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Atrial fibrillation and stroke prevention: state of the art—epidemiology and pathophysiology: new risk factors, concepts and controversies

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Atrial fibrillation (AF) increases the risk of thromboembolism, and risk assessment for thromboembolism is necessary for the management of AF patients. CHADS2 and CHA2DS2-VASc scores have been adopted in international guidelines for AF management, but the significance of each risk factor included in these risk scores are sometimes controversial, and the performance of these scores is only modest. There are several other risk factors not included in the scores such as renal dysfunction, low body weight, type of AF (paroxysmal or non-paroxysmal) as well as echocardiographic parameters and blood biomarkers, and physicians should assess patientsã risk in an integrated manner.

Introduction

Since accumulation of risk factors for thromboembolism increases the incidence of ischaemic stroke and systemic embolism in patients with atrial fibrillation (AF),[1,2] appropriate anticoagulation therapy is required to prevent cardiogenic stroke. Accordingly, risk assessment for thromboembolism is necessary for the management of patients with AF in a clinical setting, especially before initiating anticoagulation therapy. The guidelines for the management of AF were published first in 2006 from the American College of Cardiology (ACC)/American Heart Association (AHA)/European Society of Cardiology (ESC). Subsequently, several guidelines have been published from each organization or country as illustrated in *Figure 1*.

First of all, AF patients with prosthetic mechanical heart valves or moderate–severe mitral stenosis should be distinguished, since vitamin K antagonist (VKA), mainly warfarin, is the only oral anticoagulant (OAC) approved for those AF patients. In patients without those conditions, risk scores such as $CHADS_2$ score[1] and CHA_2DS_2-VASc score[3] is helpful in standardizing the risk evaluation by each physician.

Epidemiology

Prevalence of AF

Since AF is likely to be developed in the population of advanced age, the prevalence of AF in the older population was consistently higher than that in the younger population in both men and women. A further increase in the prevalence of AF is expected with an increasingly aged population worldwide.

In the Western countries

The representative four population-based surveys including several thousand subjects conducted between the 1980s and the 1990s (the Western Australia study,[4] the Rochester study,[5] the Framingham study,[6] and the Cardiovascular Health Study),[7] the prevalence of AF was 7–14% in people aged 80 years or older (*Table 1*). Based on these surveys, the prevalence of AF in the USA in 1991 was 0.89% (2.3% in

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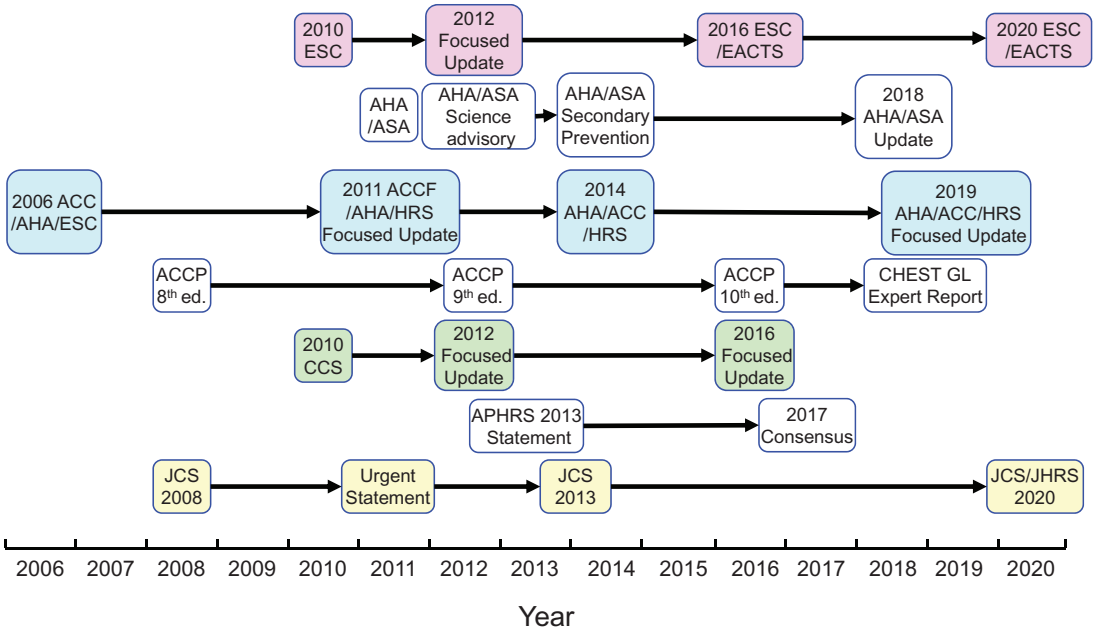

Figure 1 Updated history of guidelines for atrial fibrillation. ACC, American College of Cardiology; ACCF, American College of Cardiology Foundation; ACCP, American College of Chest Physicians; AHA, American Heart Association; APHRS, Asian-Pacific Heart Rhythm Society; ASA, American Stroke Association; CCS, Canadian Cardiovascular Society; EACTS; European Association for Cardio-Thoracic Surgery; ESC, European Society of Cardiology; HRS, Heart Rhythm Society; JCS, Japanese Society of Cardiology; JHRS, Japanese Heart Rhythm Society.

Table 1 Prevalence of atrial fibrillation in Australia, Europe, and the USA

	Western Australia			Rochester			Framingham	Cardiovascular Health Study			UK database		ATRIA study		
Report year (citation)	1989 (4)			1990 (5)			1991 (6)	1994 (7)			2001 (9)		2001 (10)		
Number of subjects (year of survey)	1770 (1966–1981)			2122 (1981)			5070	5201 (1989)			140×10^4 (1998)		189×10^4 (1996–1997)		
Age, years	Men	Women	Total	Men	Women	Total	Overall	Men	Women	Total	Men	Women	Men	Women	Total
40–44	–	–	–	0	0	0	0.1	–	–	–	0.25	0.22	0.2	0.1	–
45–49	–	–	–	0.5	0.5	0.5		–	–	–	0.66	0.44			
50–54	–	–	–				0.5	–	–	–					
55–59	–	–	–	1.0	1.5	1.2		–	–	–	1.8	1.1	0.9	0.4	0.6
60–64	1.1	2.3	1.7				1.8	–	–	–			1.7	1.0	1.4
65–69	3.3	2.7	3.0	6.0	3.0	4.6		5.9	2.8	4.0	4.6	3.3	3.0	1.7	2.5
70–74	8.6	5.5	7.0				4.8	5.8	5.9	5.8			5.0	3.4	4.3
75–79	15.0	8.4	11.6	16.1	12.2	13.7					9.1	7.2	7.3	5.0	6.3
≥80	15.0	8.4	11.6				8.8	8.0	6.7	7.3	10.6[a]	10.9[a]	10.6	8.0	9.3
Overall	5.6	4.2	4.9	4.3	3.8	4.1	2.1	4.8	6.2	5.4	1.21	1.27	1.1	0.8	0.95

The data are expressed as %.
[a]≥85 years old.

adults older than 40 years and 5.9% in those older than 65 years) and the number of people with AF was 2.23 million; thus, approximately 70% of the people with AF were within the age range of 65–85 years.[8] In a report from England and Wales using general practice research database with 1.4 million subjects, the prevalence of AF in 1998 was 1.21% in men and 1.27% in women.[9] The prevalence in subjects of advanced age was high as well, with a rate over 10% in both men and women.[9] In the ATRIA study,[10] the overall prevalence of AF was 0.95%, and it was more common in men than in women (1.1% and 0.8%), and in elders than in young people (less than 0.1% in people under 55 years and 9.3% in those aged 80 years or older). The prevalence of AF gradually increased with ageing and approximately 45% of AF subjects were aged 75 years or older.[10] Racial difference in the prevalence of AF was also found; 2.2% in White and 1.5% in Black among people aged 50 years or older.[10] In a

Table 2 Estimated age-adjusted prevalence rates of atrial fibrillation

	1990	1995	2000	2005	2010
Men					
Global, all ages	569.5 (532.8-612.7)	578.1 (541.2-620.9)	586.8 (549.8-629.5)	595.1 (557.3-639.0)	596.2 (558.4-636.7)
Age ≥35 years	1307.4 (1222.5-1407.3)	1327.3 (1243.2-1425.7)	1347.6 (1263.4-1445.8)	1366.6 (1281.0-1467.1)	1368.5 (1280.8-1462.7)
Developed countries	608.2 (547.0-693.5)	625.6 (564.0-712.5)	643.1 (580.3-730.2)	660.0 (594.5-740.8)	660.9 (597.1-738.2)
Developing countries	546.6 (503.0-599.6)	551.1 (506.6-604.8)	555.8 (511.0-610.1)	561.3 (517.5-618.4)	565.7 (522.9-617.6)
Women					
Global, all ages	359.9 (334.7-392.6)	363.4 (338.5-395.3)	366.7 (342.0-397.8)	369.6 (345.5-399.9)	373.1 (347.9-402.2)
Age ≥35 years	826.5 (768.4-902.3)	834.7 (776.6-909.2)	842.3 (784.7-915.5)	849.0 (792.4-919.6)	856.8 (797.7-923.5)
Developed countries	362.5 (319.3-422.3)	370.1 (326.7-429.5)	377.5 (334.0-436.8)	385.1 (340.1-446.8)	387.7 (343.8-450.0)
Developing countries	358.2 (329.8-393.0)	359.0 (330.8-394.0)	359.8 (331.5-395.0)	360.9 (331.6-396.0)	366.1 (337.4-400.8)

The data are expressed as prevalence rates per 100 000 population (95% uncertainty intervals). Cited from Chugh *et al.*[12]

Table 3 Prevalence of atrial fibrillation in Korea and Japan

	Korea			Japanese Circulation Society (Japan)			Kurashiki annual medical survey (Japan)			TAMA MED project-AF (Japan)		
Report year (citation)	2005 (13)			2006 (15)			2008 (16)			2019 (17)		
Number of subjects (year of survey)	14 540 (2000)			630 133 (2003)			41 436 (2006)			12 303 (2015)		
Age, years	Men	Women	Total	Men	Women	Total	Men	Women	Total	Men	Women	Total
40-44	0.12	0.06	0.1	0.2	0.04	0.1	0.5	0.2	0.2	0	0	0
45-49										0	0	0
50-54	0.7	0.4	0.5	0.8	0.1	0.4				0	0	0
55-59										0.5	0	0.2
60-64	1.8	0.2	0.9	1.9	0.4	1.0	2.3	1.0	1.5	1.0	0.1	0.4
65-69	3.9	1.0	2.2							2.7	0.4	1.3
70-74	2.5	1.1	1.7	3.4	1.1	2.1				3.9	0.6	2.0
75-79	3.4	0.5	1.9							5.6	1.1	3.2
≥80	4.5	3.5	4.0	4.4	2.2	3.2	3.5	2.5	2.8	—	—	—
Overall	1.2	0.4	0.7	1.4	0.4	0.6	2.4	1.2	1.6	2.9	0.4	1.4

The data are expressed as %.

report from Europe,[11] the prevalence of AF was 2% in a recent decade (3.7–4.2% in people aged 60–70 years and 10–17% in those aged 80 years or older; and 1.2-fold in men to women). It has been increasing since the 1990s. Possible factors include the progress of treatment for cardiac and non-cardiac diseases and the development of technology for the detection of AF in addition to ageing population.[11]

In a systematic review article including the 184 population-based studies worldwide (including 35.9% form the Europe and 35.6% from the North America) between 1980 and 2010,[12] the global prevalence of AF in 2010 was 0.60% in men and 0.37% in women; and it was 1.37% in men and 0.86% in women aged 35 years or older. It had gradually been increasing since 1990 and was higher in the developed countries than in the developing countries (*Table 2*). There was obvious regional differences in the prevalence of AF between the lowest in Asian-Pacific (0.34% in men and 0.20% in women) and the highest in North America (0.93% in men and 0.52% in women).[12]

In Asian countries

In a report from Korea,[13] the prevalence of AF in 2000 was 0.7% (1.2% in men and 0.4% in women) in adults older than 40 years and 2.1% (3.3% in men and 1.1% in women) in those older than 65 years. Approximately, 57% of the individuals with AF were older than 65 years (*Table 3*). A gender difference was also found. Reports of surveys in the other Asian countries are scarce, therefore, data from global large surveys including Asian populations are often cited for information on the prevalence of AF in Asians. For instance, in 14 670 Indo-Asians of 25 051 subjects in the west of Birmingham, the prevalence of AF in Indo-Asians aged over 50 years was 0.6%.[14] In Japan, in a report from population-based study conducted with the Japanese Circulation Society in 2003[15] including more than 630 thousand participants aged 40 years or older, the overall prevalence of AF was 0.56% (1.35% in men and 0.43% in women).[15] In another community-based study in Japan, the prevalence of AF was 1.6% in 41 436 residents aged 40 years or older in Kurashiki-city in 2006, and 3.5% in men and 2.5% in women aged

Table 4 Estimated age-adjusted incidence rates of atrial fibrillation

	1990	2010
Men		
Global, all ages	60.7 (49.2-78.5)	77.5 (65.2-95.4)
Age ≥35 years	141.0 (114.6-182.6)	181.2 (152.6-222.8)
Developed countries	78.4 (67.5-91.9)	123.4 (107.6-141.5)
Developing countries	50.0 (33.8-76.8)	53.8 (38.7-79.8)
Women		
Global, all ages	43.8 (35.9-55.0)	59.5 (49.9-74.9)
Age ≥35 years	102.0 (83.9-127.9)	139.7 (117.1-175.3)
Developed countries	52.8 (45.0-62.9)	90.4 (77.8-104.5)
Developing countries	36.0 (24.5-54.7)	40.0 (27.2-62.6)

The data are expressed as incidence rates per 100 000 person-years (95% uncertainty intervals). Cited from Chugh *et al*.[12]

80 years or older.[16] In recent population-based survey in suburb of Tokyo, the prevalence of AF in people aged 40-75 years in 2015 was 1.4% (2.9% in men and 0.4% in women).[17] Thus, it may recently be increasing even in people aged under 75 years as well as that over 75 years.[15,16]

Incidence and projected number of AF

Several epidemiological studies have reported the incidence of AF in the Western counties. In the Framingham study,[18] AF was identified in 26 in men and 16 in women aged 70-79 years per 1000 people during the 2-year follow-up period; thus, the overall incidence of AF was 0.2% per year. In the Cardiovascular Health Study,[19] among 4844 participants, 304 developed a first episode of AF during an average follow-up of 3.28 years; thus, incidence of 19.2 per 1000 person-years (17.6 and 42.7 in men and 10.1 and 21.6 in women aged 65-74 and 75-84 years, respectively). In the ATRIA study,[10] there was an estimated 2.3 million adults with AF in the USA which was comparable with the results reported by Feinberg *et al*.[8] Assuming that the prevalence of AF is consistent, the projected number of people with AF will increase to more than 5.6 million by the year 2050, with more than 50% of affected individuals being aged 80 years or older.[10] In a report of the community-based study with 4618 adult residents in Minnesota,[20] the incidence of AF increased with age, similar to the Framingham study[21] and the Cardiovascular Health Study.[19] The age- and sex-adjusted incidence rates of AF per 1000 person-years were 3.04 in 1980 and 3.68 in 2000. The incidence of AF in the overall cohort significantly increased by 12.6% for 21 years[20]; thus, the number of people with AF can be projected to be 15.9 million by 2050. Other investigators also projected the number of AF as 7.56 million in 2050.[22] The reasons of discrepancy in the projected number of AF among these studies may include the sample sizes, geographical areas, and the assumptions regarding the increase in the incidence of AF.[22]

In a systematic review article including the 184 population-based studies worldwide,[12] the incidence rates of new-onset AF in 2010 were 0.78 in men and 0.60 in women per 1000 person-years (1.81 in men and 1.40 in women in people aged 35 years or older) (*Table 4*), indicating that people with AF would increase by 4.7 million (2.7 million in men and 2.0 million in women) per year. As the prevalence, the incidence of AF is higher in men than women, and in the developed countries than in the developing countries.[12] Accordingly, number of subjects with AF in the world in 2010 was estimated to be 33.5 million (20.9 million in men and 12.6 million in women).[12]

In Japan, in a report of the observational cohort study with 28 449 participants aged 20 years or older (mean; 59.2 years) in Niigata, the incidence of AF per 1000 person-years was 4.1 in men and 1.3 in women.[23] In another community-based study with 30 010 participants aged 40 years or older (median; 73 years) in Kurashiki,[24] it was higher (13.0 in men and 7.4 in women). In a report from the Suita study including 6898 subjects aged 30-79 years, the incidence rates of new-onset AF from 1989 were 3.3 per 1000 person-years (4.7 in men and 2.1 in women).[25] In another recent population-based survey from 2008 to 2015, the incidence of AF in people aged 40-75 years was 2.5 per 1000 person-years (4.5 in men and 1.3 in women).[17] The difference in the incidence of AF among these studies might be due to the differences in geographical areas, age distribution, underlying diseases, standard therapeutic strategy among study cohorts, and so on. Based on the Japanese Registry of Residents in 2005, the number of people with AF was estimated to be 716 000 in Japan[15] and is projected to be 1.03 million in 2050. The estimation was similar to that of another report from the National Survey on Cardiovascular Diseases.[26] However, the prevalence and incidence of AF in population-based studies must be underestimated, since paroxysmal AF cannot be always detected at the time of health check-ups.

Pathophysiology

A complex interplay of triggers, perpetuators, and substrate development eventually results in AF occurrence. Several risk factors contribute to modify the atrial substrate. These risk factors include age, gender, hypertension, organic heart disease, diabetes, obesity, sleep apnoea, uric acid, smoking, alcohol, genetic factors, and so on.[27] The modified atrial substrate predisposing to develop AF consists of structural and electrical remodelling, which plays a pivotal role in initiating and maintaining AF.

Various factors cause complex atrial remodelling, including stretch-induced fibrosis, hypocontractility, fatty infiltration, inflammation, vascular remodelling, ischaemia, ion-channel dysfunction, and calcium instability.[28] All enhance ectopy and conduction disturbances, increase atrial propensity to develop/maintain AF, and facilitate the AF-associated hypercoagulable state. The resultant AF is able to self-perpetuate through intrinsic remodelling of the substrate (AF begets AF).[29] Some of rapid atrial impulses are conducted to the ventricles; some only penetrate the atrioventricular node, increasing its refractoriness; the ventricular rate and irregularity are the result of this concealed conduction of the atrial impulses. During increased sympathetic tone, the atrioventricular node refractoriness decreases steeply, leading to a disproportionate increase in heart rate.

The remodelling of the atrium results in the dysfunction of atrial contraction and dilatation of atrial chamber, which causes the stasis of blood in the atrium and thrombus formation especially in the left atrial (LA) appendage. Rapid atrial rates and AF both result in increased platelet activation and thrombin generation, and prothrombotic activation occurs to a greater extent in the left atrium compared with systemic circulation.[30] AF additionally induces endothelial dysfunction and inflammation. Thus, although rapid atrial rates increase the thrombogenic risk, AF may further potentiate this risk.

Classification of AF

AF pattern

Based on the presentation, duration, and spontaneous termination of AF episodes, AF patterns are generally classified five types such as the first diagnosed, paroxysmal, persistent, long-standing persistent, and permanent AF.[31] Note that the first diagnosed AF is not always the first AF episode in individuals, and clinically determined AF patterns do not correspond well to the AF burden measured by long-term electrocardiogram monitoring. However, the distinction between persistent and long-standing persistent is clinically important to determine the therapeutic strategy, especially for rhythm control therapy by catheter ablation.

Traditional terminology on AF

Although 'lone AF' had been used historically, true lone AF is not thought to exist.[32] Since every patient has some causes of AF based on increasing knowledge about the pathophysiology on AF, lone AF should no longer be used. 'Chronic AF' has often been used as the combination of persistent plus permanent AF. However, it is also inappropriate to use since the definition of 'chronic' is vague and variable.

In addition, AF has been conventionally divided into either 'valvular' or 'non-valvular'. In the 2012 focussed update of the ESC Guidelines for the Management of Atrial Fibrillation,[33] the term valvular AF is used to imply that AF is related to rheumatic valvular disease (predominantly mitral stenosis) or prosthetic heart valves. However, it was also described that no satisfactory or uniform definition of these terms exists.[33] In addition, among artificial valves, it has not been clearly determined whether bioprosthetic valves are included in 'valvular' or 'non-valvular'. This definition is quite important to choose an anticoagulant in patients with bioprosthetic valve because non-VKA oral anticoagulant (NOAC) is currently approved for only patients with non-valvular AF. In the Japanese Guidelines for Pharmacotherapy of Atrial Fibrillation [Japanese Society of Cardiology (JCS) 2013],[34] bioprosthetic valves were categorized as 'valvular'. However, recent reports using NOACs for patients with AF after bioprosthetic valve replacement have suggested that the efficacy of NOACs for the prevention of thromboembolism was comparable with that of warfarin[35-37] and the safety of NOACs for major haemorrhage would be superior to that of warfarin.[35] Based on these studies,[35-37] even though in which the number of subjects was relatively small, bioprosthetic valves became to be considered as 'non-valvular' in a joint consensus document from the Heart Rhythm Associations of Europe, Asia, Africa, and Latin America in 2017.[38] The 2019 AHA/ACC/Heart Rhythm Society (HRS) focused update of the 2014 AHA/ACC/HRS guideline followed this standpoint.[39] Furthermore, also in the JCS/Japanese Heart Rhythm Society (JHRS) 2020 Guideline on Pharmacotherapy of Cardiac Arrhythmias,[40] which was recently updated from the JCS 2013,[34] the definition of 'non-valvular' was altered to include bioprosthetic valves. The post-operative state of mitral valve repair (mitral annulorrhaphy or annuloplasty) and non-rheumatic mitral regurgitation remain included in 'non-valvular' as in the guidelines.[34,41] Consequently, NOACs can be currently used in patients with bioprosthetic valves including those after transcatheter aortic valve implantation.[42]

In contrast, the effectiveness or safety of NOACs for 'valvular' AF including mechanical heart valves or moderate-severe mitral stenosis has never been proven.[43,44]

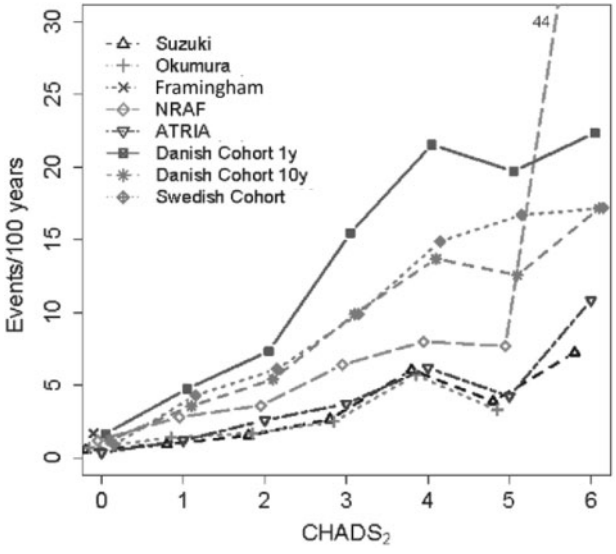

Figure 2 Incidence rates of ischaemic stroke in each $CHADS_2$ score. -△- Suzuki, Pooled analysis of the J-RHYTHM Registry, Fushimi AF Registry, and Shinken Database.[47] -+- Okumura, J-RHYTHM Registry.[48] ATRIA, the anticoagulation and risk factors in atrial fibrillation; NRTF, national registry of atrial fibrillation (cited from Olesen *et al.*[46]).

'Valvular' does not mean the echocardiographic findings of valve stenosis and/or regurgitation in patients with 'non-valvular' AF.[45] Accordingly, the latest 2020 ESC/European Association for Cardio-Thoracic Surgery (EACTS) guidelines recommend that the terminology 'valvular/non-valvular' should be abandoned, since this may be confusing.[31]

Risk assessment for thromboembolism in AF

Conventional risks in traditional risk scores

In two decades ago, Gage *et al.*[1] proposed the $CHADS_2$ score, a clinical classification scheme for predicting stroke in patients with AF. This score was formed by assigning one point each for the presence of congestive heart failure, hypertension, age ≥75 years, and diabetes mellitus and two points for prior stroke or transient ischaemic attack (TIA); thus, the maximum is six points. The incidence rate of ischaemic stroke in patients without anticoagulation therapy in each score (0–6 point) was 1.9, 2.8, 4.0, 5.9, 8.5, 12.5, and 18.2 per 100 patient-years, respectively,[1] indicating a stroke risk increased by 1.5-fold for each 1-point increase in the $CHADS_2$ score. Although these rates are often explained as a gold standard, the incidence rates of ischaemic stroke varied among studies (*Figure 2*)[46] in which study population and ethnicity were different. Especially, these rates in Japanese patients with non-valvular AF were obviously lower than those in the other countries (*Figure 2*).[46–48] Therefore, the incidence rates of the original $CHADS_2$ score[1] cannot be necessarily generalized worldwide.

On the other hand, the ESC adopted the CHA_2DS_2-VASc score[3] as a risk assessment score for thromboembolism in the 2012 focused update of the ESC Guidelines for the Management of Atrial Fibrillation.[33] This score contains age ≥75 years and a history of stroke, TIA, or thromboembolism for two points and components not included in the $CHADS_2$ score, such as vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque), age 65–74 years, and sex category (female gender) for one point (for a maximum nine points). The CHA_2DS_2-VASc score was adopted in the 2016 ESC Guidelines developed in collaboration with the EACTS,[42] as well as in the 2014 AHA/ACC/HRS Guideline[41] in the USA and Asian Pacific Heart Rhythm Society (APHRS)[49,50] except in Japan.[40] In Japanese patients with non-valvular AF not receiving anticoagulation therapy from the three major Japanese AF registries (J-RHYTHM Registry, Fushimi AF Registry, and Shinken Database),[47] the factors added to the CHA_2DS_2-VASc score (vascular disease, age 65–74 years, and female gender) were not a significant risk for ischaemic stroke, suggesting an ethnic difference in risk profiles.

Components of CHA_2DS_2-VASc score

Congestive heart failure

'Congestive heart failure' fulfils all of Virchow's triad of characteristics of a hypercoagulable state, increasing the propensity to thromboembolism, but the impact of heart failure on stroke risk has been controversial.[51] Heart failure was not an independent predictor of stroke in a pooled analysis of five randomized trials[52] or in an analysis of 2012 patients from the SPAF I–III trials.[53] The risk for thromboembolism was reported to be comparable between patients with heart failure with reduced ejection fraction and those with preserved ejection fraction.[54] Possible reasons include that current standard therapeutic drugs for heart failure differ from those in the 1990s, heart failure is a stronger risk factor for all-cause and cardiovascular deaths rather than for thromboembolism,[55] and the severity or duration of heart failure was not considered.[56,57] In a sub-analysis of the ENGAGE AF-TIMI 48 trial,[56] severe heart failure with New York Heart Association (NYHA) class III or IV was a significant risk factor for thromboembolism [hazard ratio (HR) 1.45, 95% confidence interval (CI) 1.12–1.88]. In addition, the incidence of stroke or systemic embolism markedly increased in the 30 days after admission for heart failure (HR 12.0, 95% CI 4.59–31.98) in a sub-analysis of the Fushimi AF Registry.[57]

Hypertension

'Hypertension' is a risk factor for stroke even in patients with its history and/or adequate blood pressure (BP) control under treatment in the Framingham study.[58] Therefore, the definition of hypertension in the $CHADS_2$ score included a history of hypertension in addition to the criteria of hypertension of those with a systolic BP of ≥160 mmHg in those days. In sub-analysis on hypertension of the phase III trials using NOACs, hypertension was a significant risk factor for stroke or systemic embolism in the ROCKET-AF trial,[59] and the ARISTOTLE trial,[60] but not in the RE-LY trial.[61] In sub-analysis of the J-RHYTHM Registry,[62] either hypertension (including its history and/or under treatment) or BP value at the time of enrolment was not an independent risk factor for thromboembolism, but the systolic BP ≥136 mmHg at the time closest to the event was a significant risk factor for it compared with systolic BP <114 mmHg (odds ratio 2.88, 95% CI 1.75–4.74). A sub-analysis of the Fushimi AF Registry[63] also showed that event rates in patients with hypertension was comparable to those without it, but the incidence rates of stroke/systemic embolism and haemorrhagic stroke in patients with a baseline systolic BP ≥150 mmHg were significantly higher than those with adequate BP control.

Since patients with higher BP had consistently indicated higher event rates in all studies,[59–63] appropriate BP control may result in a reduced risk of thromboembolism in patients with non-valvular AF. Visit-to-visit variability of systolic BP during the follow-up period was also a significant risk factor for major adverse outcomes.[64]

Age

'Age ≥75 years' is indicated as a strong risk factor for thromboembolism among the $CHADS_2$ score of 1.[65,66] In some Japanese registry studies, it was also shown that age ≥75 years was a strong risk factor for thromboembolism (HR 2.3–2.8).[47,62,67] Age 65–74 years was a significant risk factor for stroke in the AFI[68] and the Swedish Cohort Atrial Fibrillation study.[65] In the 2016 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation,[69] patients aged ≥65 years are recommended to receive anticoagulation therapy, regardless of other risk factors, with

nomenclature of 'CHADS65'. However, age 65–74 years has not been identified as a significant risk factor for thromboembolism in Japanese patients, although HRs were slightly high at 1.0–1.3.[47,62,70] On the other hand, the extreme elderly (age ≥85 years) was associated with a particularly higher incidence of stroke or systemic embolism (vs. −74 years: HR 3.78, 95% CI 2.46–5.80; vs. 75–84 years: HR 1.77, 95% CI 1.19–2.61) in the Fushimi AF Registry.[71]

Diabetes mellitus

'Diabetes mellitus' was identified as a risk factor for thromboembolism in some studies,[65,68] but was often not.[47,62,67] Most studies did not evaluate the status of blood glucose levels or oral hypoglycaemic agents.

Prior stroke or TIA

'Prior stroke or TIA' is defined as prior cerebral ischaemia (either stroke or TIA) and patients with it are categorized into the secondary prevention of stroke. Since this factor was recognized as a stronger risk for thromboembolism than other risk factors,[72–76] both the $CHADS_2$ and the CHA_2DS_2-VASc scores have assigned it for two points.

Vascular disease

'Vascular disease' including prior myocardial infarction,[68] aortic plaque,[77] and peripheral arterial disease[78] was identified as a risk factor for thromboembolism. However, it was not identified as a significant risk factor for thromboembolism in Japanese patients.[47,62,70]

Sex category (female gender)

'Sex category' (being female)[65,68] was not identified as a solo risk factor in AF patients aged <65 years without other organic diseases.[33,66,79] It was also true in Japanese AF registry studies.[80,81] Being female should be thought as a modifier of other risk factors independent of sex.[82,83] Thus, sex category has not been described as a solo risk factor in the recent guidelines.[40,42]

Factors not included in CHA_2DS_2-VASc score

Cardiomyopathy

'Cardiomyopathy', especially in hypertrophic cardiomyopathy, was reportedly an independent risk factor for stroke in some cohort studies of Japanese patients with non-valvular AF.[84,85] Coagulation system is known to be activated in patients with cardiomyopathy.[84,86] As indicated below in the echocardiographic findings, decreased left ventricular (LV) diastolic function due to the hypertrophy may promote blood stasis and thrombus formation in the left atrium, hence enhancing the potential for thromboembolism.

AF type

'AF type' had been thought no relation to the incidence of ischaemic stroke based on the results of the ACTIVE W Substudy.[87] However, recent studies including subanalyses of phase III trials using direct oral anticoagulants[88–91] and the Fushimi AF Registry[92] demonstrated that the risk for thromboembolism in patients with persistent or permanent AF was significantly higher than those with paroxysmal AF. In addition, the risk of adverse events was transiently elevated during the progression period from paroxysmal to sustained AF.[93]

Body weight or body mass index

'Body weight (BW)' is not only a factor for dose reduction criteria of NOACs but also a risk factor for thromboembolism. A low BW of ≤50 kg was identified as a risk factor for ischaemic stroke/systemic embolism in Japanese AF patients in subanalysis of the Fushimi AF Registry.[70] Low BW or low body mass index (BMI) often complicated with sarcopenia, frailty, and renal impairment in patients with AF, especially in elderly patients. Therefore, low BMI ($<18.5\,kg/m^2$) was a stronger risk factor for all-cause death rather than for thromboembolism.[94]

Renal dysfunction

'Renal dysfunction' is one of factors for dose reduction criteria of NOACs as well as BW. Renal dysfunction is also a risk factor for stroke or all-cause death in patients with AF[95–98] as well as in the general population.[99,100] It was also confirmed in Japanese AF patients.[101,102] However, a cut-off level of creatinine clearance (CrCl) or estimated glomerular filtration rate for thromboembolism differ among studies.

According to these findings, persistent or permanent AF, LA diameter (>45 mm), BW (≤50 kg), and renal dysfunction have been newly adopted as other risks to be considered for anticoagulation therapy in the JCS/JHRS 2020 Guideline on Pharmacotherapy of Cardiac Arrhythmias.[40] In addition, in the J-RISK AF Study, which was pooled analysis of the five major AF registries in Japan (J-RHYTHM Registry, Fushimi AF Registry, Shinken Database, Keio Interhospital Cardiovascular Studies, and Hokuriku-Plus AF Registry), previous stroke, advanced age (≥75 years), hypertension, persistent or permanent AF, and low BMI ($<18.5\,kg/m^2$) were independent risk factors associated with ischaemic stroke in patients with non-valvular AF (*Table 5*).[103] However, neither heart failure nor diabetes mellitus was identified as a risk factor for ischaemic stroke in that study[103] as in the preceding study.[47]

Echocardiographic findings

'Echocardiographic findings' including LV systolic function (LV fractional shortening <25%),[104,105] LA dysfunction,[106] and LA diameter (>45 mm) in transthoracic echocardiography[67] and dense spontaneous echocardiographic contrast (smoke-like echo) in left atrium, LA appendage thrombus, and peak LA appendage flow velocity (<20 cm/s)[77] in transoesophageal echocardiography have reportedly been risk factors for thromboembolism in patients with non-valvular AF. A recent sub-analysis of Fushimi AF Registry demonstrated that LV relative wall thickness was independently associated with ischaemic stroke among Japanese patients with non-valvular AF, suggesting the importance of LV morphology in contributing to adverse outcomes, particularly thromboembolism.[107]

Other risk scores

Several risk scores for the assessment of thromboembolic risks have been developed beyond the $CHADS_2$ and CHA_2DS_2-VASc scores by some investigators. For instance,

Table 5 Risk factors for ischaemic stroke in Japanese patients with atrial fibrillation

Characteristic	HR (95% CI)	*P*-value
Age		
<75 years	1 (Reference)	
75–84 years	1.74 (1.32–2.30)	<0.001
≥85 years	2.41 (1.63–3.56)	<0.001
Hypertension	1.60 (1.15–2.23)	0.006
Previous stroke	2.75 (2.09–3.62)	<0.001
Persistent or permanent atrial fibrillation	1.59 (1.21–2.10)	0.001
Body mass index <18.5 kg/m^2	1.55 (1.05–2.29)	0.03
No oral anticoagulant	1.86 (1.40–2.47)	<0.001

Stepwise Cox proportional hazard model.
Pooled analysis of five Japanese atrial fibrillation registries including J-RHYTHM Registry, Fushimi AF Registry, Shinken Database, Keio Interhospital Cardiovascular Studies, and Hokuriku-Plus AF Registry ($n = 12\,289$).
CI, confidence interval; HR, hazard ratio.
Adapted from Okumura *et al.*[103]

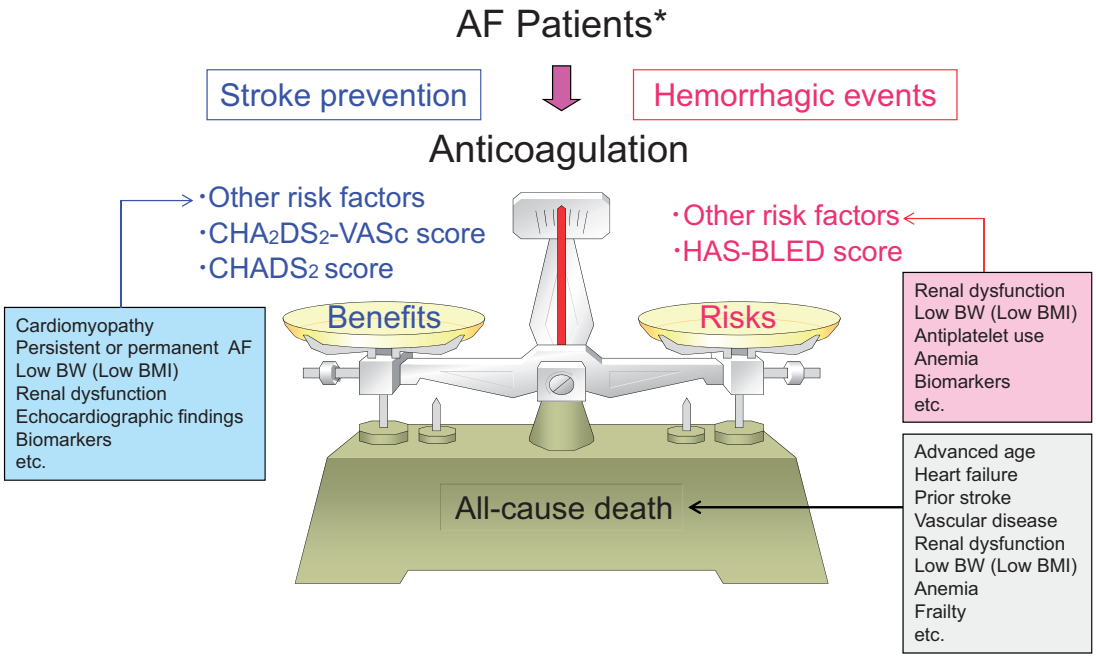

Figure 3 Risk assessment in patients with AF. AF, atrial fibrillation; BMI, body mass index, BW, body weight. *Except patients with moderate-severe mitral stenosis or mechanical prosthetic heart valve(s).

Piccini *et al.*[108] proposed the R_2CHADS_2 score by adding renal dysfunction to $CHADS_2$ score. The ABC (age, biomarkers, and clinical history) stroke risk score[109] was focused on biomarkers such as N-terminal pro brain natriuretic peptide and high-sensitivity troponin T. However, the predictive ability, which is generally determined by c-statistic, of these scores for thromboembolic events has not dramatically been improved compared with that of the $CHADS_2$[1] or CHA_2DS_2-VASc score.[3]

Another role of risk score is to detect truly low-risk patients in whom anticoagulation therapy may not be required. Approximately half of patients with non-valvular AF are corresponding a $CHADS_2$ score of 0 or 1,[66,110] for which the effectiveness of warfarin has not been proven. Since the $CHADS_2$ score cannot always stratify the risk among low-risk patients, the CHA_2DS_2-VASc score would be more useful to detect truly low-risk patients.[111,112]

Another important aspect is a dynamic nature of risk profiles. The stroke risk in patients with AF does not remain static, and with time, patients get older and accumulate more comorbidities. Researchers in Taiwan nicely demonstrated that the 'Delta CHA_2DS_2-VASc score,' which reflects the change in score between baseline and follow-up, was strongly predictive of ischaemic stroke, indicating how stroke risk in AF is a dynamic process due to increasing age and incident comorbidities.[113]

Risk assessment for major haemorrhage in AF

Since the accumulation of risk factors for haemorrhagic events increases the incidence of major haemorrhage including intracranial haemorrhage, especially during anticoagulation therapy, risk assessment for haemorrhagic events is also important for the determination of anticoagulation therapy and for the prevention from haemorrhagic complications in patients with non-valvular AF.

The HAS-BLED score[114] was adopted in the ESC guidelines in 2010 as a risk predicting score for haemorrhage.[74] This score can assess haemorrhagic risks more simply and accurately[115] compared with the preceding $HEMORR_2HAGES$ score.[116] Since hypertension, prior stroke, and advanced age were mutual factors with the $CHADS_2$ score,[1] high-risk patients for haemorrhagic events must also be at high risk for thromboembolism.[117] Note that hypertension in the HAS-BLED score is defined as a systolic BP >160 mmHg and advanced age is defined as >65 years. Labile international normalized ratio (INR) is applied for only patients receiving warfarin. Although several risk scores have been developed such as the ATRIA haemorrhagic risk score,[118] the ORBIT score,[119] the ABC bleeding risk score,[120] the predictive ability for haemorrhagic events has not been markedly improved.

The latest ESC guidelines emphasized that a high bleeding risk score should not lead to withholding OAC, as the net clinical benefit of OAC is even greater amongst such patients. The importance of managing modifiable bleeding risk factors and careful reassessment of risk at every patient contact was highlighted.[31]

Prognosis in patients with AF

The cause of death in AF patients is not always cardiogenic stroke or haemorrhagic event.[55,121,122] Non-cardiovascular death due to infection or malignancy is reportedly more common in real-world clinical setting; 35.8% in the international GARFIELD-AF registry,[121] 42.7% in a French regional registry,[122] 66.0% in a French nationwide database,[55] and 54.0% in the Fushimi AF Registry.[123] So far, the risk assessment for adverse events in AF patients has been performed to obtain the net clinical benefit[124] by comparing between the risks of thromboembolism and major haemorrhage (*Figure 3*). However, it may become necessary to assess the risks for all-cause death to consider the net clinical outcome in future. Indeed, in the J-RHYTHM Registry, low BMI ($<18.5\,kg/m^2$)[94] and low CrCl (<30 mL/min)[101] were stronger risk factors for all-cause death rather than for thromboembolism. Recently, anaemia has also been identified as a determinant factor for the prognosis in AF patients.[125–127] In addition, although digitalis, mainly digoxin, which has been used for heart rate control and heart failure management in patients with AF since ancient times, is reportedly a poor prognosis factor,[128] patient condition, comorbidities, and digoxin concentration were more strongly associated with patient prognosis rather than digoxin use itself.[129,130] Finally, recent literatures have indicated the association of frailty with worse prognosis in patients with AF; those patients are less likely to receive anticoagulation therapy and have various comorbidities predisposing to adverse events.[131–133]

Conclusive remarks

In patients with AF, physicians should consider clinical factors not included in the risk scores such as renal dysfunction, low BW (low BMI), type of AF and anaemia, as well as echocardiographic parameters and blood biomarkers in each individual, in addition to the general risk assessment for thromboembolic events using the pre-existing risk scores. This highlights the importance of total and integrated management of AF patients in a holistic manner.

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