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How do aging and comorbidities impact risk of ischemic stroke in patients with atrial fibrillation☆

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ABSTRACT

Stroke is a notorious complication in patients with atrial fibrillation (AF) and risk stratification is pivotal for stroke prevention strategy. The risk of AF-related stroke is a mixture of complex interaction between increasing age and important comorbidities. Therefore, this article aims to provide a comprehensive review on these important risk factors of stroke in AF patients, mainly focusing on the component of CHA_2DS_2-VASc score, as well as some other potential risk factors.

Background

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia with a significant and progressive increase of global burden [1]. The prevalence of AF is estimated to be 4% in 2050 and the lifetime risk of AF is appropriately 1 in 7 for subjects aged >20 years [2]. It is associated with a 2.6-fold risk of mortality, 3.3-fold risk of heart failure, 3.3-fold risk of ischemic stroke, and 1.6-fold risk of myocardial infarction [2]. Among these dreaded comorbidities, AF-related stroke is probably the most notorious one being associated with higher mortality rate, more disability, longer hospitalization days and worse function recovery as compared to non-AF-related stroke [3]. Therefore, management of AF, especially stroke prevention, has become an important issue in modern healthcare system.

Oral anticoagulant (OAC) with vitamin K antagonist (VKA) reduces the risk of ischemic stroke by 64% and all-cause mortality by 26% compared to control or placebo [4]. Recently, non-vitamin K antagonist oral anticoagulants (NOAC) have been proven to be non-inferior, or even superior in some population, to VKA for stroke prevention with significantly lower risk of bleeding. The use of anticoagulant, either VKA or NOAC, had become the cornerstone of stroke prevention in high risk AF patients [5]. Therefore, risk factor identification and stratification become more important than ever. For 2 decades, risk factors of AF-related stroke were identified from studies with different populations and designs, and variable risk stratification schemes have been formulated after weighing the predictive power of each factor, such as the $CHADS_2$, CHA_2DS_2-VASc and ATRIA scores [6–11]. (Table 1) The use of risk stratification schemes enables classifying patients into low, moderate and high-risk categories and guiding stroke prevention. Currently there is a paradigm shift toward identifying truly low-risk patients who do not need anticoagulant therapy, rather than focusing on high-risk patients, and many studies have been conducted to compare the predictive power of different risk stratification models. The $CHADS_2$ score is composed of congestive heart failure (CHF), hypertension, age ≥75 years, diabetes mellitus (DM), (1 point for each), and stroke (2 points). The CHA_2DS_2-VASc score further refined the $CHADS_2$ score by incorporates age 65–74 years, vascular disease and female sex. Olesen et al. used a nationwide cohort to compare the predictive power in the same population and found that the CHA_2DS_2-VASc score had the highest c-statistic value and could identify the truly low-risk patients. The finding that the CHA_2DS_2-VASc score outshines $CHADS_2$ score in predicting AF-related stroke was consistent in Asian regions [12]. Chao et al. performed a nationwide study enrolling 186,570 Asian AF patients without antithrombotic therapies, showing that the CHA_2DS_2-VASc score had better predictive power than the $CHADS_2$ score. Moreover, the CHA_2DS_2-VASc score is also superior to the ATRIA score in identifying patients with a truly low risk [13]. Therefore, the CHA_2DS_2-VASc score is now the recommended risk stratification model by the European, the United States of America, and the Asia Pacific region guidelines [5,14,15].

This review article aims to provide a comprehensive overview on important risk factors of stroke in AF patients, mainly focusing on the component of CHA_2DS_2-VASc score. ECG-documented AF is the entry criterion in this review and the issue of device-detected AF is not discussed in this review article. Some other potential risk factors will also be discussed.

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Table 1
Components of risk factors in each scoring model.

Scoring model	Age	Female sex	HTN	DM	Vascular diseases	CHF	Stroke/TIA	Others	Score range
SPAF, 1999 [6] (10,356,104)	>75	√	√	√			√		3 categories
$CHADS_2$, 2001 [7] (11,401,607)	2 points for age ≥75		√	√		√	√		0–6
Framingham, 2003 [8] (12,941,677)	Detailed scales for different age	√	√	√					0–31
CHA_2DS_2-VASc, 2010 [9], (19,762,550)	2 points for age ≥75; 1 point for age 65–74	√	√	√	√	√	√		0–9
R_2CHADS_2, 2012 [10] (23,212,720)	2 points for age ≥75		√	√		√	√	Renal dysfunction	0–8
ATRIA, 2013 [11] (23,782,923)	Extended range for score assignment (<65, 65–74, 75–84, ≥ 85)*	√	√	√	√	√	√	Proteinuria and eGFR	0–12 (without prior stroke); 7–15 (with prior stroke)

* Different roles of score calculation for patients with or without prior stroke. CHF = congestive heart failure, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HTN = hypertension; TIA = transient ischemic stroke.

Increasing age

While increasing age has been universally recognized as an important risk factor of ischemic stroke in AF patients, different cut-off values were observed across different studies since age is a continuum. Some studies recommended a clear-cut value of 65 or 75 years, while others used incremental risk evaluation per 5 years [16]. Overall, increasing age is associated with a 1.4- to 3.3-fold risk of stroke. Besides, a nationwide cohort study by Chao et al. found that the annual risk of stroke for AF patients 50–64 years with a CHA_2DS_2-VASc score of 0 (male) or 1 (female) was 1.5%, implying that a cut-off value of 50 years can further identify lower risk group among Asian AF patients [17]. (Table 2)

Diabetes mellitus

The presence of DM was also associated with worse AF symptoms and lower quality of life, increased hospitalization and death in AF patients [18], and it increased with risk of stroke by 1.3- to 1.9-fold with a stroke rate around 4.3% [9]. In a prospective multicenter registry (PREFER), insulin-requiring diabetes contributed most to the overall increase of thromboembolism risk [19]. In the ATRIA study, duration of diabetes rather than glycemic control could better predict ischemic stroke [20]. (Table 2) Nevertheless, the severity of diabetes being possibly associated with a worse risk of thromboembolic events in AF remains a debated issue [21].

Hypertension

Hypertension has been recognized to be a significant risk factor of AF-related ischemic stroke, but there are slight variations in the definition across different studies. Some proposed a cut-off value of systolic blood pressure more than 160 mmHg, while a broader spectrum including use of antihypertensive agents or a history of hypertension was used in most recent studies. One earlier study observed a 2.8-fold risk of stroke in chronic AF patients with left ventricular hypertrophy, which was not applied in most risk stratification models [22]. (Table 2)

Congestive heart failure

There is a complex interaction between AF and CHF since AF may precipitate CHF and CHF is also an important risk factor of AF [23]. Many studies considered CHF an important risk factor but whether it is an independent risk factor remains disputable. In the $CHADS_2$ score, the C represents congestive heart failure, which has been modified in the CHA_2DS_2-VASc score, including moderate to severe left ventricular systolic dysfunction with an ejection fraction <40%, and recent decompensated heart failure irrespective of ejection fraction [9]. Banerjee et al. also proved that in AF patients with HF, there were no differences in risk of thromboembolic events or death between different EF categories [24]. (Table 2)

Vascular diseases

Vascular diseases include myocardial infarction, peripheral artery disease and complex aortic plaque. Myocardial infarction was an independent risk factor with a 1.42-fold risk of stroke, and ischemic heart disease, on the contrary, was not [25]. Both ST-segment elevation myocardial infarction and no-ST-elevation myocardial infarction were included in this item. Of note, some patients with coronary artery disease but not myocardial infarction may have a CHA_2DS_2-VASc score of 0. Moreover, a systemic review analyzing 10 observational studies revealed that peripheral artery disease conferred a 1.3- to 2.5-fold risk of stroke [25]. Complex aortic plaque, diagnosed by transesophageal echocardiography examination, was associated with a 4-fold risk of stroke as compared to plaque-free patients based on limited data [26]. (Table 2)

Prior stroke, transient ischemic attack or systemic thromboembolism

It is universally acknowledged that prior stroke or transient ischemic stroke (TIA) is an independent risk factor, increasing at least 2-fold risk of AF-related stroke and a stroke rate of 5.9% [9,27]. Only 1 study discussed about systemic thromboembolism being associated with increased stroke rate, 2.5% per year [28]. (Table 2)

Gender

Biological sex is thought to be a risk factor of stroke but there remains room for discussion regarding which sex weighs more in risk prediction. Male sex has been proposed to be a risk factor (odds ratio 2.0) in one small, old study incorporating 740 patients [29] , but more recent studies and meta-analysis identified female sex to be more powerful with a 1.3-fold increased risk of stroke [9,30]. Female sex was thus included in the CHA_2DS_2-VASc score. Interestingly, Nielsen et al. found that female AF patients had similar thromboembolic risk with male AF patients with no additional risk factor (i.e. a score of 0), and the thromboembolic risk ratio

Table 2
Studies about important risk factors of AF-related ischemic stroke.

Study	Definition	Patient number	Risk of stroke	Comments
Risk factor: increasing age				
Hart RG, 1999 [6] (10,356,104)	incremental risk per decade	2012	RR 1.8	
Inoue H, 2000 [27] (11,024,400)	age >65 years	740	RR 3.33	
Lip GYH, 2010 [9] (19,762,550)	age > 75 vs. ≤ 75 years	1577	OR 1.46	stroke rate 3.6%
Van Staa TP, 2011 [16] (21,029,359)	age 70–79 vs. 60–69 years age ≥ 80 vs. 60–69 years	79,844	RR 1.42 RR 2.22	
Chao TF, 2015 [17]	age 50–54 vs. age <50 years age 55–59 vs. age <50 years age 60–64 vs. age <50 years	15,806	HR 4.105 HR 4.891 HR 7.598	annual stroke rate: ≥ 50 vs. < 5 0 years: 1.78% vs. 0.53%
Risk factor: diabetes mellitus				
Hart RG, 1999 [6] (10,356,104)		2012	RR 1.9	
Lip GYH, 2010 [9] (19,762,550)		1577	OR 1.79	stroke rate 4.3%
Van Staa TP, 2011 [16] (21,029,359)		79,844	RR 1.33	
Risk factor: hypertension				
Hart RG, 1999 [6] (10,356,104)	Systolic blood pressure >160 mmHg	2012	RR 2.3	
	history of hypertension	2012	RR 2.0	
Lip GYH, 2010 [9] (19,762,550)	history of hypertension	1084	OR 1.01	stroke rate 2.6%
Risk factor: congestive heart failure				
Lip GYH, 2010 [9] (19,762,550)	left ventricular ejection fraction <40%	1577	OR 0.34 (adjusted with other risk factors)	stroke rate 0.8%
Lin LY, 2011 [23] (21,513,938)	CHF	7920	OR 1.611	
Van Staa TP, 2011 [16] (21,029,359)	CHF	79,844	RR 1.26	
Risk factor: vascular disease				
SPAF III, 1998 [24] (9,537,937)	complex aortic plaque	382	Univariate relative risk 12.3%	stroke rate 4%
Lip GYH, 2010 [9] (19,762,550)	vascular disease	1577	OR 2.27	stroke rate 3.6%
Lin LY, 2011 [23] (21,513,938)	myocardial infarction	7920	OR 1.42	
Lin LY, 2011 [23] (21,513,938)	peripheral artery disease	7920	OR 1.81	
Risk factor: prior stroke, transient ischemic attack or systemic thromboembolism				
Hart RG, 1999 [6] (10,356,104)		2012	RR 2.9	
Lip GYH, 2010 [9] (19,762,550)		1577	OR 2.22	stroke rate 5.9%
Van Staa TP, 2011 [16] (21,029,359)		79,844	RR 2.86	
Risk factor: female gender				
Hart RG, 1999 [6] (10,356,104)		2012	RR 1.6	
Inoue H, 2000 [27] (11,024,400)	male vs. female	740	OR 2.00	
Lip GYH, 2010 [9] (19,762,550)		1084	OR 2.53	stroke rate 3.6%
Van Staa TP, 2011 [16] (21,029,359)	male vs. female	79,844	RR 0.95	
Chao TF, 2012 [28] (22,871,677)	female vs. male	829	HR 7.77 vs 1.27	stroke rate 4.4% vs 1.6%

CHF = congestive heart failure; HR = hazard ratio; OR = odds ratio; RR = risk ratio

Table 3
Summary of guideline recommendation for stroke prevention.

Society	Risk model	Score	Antithrombotic strategy
ACC/AHA/HRS, 2014 [14] 24,685,669	CHA_2DS_2-VASc	0	No antithrombotic
		1	No antithrombotic or OAC or aspirin
		≥2	VKA or NOAC
NICE guideline, 2014 [37] 25,059,099	CHA_2DS_2-VASc	0	No antithrombotic
		1 (female)	No antithrombotic
		1 (male)	VKA (or NOAC if poor control)
		≥2	VKA (or NOAC if poor control)
CCS guideline, 2014 [38]	CCS algorithm (stepwise algorithm)	Age ≥ 65	NOAC (or VKA)
25,262,857		Any of the $CHADS_2$ component (except age)	NOAC (or VKA)
		CAD or arterial vascular disease (coronary, aortic, peripheral)	Aspirin
		None of the above	No antithrombotic
ESC, 2016 [5] 27,567,465	CHA_2DS_2-VASc	0	No antiplatelet or antithrombotics
		1 (female)	No antiplatelet or antithrombotics
		1 (male)	OAC should be considered
		≥2	NOAC (or VKA)
APHRS, 2017 (15] 28,765,771	CHA_2DS_2-VASc	0	No antithrombotic
		1 (female)	No antithrombotic
		1 (male)	NOACs or well controlled VKA
		≥2	NOACs or well controlled VKA

ACC = American College of Cardiology; AHA = American Heart Association; APHRS = Asia Pacific Heart Rhythm Society; CCS = Canadian Cardiovascular Society; HRS = Heart Rhythm Society; NICE = National Institute for Health and Care Excellence; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant; VKA = vitamin-K antagonist

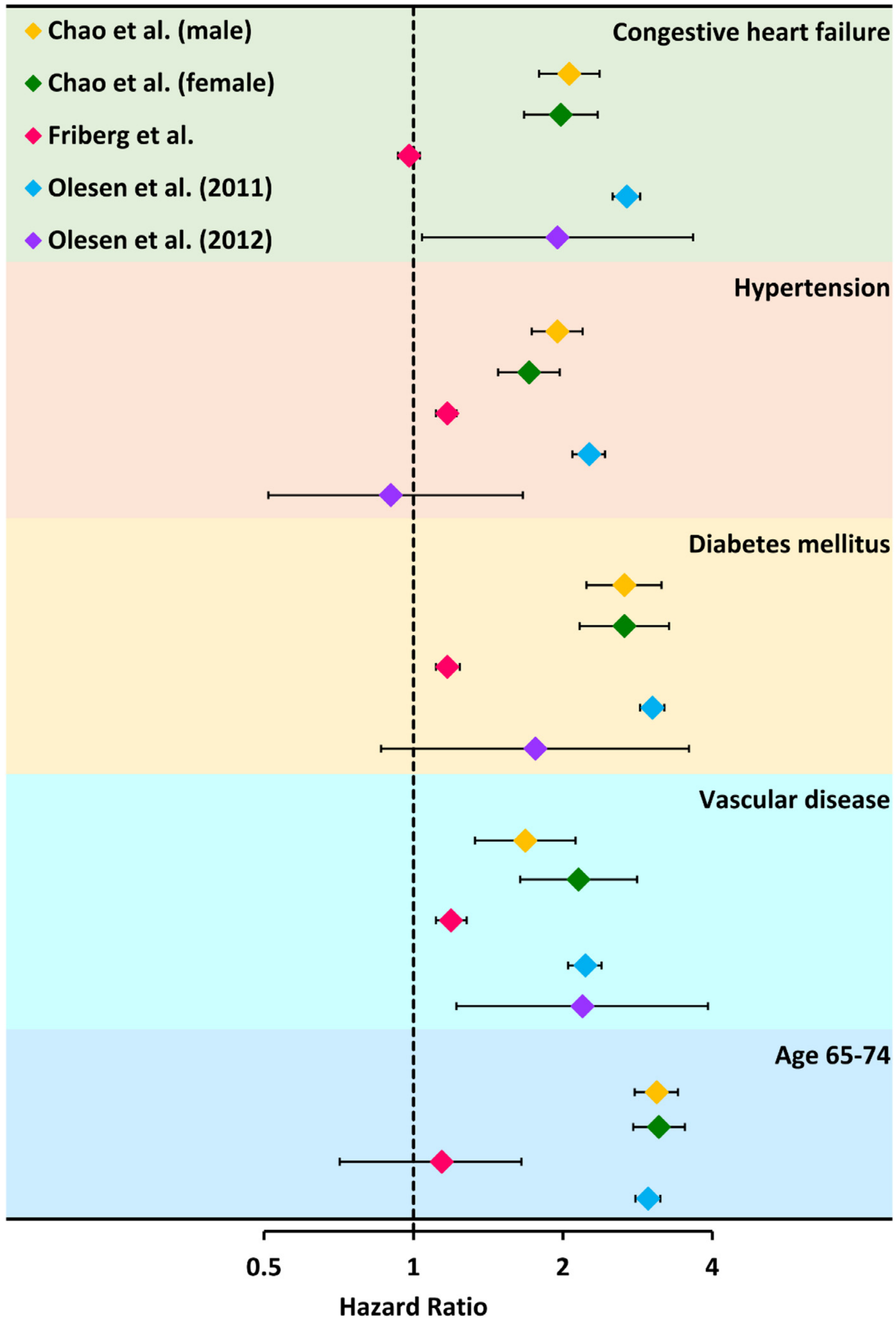

Fig. 1. Hazard ratios of each risk factor in patients with a CHA_2DS_2-VASc score 1 from different studies [47–50]. Age 65–74 years was associated with the highest risk of stroke in most studies, while variation among different studies was observed for the remaining risk factors.

was higher for female patients with a score of 1–6. These observations implied that female sex acts differently across different scores and further modified the risk of stroke. Therefore, instead of an overall risk factor, female sex is more like a risk modifier [31], which partly underlies the background that the ESC guideline on AF management recommends no anticoagulant use for female patients younger than 65 years with no other risk factors [5]. (Table 2) The reasons underlying this observation are not understood yet, but a longer life expectancy of women than men may partly explain this phenomenon [32].

Other risk factors not included in CHA_2DS_2-VASc score

About one third of AF patients had an eGFR < 60 ml/min, and the presence of renal impairment increased risk of stroke in AF patients [33,34]. On the other hand, patients with chronic kidney disease (CKD) had a 2.26-fold increased risk of incident AF, which also increased significantly with increasing severity of CKD [35]. Nonetheless, controversies remain regarding whether chronic kidney disease is an independent risk factor of AF-related stroke. A nationwide database analysis revealed no significant association of chronic renal insufficiency with increased risk of stroke [25]. Also adding CKD to the $CHADS_2$ and CHA_2DS_2-VASc score failed to improve the prediction power [36]. Therefore, it is essential to evaluate renal function for AF patients since it confers a worse overall prognosis, but more studies are warranted for further exploration on this issue.

Hyperuricemia has been recognized as a risk factor of ischemic stroke, but information about its association with AF-related stroke remains limited [37]. Chao et al. found hyperuricemia significantly predicted stroke with a hazard ratio of 1.28 even after adjustment for CHA_2DS_2-VASc score and other comorbidities. Moreover, the presence of hyperuricemia can identify a higher risk group among AF patients with a CHA_2DS_2-VASc score of 0, with the stroke rate of 7.1% ($p = 0.020$) [38]. The detailed mechanism about its interaction with ischemic stroke in AF patients remains unclear, but probably involves increased systemic inflammation, insulin resistance and a large left atrial size [39]. A randomized clinical trial is needed for the role of hyperuricemia on risk stratification.

Aside from clinical factors in estimating risk of embolic stroke in patients with AF, cardiac imaging has been used for risk stratification of embolic stroke in AF patients. Most were derived from echocardiography, while more recent studies also used cardiac magnetic resonance imaging [40]. The identified parameters included LA size, LA volume, LA function derived from tissue Doppler imaging or speckle tracking analysis, and LA appendage flow velocity [41,42]. Generally speaking, a larger LA volume and worse LA function were associated with higher risk of embolic stroke, but how to incorporate clinical covariates with imaging parameters in risk prediction warrants more studies.

Should AF patients with one single risk factor receive anticoagulant?

Although the CHA_2DS_2-VASc score was accepted for risk stratification in the American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS), European Society of Cardiology (ESC) and Asia Pacific Heart Rhythm Society (APHRS) guidelines, there are differences regarding the strategy of stroke prevention in patients with one single risk factor (beyond sex), possibly due to the lack of randomized controlled trials on this issue. Most evidence about anticoagulant in AF patients with one single risk factor other than sex comes from observational studies [43,44]. The ESC and APHRS guideline suggested anticoagulant therapy for AF patients with at least one risk factor other than sex (class IIaB recommendation, level of evidence B in ESC guideline), but no anticoagulant for AF females without other risk factors [5,15]. The 2014 ACC/AHA/HRS guideline, however, leaves more room in this issue, suggesting no antithrombotic therapy or treatment with an oral anticoagulant or considering aspirin for patients with a CHA_2DS_2-VASc score of 1 (class IIb recommendation, level of evidence C) [14]. The detailed recommendations of different guidelines are listed in Table 3 [5,14,15,45,46]. Another issue comes across with this variation of guideline recommendations, that is, are all risk factors equal in risk prediction? Risk stratification schemes were created under the assumption that most risk factors confer equal risk, but study results are opposite. Several studies compared the risk of ischemic stroke in patients with one single risk factor other than sex (i.e., a $CHA_2DS_2\text{-VASc} = 1$ in males or 2 in females) and different weight for each factor was observed. Overall, most studies agreed that age 65–74 years was associated with the highest risk of stroke, followed by the presence of DM [47]. The figure illustrated hazard ratios for each risk factor in different studies [47–50]. (Fig. 1)

Conclusion

There is an increasing body of evidence on predictor identification and risk stratification as the risk of AF-related stroke has been well recognized. A judicious assessment of individual risk profile can aid efficient stroke prevention while avoiding adverse events. It is also important to recognize that the risk of AF patients is not static and the CHA_2DS_2-VASc score of patients should be reassessed regularly [51]. Although many comorbidities have been found to be important risk factors, including age, gender, CHF, HTN, DM and prior stroke/TIA, uncertainty persists for other risk factors. The overall risk of stroke is the result of complicated interaction with multiple comorbidities and more studies are warranted for better understanding.

References

[1] Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, et al. Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 study. Circulation 2014;129(8):837–47.
[2] Chao TF, Liu CJ, Tuan TC, Chen TJ, Hsieh MH, Lip GYH, et al. Lifetime risks, projected numbers, and adverse outcomes in asian patients with atrial fibrillation: a report from the taiwan nationwide AF cohort study. Chest 2018;153(2):453–66.
[3] Lip GY. Stroke and bleeding risk assessment in atrial fibrillation: when, how, and why? Eur Heart J. 2013;34(14):1041–9.
[4] Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 2007;146(12):857–67.
[5] Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Europace 2016;18(11):1609–78.
[6] Hart RG, Pearce LA, McBride R, Rothbart RM, Asinger RW. Factors associated with ischemic stroke during aspirin therapy in atrial fibrillation: analysis of 2012 participants in the SPAF I-III clinical trials. The Stroke Prevention in Atrial Fibrillation (SPAF) Investigators. Stroke 1999;30(6):1223–9.
[7] 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):2864–70.
[8] Wang TJ, Massaro JM, Levy D, Vasan RS, Wolf PA, D'Agostino RB, et al. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. JAMA 2003;290(8):1049–56.
[9] Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. 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):263–72.
[10] Piccini JP, Stevens SR, Chang Y, Singer DE, Lokhnygina Y, Go AS, 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):224–32.
[11] Singer DE, Chang Y, Borowsky LH, Fang MC, Pomernacki NK, Udaltsova N, 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):e000250.
[12] Chao TF, Liu CJ, Tuan TC, Chen SJ, Wang KL, Lin YJ, et al. Comparisons of CHADS2 and CHA2DS2-VASc scores for stroke risk stratification in atrial fibrillation: which scoring system should be used for Asians? Heart Rhythm 2016;13(1):46–53.
[13] Chao TF, Liu CJ, Wang KL, Lin YJ, Chang SL, Lo LW, et al. Using the CHA2DS2-VASc score for refining stroke risk stratification in 'low-risk' Asian patients with atrial fibrillation. J Am Coll Cardiol 2014;64(16):1658–65.
[14] January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2014;64(21):e1–76.
[15] Chiang CE, Okumura K, Zhang S, Chao TF, Siu CW, Wei Lim T, et al. 2017 consensus of the Asia Pacific Heart Rhythm Society on stroke prevention in atrial fibrillation. J Arrhythm. 2017;33(4):345–67.
[16] Van Staa TP, Setakis E, Di Tanna GL, Lane DA, Lip GY. A comparison of risk stratification schemes for stroke in 79,884 atrial fibrillation patients in general practice. J Thromb Haemost. 2011;9(1):39–48.
[17] Chao TF, Wang KL, Liu CJ, Lin YJ, Chang SL, Lo LW, et al. Age Threshold for increased stroke risk among patients with atrial fibrillation: a nationwide cohort study from Taiwan. J Am Coll Cardiol. 2015;66(12):1339–47.
[18] Echouffo-Tcheugui JB, Shrader P, Thomas L, Gersh BJ, Kowey PR, Mahaffey KW, et al. Care patterns and outcomes in atrial fibrillation patients with and without diabetes: ORBIT-AF registry. J Am Coll Cardiol. 2017;70(11):1325–35.
[19] Patti G, Lucerna M, Cavallari I, Ricottini E, Renda G, Pecen L, et al. Insulin-requiring versus noninsulin-requiring diabetes and thromboembolic risk in patients with atrial fibrillation: PREFER in AF. J Am Coll Cardiol. 2017;69(4):409–19.
[20] Ashburner JM, Go AS, Chang Y, Fang MC, Fredman L, Applebaum KM, et al. Effect of diabetes and glycemic control on ischemic stroke risk in AF patients: ATRIA study. J Am Coll Cardiol 2016;67(3):239–47.
[21] Lip GYH, Clementy N, Pierre B, Boyer M, Fauchier L. The impact of associated diabetic retinopathy on stroke and severe bleeding risk in diabetic patients with atrial fibrillation: the loire valley atrial fibrillation project. Chest 2015;147(4):1103–10.
[22] Aronow WS, Ahn C, Kronzon I, Gutstein H. Risk factors for new thromboembolic stroke in patients >or = 62 years of age with chronic atrial fibrillation. Am J Cardiol. 1998;82(1):119–21.

[23] Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. Circulation 2003;107(23):2920–5.
[24] Banerjee A, Taillandier S, Olesen JB, Lane DA, Lallemand B, Lip GY, 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.
[25] Lin LY, Lee CH, Yu CC, Tsai CT, Lai LP, Hwang JJ, et al. Risk factors and incidence of ischemic stroke in Taiwanese with nonvalvular atrial fibrillation– a nation wide database analysis. Atherosclerosis 2011;217(1):292–5.
[26] Transesophageal echocardiographic correlates of thromboembolism in high--risk patients with nonvalvular atrial fibrillation The stroke prevention in atrial fibrillation investigators committee on echocardiography. Ann Intern Med 1998;128(8):639–47.
[27] Stroke Risk in Atrial Fibrillation Working G Independent predictors of stroke in patients with atrial fibrillation: a systematic review. Neurology 2007;69(6):546–54.
[28] Predictors of thromboembolism in atrial fibrillation: I. Clinical features of patients at risk The stroke prevention in atrial fibrillation investigators. Ann Intern Med 1992;116(1):1–5.
[29] Inoue H, Atarashi HResearch Group for Antiarrhythmic Drug T. Risk factors for thromboembolism in patients with paroxysmal atrial fibrillation. Am J Cardiol 2000;86(8):852–5.
[30] Chao TF, Liu CJ, Chen SJ, Wang KL, Lin YJ, Chang SL, et al. Atrial fibrillation and the risk of ischemic stroke: does it still matter in patients with a CHA2DS2-VASc score of 0 or 1? Stroke 2012;43(10):2551–5.
[31] Nielsen PB, Skjoth F, Overvad TF, Larsen TB, Lip GYH. 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):832–40.
[32] Avgil Tsadok M, Jackevicius CA, Rahme E, Humphries KH, Behlouli H, Pilote L. Sex differences in stroke risk among older patients with recently diagnosed atrial fibrillation. JAMA 2012;307(18):1952–8.
[33] Hart RG, Eikelboom JW, Brimble KS, McMurtry MS, Ingram AJ. Stroke prevention in atrial fibrillation patients with chronic kidney disease. Can J Cardiol 2013;29(7 Suppl):S71–8.
[34] Baber U, Howard VJ, Halperin JL, Soliman EZ, Zhang X, McClellan W, et al. Association of chronic kidney disease with atrial fibrillation among adults in the United States: Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. Circ Arrhythm Electrophysiol 2011;4(1):26–32.
[35] Liao JN, Chao TF, Liu CJ, Wang KL, Chen SJ, Lin YJ, et al. Incidence and risk factors for new-onset atrial fibrillation among patients with end-stage renal disease undergoing renal replacement therapy. Kidney Int 2015;87(6):1209–15.
[36] Roldan V, Marin F, Manzano-Fernandez S, Fernandez H, Gallego P, Valdes M, et al. Does chronic kidney disease improve the predictive value of the CHADS2 and CHA2DS2-VASc stroke stratification risk scores for atrial fibrillation? Thromb Haemost 2013;109(5):956–60.
[37] Bos MJ, Koudstaal PJ, Hofman A, Witteman JC, Breteler MM. Uric acid is a risk factor for myocardial infarction and stroke: the Rotterdam study. Stroke 2006;37(6):1503–7.
[38] Chao TF, Liu CJ, Chen SJ, Wang KL, Lin YJ, Chang SL, et al. Hyperuricemia and the risk of ischemic stroke in patients with atrial fibrillation–could it refine clinical risk stratification in AF? Int J Cardiol 2014;170(3):344–9.
[39] Chao TF, Hung CL, Chen SJ, Wang KL, Chen TJ, Lin YJ, et al. The association between hyperuricemia, left atrial size and new-onset atrial fibrillation. Int J Cardiol 2013;168(4):4027–32.
[40] Inoue YY, Alissa A, Khurram IM, Fukumoto K, Habibi M, Venkatesh BA, et al. Quantitative tissue-tracking cardiac magnetic resonance (CMR) of left atrial deformation and the risk of stroke in patients with atrial fibrillation. J Am Heart Assoc 2015;4(4).
[41] Providencia R, Trigo J, Paiva L, Barra S. The role of echocardiography in thromboembolic risk assessment of patients with nonvalvular atrial fibrillation. J Am Soc Echocardiogr 2013;26(8):801–12.
[42] Zuo K, Sun L, Yang X, Lyu X, Li K. Correlation between cardiac rhythm, left atrial appendage flow velocity, and CHA2 DS2 -VASc score: Study based on transesophageal echocardiography and 2-dimensional speckle tracking. Clin Cardiol 2017;40(2):120–5.
[43] Lip GY, Skjoth F, Rasmussen LH, Nielsen PB, Larsen TB. Net clinical benefit for oral anticoagulation, aspirin, or no therapy in nonvalvular atrial fibrillation patients with 1 additional risk factor of the CHA2DS2-VASc score (Beyond Sex). J Am Coll Cardiol 2015;66(4):488–90.
[44] Fauchier L, Lecoq C, Clementy N, Bernard A, Angoulvant D, Ivanes F, et al. oral anticoagulation and the risk of stroke or death in patients with atrial fibrillation and one additional stroke risk factor: the loire valley atrial fibrillation project. Chest 2016;149(4):960–8.
[45] Senoo K, Lau YC, Lip GY. Updated NICE guideline: management of atrial fibrillation (2014). Expert Rev Cardiovasc Ther 2014;12(9):1037–40.
[46] Verma A, Cairns JA, Mitchell LB, Macle L, Stiell IG, Gladstone D, et al. 2014 focused update of the Canadian Cardiovascular Society Guidelines for the management of atrial fibrillation. Can J Cardiol 2014;30(10):1114–30.
[47] Chao TF, Liu CJ, Wang KL, Lin YJ, Chang SL, Lo LW, 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):635–42.
[48] Friberg L, Rosenqvist M, Lip GY. 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):1500–10.
[49] Olesen JB, Lip GY, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ 2011;342:d124.
[50] Olesen JB, Fauchier L, Lane DA, Taillandier S, Lip GYH. Risk factors for stroke and thromboembolism in relation to age among patients with atrial fibrillation: the Loire Valley Atrial Fibrillation Project. Chest 2012;141(1):147–53.
[51] Chao TF, Lip GYH, Liu CJ, Lin YJ, Chang SL, Lo LW, et al. Relationship of aging and incident comorbidities to stroke risk in patients with atrial fibrillation. J Am Coll Cardiol 2018;71(2):122–32.