that contributes to a significant proportion of stroke in AF patients globally. We review the evolution of stroke risk stratification and summarize the guidelines for stroke prevention in non-valvular AF as well as AF with valvular heart disease, and the most recent recommendations on stroke prevention in AF patients.

Abbreviations: AF: Atrial Fibrillation; ACS: Acute Coronary Syndrome; CAD: Coronary Artery Disease; CCF: Congestive Cardiac Failure; DM: Diabetes Mellitus; EHRA: Evaluated Heartvalves, Rheumatic or Artificial; ICH: Intracranial Hemorrhage; NOACs: Novel Oral Anticoagulants; OAC: Oral Anticoagulants; PAD: Peripheral Arterial Disease ; TIA: Transient Ischemic Attack; VHD: Valvular Heart Disease.

1. Introduction

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function [1]. As one of the most studied cardiovascular diseases, its understanding has evolved through decades. Currently affecting about 2.7–6.1 million people in the USA [1] and 33 million people worldwide [2], with an annual risk of ischemic stroke estimated to be about 5–7%[3], the cornerstone of management remains interventions for rate control, rhythm control and thromboprophylaxis. More recently, the focus has been to streamline patient management pathways, to approach AF management in a holistic or integrated manner, as follows (the ABC or Atrial fibrillation Better Care Pathway- Figure 1): 'A' Avoid stroke with Anticoagulation; 'B' Better symptom care, with patient-centred symptom directed decisions on rate or rhythm control; and 'C' Cardiovascular and comorbidity risk management, including attention to risk factors and lifestyle changes [4]. The ABC approach has shown that compliance with such optimised care is associated with a significant reduction in mortality and hospitalisations [5], and a reduction in healthcare cost associated with cardiovascular events [6]. This review aims to provide a historic perspective on the evolution of stroke risk classifications in AF with particular emphasis on the most widely used system – the CHA$_2$DS$_2$VASc score, its individual components and their contribution to the overall risk of stroke.

2. Individual risk factors for stroke in atrial fibrillation

Among many other factors that increase the risk of stroke, AF is an independent risk factor for ischemic stroke and studies showed that this risk is increased by a factor of five in patients with AF [7,8]. AF is associated with major systemic thromboembolism and about a third of patients with ischemic stroke have been found to have either clinical or subclinical AF [9] due to high prevalence of left atrial thrombosis [10]. Since oral anticoagulation (OAC) is known to reduce the incidence of stroke in AF, timely diagnosis and use of anticoagulant is imperative for stroke prevention [11].

Over the years several stroke risk stratification systems have been developed using common and validated stroke risk factors in patients with AF, to aid decision-making for thromboprophylaxis. Most of these systems utilise acronyms to represent various individual risk factors and are scored accordingly. Although stroke risk is a continuum, patients have been artificially classified as low, intermediate and high risk for stroke and decision to commence thromboprophylaxis are made to avoid
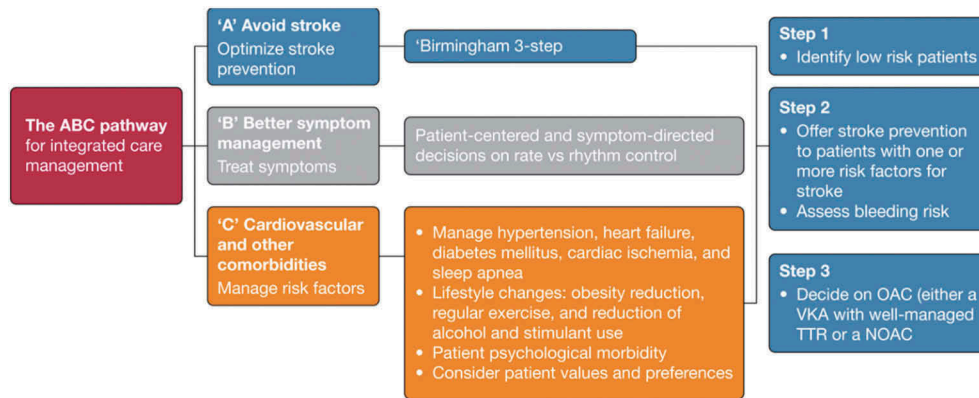
Figure 1. Illustrating the atrial fibrillation better care pathway for integrated management of patients with atrial fibrillation [4].

unnecessary use of OAC [12]. A major shift in the stroke risk stratification is the identification of low risk group to minimize needless anticoagulation.

One of the earliest stroke risk stratification system was the Framingham score [13], a points-based system assessed various clinical factors and assigned scores as follows: Age (0–10), female sex (6), systolic hypertension (0–4), diabetes mellitus (5), and prior stroke or transient ischemic attack (TIA) (6). Scores >8 were considered increased risk and required thromboprophylaxis [14]. The Atrial Fibrillation Investigators (AFI) sought to identify patient features predictive of stroke risk and found that patients with AF less than 65 years without hypertension, previous stroke or transient ischemic attack or diabetes were at very low risk for stroke and were not anticoagulated [15,16]. The stroke prevention in atrial fibrillation (SPAF) trial also identified recent congestive heart failure (within 3 months), history of hypertension (systolic blood pressure >160 mmHg) and previous arterial thromboembolism as independent risk factors for thromboembolism in atrial fibrillation [17]. In 2001, Gage et al devised the $CHADS_2$ score by merging the AFI and SPAF classification schemes, testing this in a cohort of hospitalised AF admissions [18]. The $CHADS_2$ score assesses the individual risk factors and scores 1 point for congestive cardiac failure, hypertension, age 75 years and above and diabetes mellitus. Prior stroke or transient ischemic attack is assigned 2 points [18].

In 2010, a revised clinical risk stratification tool for predicting stroke and thromboembolism in AF [19] provided some improvement in the predictive value of the existing $CHADS_2$ schema by including age 65–74 years, vascular disease and female gender to form the CHA_2DS_2VASc score (Table 1). This is currently a widely used scoring system in guidelines for stroke in AF as it usefully identifies low risk patients with AF. Piccini et al in 2012 noted that renal dysfunction was an independent risk factor for stroke in patients with AF and thus the R_2CHADS_2 scoring system was introduced with 2 points assigned to creatinine clearance less than 60ml/min [20]. This is perhaps unsurprising as renal impairment often coexists with components of the $CHADS_2$ and CHA_2DS_2-VASc scores. Latter studies disputed the relevance of renal impairment as an independent risk factor for stroke in AF as it failed to improve the predictive ability of $CHADS_2$ and CHA_2DS_2-VASc score [21]. Despite the use of the various risk stratification systems, a significant number of strokes are still noted in patients with AF classified as low risk and not requiring thromboprophylaxis. The need to further identify other risk factors for thromboembolic event led to the introduction of the ATRIA (anticoagulant and risk factors in atrial fibrillation) score [22] which in addition to existing risk factors, also included age categories, presence of proteinuria and estimated glomerular filtration rate less than 45 or end stage renal disease. While a study by Van Den Ham et al noted that the ATRIA score better identified low risk patients for stroke than the CHA_2DS_2-VASc score [23], various other cohort studies concluded that CHA_2DS_2-VASc score had better correlation with thromboembolism in non-anticoagulated patients with AF than the newer R_2CHA_2DS, ABC-stroke score and ATRIA scoring systems [24,25] The Canadian Cardiovascular Society adopted the CHADS65 risk score, which incorporated the $CHADS_2$ and CHA_2DS_2-VASc risk factors proposing a guideline for thromboprophylaxis in patients with AF. This risk score considered age 65 years and above as a cut-off and recommend the use of OAC in AF patients with $CHADS_2 \geq 1$ and age $\geq$ 65 years. Aspirin was recommended for patients with stable coronary artery disease (CAD)/peripheral vascular disease (PVD), or those age< 65 years, and no

Table 1. Individual components of the CHA2DS2-VASc risk factors [19]. CHA_2DS_2-VASc score.

Risk Factors	Scores
Congestive heart failure/Left ventricular dysfunction	1
Hypertension	1
Age ≥75Yrs	2
Diabetes mellitus	1
Stroke/TIA	2
Vascular disease (prior myocardial infarction, peripheral artery disease	1
Age 65 to 74 years	1
Sex category (female)	1

thromboprophylaxis in patients < 65 with $CHADS_2$ of 0, in the absence of CAD/PVD [26]. In 2013, Hippisley-Cox et al developed and published the Qstroke algorithm, which is an electronic model that calculates the risk of stroke or TIA without prior stroke or TIA based on several risk factors such as age, ethnicity, sex, smoking status, clinical diagnosis of diabetes, treated hypertension, kidney disease, rheumatoid arthritis, angina, coronary heart disease, congestive cardiac failure, valvular heart disease, and clinical values including ratio of total serum cholesterol to high density lipoprotein cholesterol concentrations, body mass index as well as family history of coronary heart disease in first degree relative under 60 years. Its performance was compared to the existing scoring systems mainly the $CHADS_2$ and CHA_2DS_2 VASc scores. Qstroke was found to improve the performance of both $CHADS_2$ and CHA_2DS_2VASc in assessing high risk patients who might benefit from anticoagulation [27]. The quest to find an ideal stroke risk stratification tool continued as a significant population of non-anticoagulated low risk patient was seen to have thromboembolic events. The Global Anticoagulant Registry in the FIELD–Atrial Fibrillation (GARFIELD study) [28] used a computer-generated risk model that predicted all-cause mortality, ischaemic stroke/systemic embolism (SE) and haemorrhagic stroke/major bleeding in low-risk atrial fibrillation (AF) patients – and proposed the GARFIELD-AF score which was superior to CHA_2DS_2-VASc in predicting risk of ischemic stroke in AF patients with low risk of stroke [29]. In the Southern hemisphere, the National Heart Foundation of Australia (NHF) and the Cardiac Society of Australia and New Zealand (CSANZ) published a national guideline for stroke prevention in patients with AF. They recommended the use of the 'sexless CHA_2DS_2-VASc score' ie. the CHA_2DS_2-VA risk score, and preference was given to non-vitamin K antagonist oral anticoagulants (NOACs) over vitamin K antagonists (VKA) in patients with scores ≥ 1 [30].

Currently, given its relative simplicity the CHA_2DS_2-VASc score is still the most widely used scoring system and the 2018 American College of Chest Physicians (ACCP) CHEST guidelines recommend the use of oral anticoagulants, preferably NOACs for patients with a single non-sex CHA_2DS_2-VASc risk factor (score of ≥ 1 in males, ≥ 2 in females) rather than no anticoagulation or use of single or dual anti-platelet therapy [31].

2.1. AF patients with valvular heart disease

Much emphasis has been placed on the risk of thromboembolism in patients with non-valvular AF. Nevertheless, there remains a significant risk of thromboembolism in AF with valvular heart disease (VHD). This category refers to AF in patients with rheumatic mitral valve stenosis or mechanical prosthetic valve [32]. Unlike in non-valvular AF where left atrial thrombus is mostly formed, patients with AF with VHD are at much higher risk of thromboembolism and the formation of the thrombus occurs mostly outside the left atrium for unclear reasons. This risk is not only related to the degree of valvular disease, but it is also affected by various CHA_2DS_2-VASc risk factors [32]. Over the years, there has been confusion regarding the type of anticoagulation therapy to be used in patients with non-valvular AF and patients with AF with valvular heart disease with respect to VKA vs NOACs.

With the need to address this, the European Heart Rhythm Association (EHRA) published a consensus document which proposed categorizing patients with AF into 2 groups based on the type of OAC used for thromboprophylaxis thus the EHRA (**E**valuated **H**eartValves, **R**heumatic or **A**rtificial) [32]. EHRA Type 1 patients are those with AF and VHD requiring therapy with VKA. The VHD considered in this category are only mechanical prosthetic valves or rheumatic mitral stenosis with moderate-severe dysfunction. The options of NOACs versus VKA for anticoagulation in patients with valvular AF was explored by the RE-ALIGN trial which compared Dabigatran an oral direct thrombin inhibitor against Warfarin in AF patients with mechanical valve [33]. The study concluded that Dabigatran was less effective compared to Warfarin and associated with increased risk of bleeding and thromboembolic event [34]. Contrary to this finding, a prospective DAWA-study reported that NOACs are as effective as VKA in valvular AF [34]. However, the study had several shortcomings notably the small sample size and premature termination of the study due to poor enrolment. Further studies are needed to determine the benefits of NOACs over Warfarin for patients with valvular AF.

EHRA Type 2 patients are those with AF and VHD requiring therapy with either VKA or NOACs based on CHA_2DS_2-VASc risk levels. The VHD considered in this category includes mitral regurgitation, mitral valvular repair, aortic stenosis and regurgitation, bioprosthetic valves, pulmonary valve stenosis and regurgitation, tricuspid valve stenosis and regurgitation, and a trans-aortic valve intervention. However, it is important to note that while patients with bioprosthetic valves were excluded from the NOAC trials namely ROCKET-AF [35], RE-LY [36] and ARISTOTLE [37], their use is considered acceptable. Although bioprosthetic valves are known to be less thrombogenic, further research is required to determine long term safety of NOACs in patients with bioprosthetic valves requiring anticoagulation.

3. Congestive heart failure

Congestive heart failure (CHF) which represents the 'C' in the CHA_2DS_2VASc scoring system, is considered a cause and effect of AF and is associated with increased morbidity and mortality [38]. In older scoring systems such as $CHADS_2$, heart failure only referred to recent

decompensated heart failure and there was some uncertainty as to whether or not heart failure with preserved ejection fraction (HFpEF; left ventricular ejection fraction >50%) or heart failure with reduced ejection fraction (HFrEF; left ventricular ejection fraction <40%) or asymptomatic systolic or diastolic dysfunction was being included.

Banerjee et al sought to establish the role of ejection fraction in risk prediction in patients with non-valvular AF and heart failure. They found no difference in rates of stroke, systemic thromboembolism or death between the different heart failure categories [39]. Sandhu et al also assessed this relationship among participants of ACTIVE (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events) trial in which, among patients with heart failure, neither the presence of left ventricular systolic dysfunction nor the degree of symptom severity influenced the risk for embolic events [40]. Therefore, the decision about risks and benefits of anticoagulation for heart failure patients with AF should not be influenced by ejection fraction or symptom status.

4. Hypertension

Hypertension is the most prevalent risk factor for new-onset atrial fibrillation. Controlled or uncontrolled hypertension and history of hypertension scores a point in the CHA_2DS_2VASc score. In one study, the observed absolute stroke risk from hypertension alone as a risk factor in non-anticoagulated patients with atrial fibrillation was about 1.5–3.0% per year [41].

A cross-sectional longitudinal analysis using data from Stroke prevention using an Oral Thrombin inhibitor in atrial Fibrillation (SPORTIFF) III and V trials showed an increase in stroke rate with increasing systolic blood pressure in patients with AF. Hypertension contributes to increased stroke with events rates increased at systolic blood pressure (SBP) levels of 140 mmHg and above. However, controlled hypertension with mean SBP <140 mmHg, is associated with a lower risk of stroke compared with patients with poorly controlled hypertension. Notably, in the aspirin arm of SPAF III trial, even subjects with a history of hypertension had an increased risk of stroke in AF [42].

5. Age

The Framingham study and more recent studies established age as a significant and independent risk factor for AF associated stroke [7,43–45]. Studies also showed that in patients with lone AF (without other risk factors), the risk of stroke significantly increased in patients >60 years [46]. Studies have also shown that the highest risk of stroke in AF was found in patients aged 75 years and above. For this reason, the CHA_2DS_2-VASc score assigned a score of 2 for age ≥ 75 years and 1

for ages 65–74 years. In Asia, the age threshold may even be lower, with ischemic stroke rates approximately 1.5%/year in patients 50–64 years [47] leading to a suggestion of a modified CHA_2DS_2VASc score for Asians, with 1 point given for age 50–74 years.

Physicians are often reluctant to use OAC in elderly patients due to the potential life-threatening complications associated with its use. Studies have shown that the benefits of OAC also increases with advancing age as stroke is known to increase with age. A large cohort study in Asia demonstrated that among patients >90 years, warfarin use was associated with a lower risk of ischemic stroke (HR, 0.69 [0.49–0.96]) and a positive net clinical benefit [47]. NOACs were associated with lower risk of ICH (HR, 0.32 [0.10–0.97]) without difference in ischemic stroke risk compared to warfarin.

Although age is a component of several bleeding risk scores, it should not be used solely to negate the use of OACs in elderly patients [45]. Anticoagulation in elderly often requires benefit-risk conversation with patients and relatives. It is also important not to over-emphasize the bleeding risk associated with elderly falls as studies have shown that the absolute risk of bleed in those on anticoagulants is small [48].

6. Diabetes mellitus

Diabetes mellitus (DM) is known to increase both the risk of AF and development of stroke in AF [49–51]. Arrhythmogenicity may be associated with the accelerated atherosclerosis in diabetes with structural, electrical and autonomic remodelling [52]. DM independently increases the risk of stroke in patients with AF by 1.7 fold with other studies noting an absolute stroke rate of 2.0–3.5% per year in the absence of other risk factors in non-anticoagulated AF patient [46].

Among participants of the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) study, duration of diabetes (>3 years) was strongly associated with increased risk of stroke compared to having diabetes for less than 3 years (HR: 1.74, 95% CI 1.10–2.76). They also found that neither poor glycemic control (HA1c > 9.0%, HR 1.04, 95% CI: 0.57–1.92) nor moderately increased HA1c (7.0–8.9%, adjusted HR: 1.21, 95% CI: 0.77–1.91) were significantly associated with an increased rate of ischemic stroke compared with patients who had HA1c <7.0%. Therefore, duration of diabetes is a more important predictor of ischemic stroke than glycemic control in diabetic patients with AF [53].

A study by Fangel et al using data from Danish nationwide registry also found that among patients <65 years, there was higher risk of thromboembolism among those with type 2 diabetes compared to those with type 1 diabetes. However, overall no independent association was found between type of diabetes (type 1 versus type 2) and the risk of

thromboembolism in non-anticoagulated patients with AF [54].

7. Stroke/transient ischemic attack

Previous stroke or transient ischemic attack (TIA) is perhaps the strongest independent risk factor for stroke in patients with AF. Studies have shown that this risk is increased by 2.5-fold following a previous stroke of TIA [55]. Interestingly, a significant association was found between prior intracranial hemorrhage (ICH) and ischemic stroke in patients with AF in a study by Friberg et al. whereby AF patients with prior ICH are at increased risk of having an ischemic stroke [56].

8. Vascular disease

This component is unique to the CHA_2DS_2-VASc scoring system and not present in other stroke risk scores. This refers to atherosclerotic vascular diseases such as prior myocardial infarction, complex aortic plaques (>4mm thick or presence of mobile debris [57]) and peripheral arterial disease [58]. Peripheral arterial disease (PAD) is also observed to increase the risk of incident AF in elderly patients with risk increasing with progressively lower ankle-brachial pressure index (ABPI).

Recent evidence showed that vascular diseases including acute coronary syndrome (ACS) and peripheral artery disease (PAD) are a predictor of AF related stroke and thromboembolism and improves the predictive ability of $CHADS_2$ score [59]. Studies showed that peripheral artery disease alone increases the risk of stroke with poor outcome in patients with AF whereas an uncomplicated ACS is less a risk factor than myocardial infarction and angina pectoris [60]. In patients with atrial fibrillation and vascular disease with no additional non-sex risk factors, the risk of ischemic stroke was increased by 1.68 in males and 2.15 in females [61].

In a large cohort study using the Danish National Patient Registry, coronary artery disease (defined as obstructive (≥50%) coronary stenosis in ≥1 coronary vessel or non-obstructive coronary stenosis in ≥2 coronary vessels) conferred a 29% increased risk of ischemic stroke, TIA or thromboembolism among patients with AF suggesting that coronary artery disease (CAD) was an independent risk factor for ischemic stroke hence the recommendation to include this component in stroke risk scores among AF patients [62].

9. Sex category

Even in the absence of atrial fibrillation, women have higher lifetime risk of stroke than men. The CHA_2DS_2-VASc scoring system introduced sex as a factor for stroke in AF. Various studies showed that female sex is a strong independent risk factor [63–65]. This may be related to post-menopausal vascular changes related to the reduction in estrogen. This affects lipid metabolism, increases the risk of left ventricular remodelling and hypertension, and leads to increase in inflammatory and procoagulant markers all contributing to thromboembolism [64]. In a large cohort study using data from Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, hormone replacement therapy (HRT) did not independently predict mortality, thromboembolism or bleeding among women with atrial fibrillation [66].

A score of 1 point is attributed to the female gender in the CHA_2DS_2-VASc score. In a cohort study using the Danish national register involving 87,202 patients with atrial fibrillation, the risk of stroke and thromboembolism in females less than 74 years was not increased compared to men; however, females aged ≥ 75 years had increased stroke rates compared to males in the same group with HR 1.20 (95% CI 1.12–1.28) recommending that female sex should not be an independent score in the absence of other risk factors [63].

In a meta-analysis of 17 studies comparing males and females with atrial fibrillation for the outcome of stroke and thromboembolism, 10 demonstrated increased risk of stroke in women revealing 1.31 fold (95% CI 1.18–1.46) elevated risk of stroke in women with atrial fibrillation, more so in women aged 75 years or more [67]. The annual stroke rate for males with only one risk factor and a CHA_2DS_2-VASc score of 1 is similar to that of females with 1 additional risk factor and CHA_2DS_2-VASc a score of 2 (1.96–3.50% versus 1.91–3.34%).

Thus, the female gender should be considered a *risk modifier* rather than a risk factor on its own in the absence of other risk indices in patients with AF and the decision to start OAC should be guided by the CHA_2DS_2-VASc score without the sex category component because the sex category risk component accentuates the stroke risk in women already eligible for OAC based on the presence of 2 or more risk factors [61,68].

10. Non CHA_2DS_2-VASc risk factors

Apart from the well-established CHA_2DS_2-VASc risk factors, other factors may independently contribute to increased stroke risk in AF patients, one of such is obstructive sleep apnea (OSA). Several studies noted an association between OSA and increased risk of ischemic stroke [69,70]. It remains unclear whether OSA should be factored independently into the risk stratification as patients with OSA may have co-existing CHA_2DS_2-VASc factors. Kabra et al proposed a modification of the

CHA$_2$DS$_2$-VASc score to the CHA$_2$DS$_2$-VASc-R score based on the findings of increased risk of stroke in African-American patients with AF [71]. However, the conclusion that race presented an additional risk in patients with AF was met with scepticism [72,73]. Studies have linked inflammation to the risk of AF and AF related thromboembolism. Higher levels of pro-Inflammatory cytokines have been documented in patients with AF, although it remains unclear whether the raised levels are directly due to AF or an underlying cardiovascular disease [74]. Irrespective of this fact, inflammation confers a prothrombotic state and increases stroke risk in AF patients [74]. The role of inflammatory makers in AF management and risk stratification is still undetermined.

11. Conclusion

Atrial fibrillation is a major risk factor for stroke and the incidence of stroke remains high in patients with AF with or without valvular heart disease. As the prevalence of AF approaches epidemic proportions, stroke prevention remains one of the cornerstones of management. To minimize the risk of stroke, careful evaluation of stroke and bleeding risk must be undertaken with prompt initiation of thromboprophylaxis where necessary. The development of various scoring systems over the years has simplified the evaluation, with the CHA$_2$DS$_2$VASc scoring system being the most widely used. Use of the CHA$_2$DS$_2$VASc scoring system reliably excludes patients at low risk for thromboembolism. Current guidelines recommend prompt initiation of thromboprophylaxis, preferably NOACs for AF patients with one or more non-sex CHA$_2$DS$_2$VASc risk factor (≥1 in males, ≥2 in females).

Acknowledgments

Disclosure statement

References

[1] January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American college of cardiology/American heart association task force on practice guidelines and the heart rhythm society. Circulation. 2014;130(23):2071–2104.

[2] Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 study. Circulation. 2014;129(8):837–847.

[3] Friberg L, Hammar N, Ringh M, et al. Stroke prophylaxis in atrial fibrillation: who gets it and who does not?Report from the stockholm cohort-study on atrial fibrillation (SCAF-study). Eur Heart J. 2006;27 (16):1954–1964.

[4] Lip GYH. The ABC pathway: an integrated approach to improve AF management. Nat Rev Cardiol. 2017;14 (11):627–628.

[5] Proietti M, Romiti GF, Olshansky B, et al. Improved outcomes by integrated care of anticoagulated patients with atrial fibrillation using the simple ABC (atrial fibrillation better care) pathway. Am J Med. 2018;131(11):1359–1366.

[6] Pastori D, Farcomeni A, Pignatelli P, et al. ABC (atrial fibrillation better care) pathway and healthcare costs in atrial fibrillationRStudy. Am J Med. 2019 Jan. DOI:10.1016/j.amjmed.2019.01.003

[7] Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. Stroke. 1991;22(8):983–988.

[8] Wolf PA, Dawber TR, Thomas HE, et al. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. Neurology. 1978;28 (10):973–977.

[9] Freedman B, Potpara TS, Lip GYH. Stroke prevention in atrial fibrillation. Lancet. 2016;388(10046):806–817.

[10] Fadhlullah AA, Abdalgbar AA, Altalhi HK. Non rheumatic atrial fibrillation as risk of stroke. Am J Internal Med. 2016;4(6):117.

[11] Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators, Singer DE, Hughes RA, et al. The effect of low-dose Warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. N Engl J Med. 1990;323(22):1505–1511.

[12] Olesen JB, Lip GYH, 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.

[13] Schnabel RB, Sullivan LM, Levy D, et al. Development of a risk score for atrial fibrillation (Framingham heart study): a community-based cohort study. Lancet. 2009;373(9665):739–745.

[14] Fang MC, Go AS, Chang Y, et al. Comparison of risk stratification schemes to predict thromboembolism in people with nonvalvular atrial fibrillation. J Am Coll Cardiol. 2008;51(8):810–815.

[15] A Laupacis, S Connolly, Gudrun Boysen, et al. 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(13):1449–1457.

[16] The Atrial Fibrillation Investigators. The efficacy of aspirin in patients with atrial fibrillation. Analysis of pooled data from 3 randomized trials. Arch Intern Med. 1997;157(11):1237–1240.

[17] Stroke Prevention in Atrial Fibrillation Investigation. Risk factors for thromboembolism during aspirin therapy in patients with atrial fibrillation: the stroke prevention in atrial fibrillation study. J Stroke Cerebrovascular Dis. 1995;5(3):147–157.

[18] Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the national registry of atrial fibrillation. JAMA. 2001;285(22):2864–2870.

[19] Lip GYH, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010;137(2):263–272.

[20] Piccini JP, Stevens SR, Chang Y, et al.. Renal dysfunction as a predictor of stroke and systemic embolism in patients

with nonvalvular atrial fibrillation: validation of the R(2) CHADS(2) index in the ROCKET AF (rivaroxaban once-daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation) and ATRIA (anticoagulation and risk factors in atrial fibrillation) study cohorts. Circulation. 2013;127(2):224–232.

[21] Banerjee A, Fauchier L, Vourc'h P, et al. Renal impairment and ischemic stroke risk assessment in patients with atrial fibrillation: the loire valley atrial fibrillation project. J Am Coll Cardiol. 2013;61(20):2079–2087.

[22] Singer DE, Chang Y, Borowsky LH, et al. A new risk scheme to predict ischemic stroke and other thromboembolism in atrial fibrillation: the ATRIA study stroke risk score. J Am Heart Assoc. 2013;2(3). DOI:10.1161/JAHA.113.000250

[23] van den Ham HA, Klungel OH, Singer DE, et al. Comparative performance of ATRIA, CHADS2, and CHA2DS2-VASc risk scores predicting stroke in patients with atrial fibrillation: results from a national primary care database. J Am Coll Cardiol. 2015;66(17):1851–1859.

[24] Lip GYH, Nielsen PB, Skjøth F, et al. The value of the European society of cardiology guidelines for refining stroke risk stratification in patients with atrial fibrillation categorized as low risk using the anticoagulation and risk factors in atrial fibrillation stroke score: a nationwide cohort study. Chest. 2014;146(5):1337–1346.

[25] Abumuaileq RR-Y, Abu-Assi E, López-López A, et al. Comparison between CHA2DS2-VASc and the new R2CHADS2 and ATRIA scores at predicting thromboembolic event in non-anticoagulated and anticoagulated patients with non-valvular atrial fibrillation. BMC Cardiovasc Disord. 2015;15. DOI:10.1186/s12872-015-0149-3

[26] Macle L, Cairns JA, Andrade JG, et al. The 2014 atrial fibrillation guidelines companion: a practical approach to the use of the Canadian cardiovascular society guidelines. Can J Cardiol. 2015;31(10):1207–1218.

[27] Hippisley-Cox J, Coupland C, Brindle P. Derivation and validation of QStroke score for predicting risk of ischaemic stroke in primary care and comparison with other risk scores: a prospective open cohort study. BMJ. 2013;346:f2573.

[28] Kakkar AK, Mueller I, Bassand J-P, et al. International longitudinal registry of patients with atrial fibrillation at risk of stroke: global anticoagulant registry in the FIELD (GARFIELD). Am Heart J. 2012;163(1):13–19.e1.

[29] Fox KAA, Lucas JE, Pieper KS, et al. Improved risk stratification of patients with atrial fibrillation: an integrated GARFIELD-AF tool for the prediction of mortality, stroke and bleed in patients with and without anticoagulation. BMJ Open. 2017;7(12):e017157.

[30] NHFA CSANZ Atrial Fibrillation Guideline Working Group, Brieger D, Amerena J, et al. National heart foundation of Australia and the cardiac society of Australia and New Zealand: Australian clinical guidelines for the diagnosis and management of atrial fibrillation 2018. Heart Lung Circ. 2018;27(10):1209–1266.

[31] Lip GYH, Banerjee A, Boriani G, et al. Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report. Chest. Aug 2018. DOI:10.1016/j.chest.2018.07.040

[32] Lip GYH, Collet JP, de Caterina R, et al. Antithrombotic therapy in atrial fibrillation associated with valvular heart disease: executive summary of a joint consensus document from the European Heart Rhythm Association (EHRA) and European society of cardiology working group on thrombosis, endorsed by the ESC working group on valvular heart disease, cardiac arrhythmia society of Southern Africa (CASSA), heart rhythm society (HRS), Asia Pacific heart rhythm society (APHRS), South African heart (SA Heart) association and sociedad latinoamericana de estimulación cardíaca y electrofisiología (SOLEACE). Thromb Haemost. 2017;117(12):2215–2236.

[33] Eikelboom JW, Connolly SJ, Brueckmann M, et al. Dabigatran versus Warfarin in patients with mechanical heart valves. N Engl J Med. 2013;369(13):1206–1214.

[34] Durães AR, de Souza Roriz P, de Almeida Nunes B, et al. Dabigatran versus Warfarin after bioprosthesis valve replacement for the management of atrial fibrillation postoperatively: DAWA pilot study. Drugs R D. 2016;16(2):149–154.

[35] Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. N Engl J Med. 2011;365(10):883–891.

[36] Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus Warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361(12):1139–1151.

[37] Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981–992.

[38] Lubitz SA, Benjamin EJ, Ellinor PT. Atrial fibrillation in congestive heart failure. Heart Fail Clin. 2010;6(2):187–200.

[39] Banerjee A, Taillandier S, Olesen JB, et al. Ejection fraction and outcomes in patients with atrial fibrillation and heart failure: the loire valley atrial fibrillation project. Eur J Heart Fail. 2012;14(3):295–301.

[40] Sandhu RK, Hohnloser SH, Pfeffer MA, et al. Relationship between degree of left ventricular dysfunction, symptom status, and risk of embolic events in patients with atrial fibrillation and heart failure. Stroke. 2015;46(3):667–672.

[41] Mitrousi K, Lip GYH, Apostolakis S. Age as a risk factor for stroke in atrial fibrillation patients: implications in thromboprophylaxis in the era of novel oral anticoagulants. J Atr Fibrillation. 2013;6(1). DOI:10.4022/jafib.783

[42] SPORTIF Invetigators, Lip GYH, Frison L, Grind M. Effect of hypertension on anticoagulated patients with atrial fibrillation. Eur Heart J. 2007;28(6):752–759.

[43] Stöllberger C, Chnupa P, Abzieher C, et al. Mortality and rate of stroke or embolism in atrial fibrillation during long-term follow-up in the embolism in left atrial thrombi (ELAT) study. Clin Cardiol. 2004;27(1):40–46.

[44] van Walraven C, Hart RG, Connolly S, et al. Effect of age on stroke prevention therapy in patients with atrial fibrillation: the atrial fibrillation investigators. Stroke. 2009;40(4):1410–1416.

[45] Marinigh R, Lip GYH, Fiotti N, et al. Age as a risk factor for stroke in atrial fibrillation patients: implications for thromboprophylaxis. J Am Coll Cardiol. 2010;56(11):827–837.

[46] Fohtung RB. Identification of patients at risk of stroke from atrial fibrillation. US Cardiol Rev. 2016;102:1. Washington University School of MediRgton University School of Medicine, St Louis, MO.

[47] Chao T-F, Liu C-J, Lin Y-J, et al. Oral anticoagulation in very elderly patients with atrial fibrillation: a nationwide cohort study. Circulation. 2018;138(1):37–47.

[48] Hagerty T, Rich MW. Fall risk and anticoagulation for atrial fibrillation in the elderly: A delicate balance. Cleve Clin J Med. 2017;84(1):35–40.

[49] Movahed M-R, Hashemzadeh M, Jamal MM. Diabetes mellitus is a strong, independent risk for atrial fibrillation and flutter in addition to other cardiovascular disease. Int J Cardiol. 2005;105(3):315–318.

[50] Krahn AD, Manfreda J, Tate RB, et al. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the manitoba follow-up study. Am J Med. 1995;98(5):476–484.

[51] Dublin S, Glazer NL, Smith NL, et al. Diabetes mellitus, glycemic control, and risk of atrial fibrillation. J Gen Intern Med. 2010;25(8):853–858.

[52] Tadic M, Cuspidi C. Type 2 diabetes mellitus and atrial fibrillation: from mechanisms to clinical practice. Arch Cardiovasc Dis. 2015;108(4):269–276.

[53] Ashburner JM, Go AS, Chang Y, et al. Impact of diabetes and glycemic control on ischemic stroke risk in AF patients: ATRIA study. J Am Coll Cardiol. 2016;67(3):239–247.

[54] Fangel MV, Nielsen PB, Larsen TB, et al. Type 1 versus type 2 diabetes and thromboembolic risk in patients with atrial fibrillation: a Danish nationwide cohort study. Int J Cardiol. 2018;268:137–142.

[55] Stroke Risk in Atrial Fibrillation Working Group. Independent predictors of stroke in patients with atrial fibrillation: a systematic review. Neurology. 2007;69(6): 546–554.

[56] Friberg L, Rosenqvist M, Lip GYH. 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):1500–1510.

[57] Meissner I, Khandheria BK, Sheps SG, et al. Atherosclerosis of the aorta: risk factor, risk marker, or innocent bystander? A prospective population-based transesophageal echocardiography study. J Am Coll Cardiol. 2004;44(5):1018–1024.

[58] Anandasundaram B, Lane DA, Apostolakis S, et al. The impact of atherosclerotic vascular disease in predicting a stroke, thromboembolism and mortality in atrial fibrillation patients: a systematic review. J Thromb Haemost. 2013;11(5):975–987.

[59] Olesen JB, Lip GYH, Lane DA, et al. Vascular disease and stroke risk in atrial fibrillation: a nationwide cohort study. Am J Med. 2012;125(8):826.e13-23.

[60] Atrial fibrillation and vascular disease—a bad combination - bjerring olesen - 2012 - clinical cardiology - Wiley online library. https://onlinelibrary.wiley.com/doi/abs/10.1002/clc.20955. Accessed Aug 31, 2018.

[61] Chao T-F, Liu C-J, Wang K-L, et al. Should atrial fibrillation patients with 1 additional risk factor of the CHA2DS2-VASc score (beyond sex) receive oral anticoagulation? J Am Coll Cardiol. 2015;65(7):635–642.

[62] Steensig K, Olesen KKW, Thim T, et al. Coronary artery disease is independent risk factor for stroke among patients with atrial fibrillation. J Am Coll Cardiol. 2018 Aug. DOI:10.1016/j.jacc.2018.08.1046

[63] Mikkelsen AP, Lindhardsen J, Lip GYH, et al. Female sex as a risk factor for stroke in atrial fibrillation: a nationwide cohort study. J Thromb Haemost. 2012;10(9):1745–1751.

[64] Cove CL, Albert CM, Andreotti F, et al. Female sex as an independent risk factor for stroke in atrial fibrillation: possible mechanisms. Thromb Haemost. 2014;111(3):385–391.

[65] Christiansen CB, Gerds TA, Olesen JB, et al. Atrial fibrillation and risk of stroke: a nationwide cohort study. Europace. 2016;18(11):1689–1697.

[66] Apostolakis S, Sullivan RM, Olshansky B, et al. Hormone replacement therapy and adverse outcomes in women with atrial fibrillation: an analysis from the atrial fibrillation follow-up investigation of rhythm management trial. Stroke. 2014;45(10):3076–3079.

[67] Wagstaff AJ, Overvad TF, Lip GYH, et al. Is female sex a risk factor for stroke and thromboembolism in patients with atrial fibrillation? A systematic review and meta-analysis. QJM. 2014;107(12):955–967.

[68] Nielsen PB, Skjøth F, Overvad TF, et al. Female sex is a risk modifier rather than a risk factor for stroke in atrial fibrillation: should we use a CHA2DS2-VA score rather than CHA2DS2-VASc? Circulation. 2018;137 (8):832–840.

[69] Yaranov DM, Smyrlis A, Usatii N, et al. Effect of obstructive sleep apnea on frequency of stroke in patients with atrial fibrillation. Am J Cardiol. 2015;115(4):461–465.

[70] Chang -C-C, Chiu -C-C, Chiang C-H, et al. Obstructive sleep apnea and the risk of ischemic stroke in patients with atrial fibrillation. Int J Cardiol. 2015;181:144–146.

[71] Kabra R, Girotra S, Sarrazin MV. Refining stroke prediction in atrial fibrillation patients by addition of African-American ethnicity to CHA2DS2-VASc score. J Am Coll Cardiol. 2016;68(5):461–470.

[72] Johnson AE, Magnani JW. Race and stroke risk in atrial fibrillation. J Am Coll Cardiol. 2017;69 (7):906–907.

[73] Nishimura M, Hsu JC. A cautionary tone before expanded adoption of the proposed CHA2DS2-VASc R score. J Am Coll Cardiol. 2017;69(2):251.

[74] Guo Y, Lip GYH, Apostolakis S. Inflammation in atrial fibrillation. J Am Coll Cardiol. 2012;60(22):2263–2270.