Editorial

The Unmet Need of Stroke Prevention in Atrial Fibrillation in the Far East and South East Asia

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Abstract

The prevalence of atrial fibrillation (AF) is high in both community- and hospital-based studies in the Far East and South East Asia. Hypertension is the most common risk factor, but coronary heart disease and diabetes mellitus are other important co-morbidities in these countries. Anticoagulant therapy use was low, being 0.5%–28% in Malaysia, Singapore, and China. The reported rate of stroke related to AF was 13.0%–15.4% based on community studies in those countries and was 3.1%–24.2% of stroke rate in hospital-based cohorts. Better assessment of thromboembolic and bleeding risks is important. International guidelines now recommend the use of the CHA_2DS_2-VASc score to identify the "truly low-risk" AF patients, who do not need antithrombotic therapy, whilst those with ≥ 1 stroke risk factors can be offered oral anticoagulation. Aspirin is ineffective and may not be any safer than oral anticoagulants, especially in the elderly. It is anticipated that the availability of the new oral anticoagulant drugs would improve our efforts for stroke prevention in the Far East and South East Asia, especially where anticoagulation monitoring for warfarin is suboptimal.

Keywords: *anticoagulation, atrial fibrillaton, burden, Far East, stroke*

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. Stroke and systemic thromboembolism are its major complications, resulting in substantial morbidity and mortality. The management of AF has evolved greatly in the past few years, and the burden of AF and the need of stroke prevention strategies have been well documented in North America and Europe (1). However, the burden of AF in the Far East and South East Asia is also great, necessitating improvement of thromboprophylaxis strategies in these countries.

A systematic review of the global burden of AF, with particular focus on non-European and non-American countries, has recently been published (2). The prevalence of AF in community-based studies ranges from 0.1%–2.8% in Far East, with various studies reporting 0.8%–2.8% in China, 0.6%–1.6% in Japan, 0.4%–2.2% in Thailand, 1.4% in Singapore, and 0.1% in India (2). In hospital-based studies, the prevalence of AF was (unsurprisingly) higher, ranging from 2.8%–14% (2). Amongst hospital admissions, the prevalence of AF was 2.8% in Malaysia, 7.9% in China, and 12%–14% in Japan (Table 1) (2).

In keeping with epidemiological data from white populations, increasing age could subsequently increase the prevalence and

Table 1: Prevalence and incidence of atrial fibrillation in Far East

Area	Study date	Design/patients	Prevalence/Incidence
Community-based studies			
China	2003	Prospective, cross-sectional N = 29 079 Age ≥ 30 years	Overall: 0.77% Male: 0.91% Female: 0.63%
	2004	Prospective, random cluster sampling N = 18 615 Age ≥ 35 years	Overall: 1.04% Male: 1.09% Female: 1.00%
	2003–2006	Prospective, cross-sectional N = 19 964 Age ≥ 50 years	Overall: 0.80% Male: 1.15% Female: 0.66%
	2009	Prospective N = 30 000 Mean age: 50.5 (30.5) years	Overall: 2.83% Male: 5.66% Female: 2.87%
Japan	1963–1966 1972–1975 1984–1987	Prospective, cross-sectional N = 8539 Age: 40–69 years	Male: 1.1%, Female: 0.6% (1963 = 43) Male: 1.1%, Female: 0.6% (1972 = 75) Male: 1.7%, Female: 0.6% (1984 = 98)
	1980	Retrospective review of prospective national survey N = 9 483 Age ≥ 30 years	Overall: 0.64% Male: 0.65% Female: 0.62%
	1996–1998	Prospective cohort N = 235 818 Age ≥ 20 years	Overall: 0.7%
	1980, 1990, 2000	Retrospective analysis of prospective national surveys N = 23 713 Age ≥ 30 years	Male: 1.0% Female: 0.6%
	1998–2000	Prospective, cross-sectional N = 1 098 Age: 25–83 years	11 / 1098 (Lone AF or atrial flutter)
	2002–2004	Prospective N = 26 472 Age ≥ 18 years	Overall: 1.56% Male: 3.29% Female: 0.64%
	2003	Retrospective N = 630 138 Age ≥ 40 years	Male: 1.35% Female: 0.43%
	2005–2007	Multi-center, prospective N = 2 242 Age: 20–90 years	14.3%

Area	Study date	Design/patients	Prevalence/Incidence
Community-based studies			
	2006	Prospective N = 41 436 Age ≥ 40 years	Overall: 1.6% Male: 2.4% Female: 1.2%
Singapore	2008	Prospective N = 1 839 Age ≥ 55 years	Overall: 1.4% Male: 2.6% Female: 0.6%
South Korea	2000	Prospective N = 14 540 Age: 40–92 years	Overall: 0.7% Male: 1.2% Female: 0.4%
Taiwan	1990–2000, with follow-up 9 years	Prospective N = 3 580 Age ≥ 35 years	Overall: 1.07% Male: 1.4% Female: 0.7%
Thailand	1991	Prospective N = 8 791 Age ≥ 30 years	Overall: 0.39% Male: 0.39% Female: 0.38%
	2002	Prospective N = 963 Age ≥ 60 years	Overall: 2.2% Male: 1.8% Female: 2.3%
Hospital-based studies			
China	1999–2001	Retrospective N = 9 297 Age: 18–99 years	Incidence: 7.9% per year
Japan	1995	Prospective N = 19 825 Mean age: 63 (13) years	Overall: 14% Male: 17% Female: 10%
	2004–2008	Prospective N = 4 719 Mean age: 53.8 (15.3) years	Overall: 12.2%
Malaysia	2000	Prospective N = 1 435	Overall: 2.8% Male: 21 Female: 19
Taiwan	1997–2002	Retrospective N = 162 340	Overall incidence: Annual mean 127 per 100 000 Male: 137 per 100 000 Female: 116 per 100 000

Abbreviation : AF = atrial fibrilation.
[a] Source: Lip GY, et al. *Chest*. 2012.

incidence of AF in the Far East and South East Asia. Overall 57%–98% of patients with AF were aged 60 years or older in most studies (2). Men were more likely to develop AF than women, with 4.4%–7.9% in men and 2.2%–6.4% in men among patients aged over 80 years in the studies (2). 40% of patients with AF had hypertension in Malaysia, compared to 51.4%–56.3% in China, 24.4%–57.7% in Japan, and 73.1% in Singapore (2). 45% of patients had coronary heart disease in Malaysia (2). Valvular heart disease was also reported as a common comorbidity in Chinese and Japanese cohorts with AF (Table 2).

Suboptimal stroke prevention is fairly common in the Far East and South East Asia. The rate of anticoagulation use is low and aspirin is

Table 2: Risk factors for AF/AF comorbidities in Far East

Area	Age	Gender	Hypertension	CHD
China	Age ≥ 60: 72.8% Age ≥ 70: 31.4%	Male: 40.9%–54.9%	51.4%–56.3%	13.0%–34.8% (MI 8.3%)
Japan	Age ≥ 80: 3.0%–37%	Male: 50.2%–68.8%	24.4%–57.7%	9.3%–16.8% (MI 3.5%)
Singapore	**	Male: 73.1%	73.1%	**
South Korea	Age ≥ 65: 56.6%	Male: 71.7%	27.4%	**
Taiwan	Age ≥ 75: 23.7%	Male: 63.2%	52.6%–56.8%	38.6%
Malaysia	**	**	40%	45%
Area	**Diabetes**	**CHF**	**Previous stroke/TE**	
China	4.1%–23.6%	7.7%–3.9%	13.4%	
Japan	10.4%–20%	21.8%–22.7%	**	
Singapore	**	15.4%	15.4%	
South Korea	3.8%	**	**	
Taiwan	**	32.7%	15% (TE)	
Malaysia	**	**	**	

Abbreviations: AF = Atrial fibrillation, CHD = Coronary artery disease, CHF = Congestive heart failure, MI = Myocardial infarction, TE = Thromboembolism.
[a] Lip GY, et al. *Chest*. 2012. ** No available data.

still commonly used in many Far East countries. Indeed, oral anticoagulation use ranges between 0.5%–28% in Malaysia, Singapore, and China (Table 3). In Malaysia, for example, the rate of warfarin usage was 20%. The proportion of patients receiving antiplatelet therapy was 18%–58%, although there was significant variability. Of concern, 22%–47% patients with AF did not receive any antithrombotic drugs. In one Chinese retrospectively hospital-based study, for example, no antithrombotic therapy was evident in 35.5%. The rate of stroke related to AF was similar in community-based cohort (5 studies), which was 13.0%–15.4% in China, Japan, and Singapore (2). The stroke rate was 3.1%–24.2% in hospital-based cohorts (8 studies) (2) (Table 3).

Are things better elsewhere? Perhaps not. Indeed, 53% patients were treated with oral anticoagulants in 1996–1997 in North America and 64.8% in the Euro Heart survey (4,5). The annual rate of ischemic stroke or systemic embolism was 1.27% in patients on warfarin (4). The Swedish nationwide AF cohort study in 2005–2008 showed that only 40% patients with AF were on warfarin (6); of note, the 3-year incidence of ischemic stroke decreased from 8.7% for patients with AF in 1987–1991 to 6.6% in 2002–2006 in Sweden (7).

The management focus, at least until recently was the identification of "high risk" patients who would be candidates for an inconvenient anticoagulant drug, warfarin. Thus, warfarin use was suboptimal in the Far East and South East Asia, especially where anticoagulation monitoring infrastructures may be less evident. However, the requirements for regular monitoring, the various food or drug interactions still make warfarin a rather inconvenient drug, even in Western countries with excellent anticoagulation clinics (e.g., Sweden).

How can things change? The focus has recently shifted towards identification of "truly low risk" patients who do not need any antithrombotic therapy, whilst those with 1 or more stroke risk factors can be offered effective stroke prevention, which is oral anticoagulation–whether will well-managed warfarin or 1 of the new oral anticoagulants (e.g., dabigatran, rivaroxaban) that overcome the many limitations of warfarin (8,10–13).

Until recently the $CHADS_2$ score (Cardiac Failure, Hypertension, Age, Diabetes, and Stroke [double]) was the most widely recommended

Table 3: Antithrombotic treatment and stroke/TE among patients with AF in Far East

Area	Study date	Design/patients ( )	Antithrombotic therapy	Prevalence/Incidence for stroke/TE
China	2003–2004	Community-based Prospective N = 18 615–2 979 Age ≥ 30 years	Warfarin: 0.5%–2.7% ASA: 28.4%–37.9%	Stroke: 13.0%–13.4%
	1999–2002	Hospital-based Retrospective N = 3 425–9 297	Warfarin: 6.6%–9.1% ASA: 56%–57.9% No-ATT: 35.5%	Stroke: 17.5%–24.2%
Japan	2005–2007	Community-based Prospective N = 2 242 Age: 20–90 years	Warfarin: 70.1% ASA: 31.0% Ticlopidine: 4.1%	Stroke: 14.3%
	1991–2008	Hospital-based Prospective/ Retrospective N = 1 810–19 825	Warfarin: 9.3%–57% ASA: 18%–28.5% Ticlopidine: 7.5%–7.9%	Cerebral infarction: 3.1% Ischemic events: 4.6% (1.7 years follow-up) Embolic events: 8.6% (4.6 years follow-up)
Singapore	2008	Community-based Prospective N = 1 839 Age ≥ 55	Warfarin: 3/26	Stroke: 15.4%
South Korea	2000	Community-based Prospective N = 14 540 Age: 40–92 years		Stroke: 2.8%
Taiwan	1990–2009	Community-based Prospective/ Retrospective N= 3 580–39 541 Age ≥ 35 years Mean age: 70.1 (12.1) years	Warfarin: 21.1% ASA: 46.7% Ticlopidine/clopidogrel: 5.4%	Stroke incidence: 37.7 per 1000 person-years Prevalence previous TE: 15.0%
	1997–2002	Hospital-based Prospective/ Retrospective N = 4 435–162 340	Warfarin: 28.3% ASA: 37.9% Any ATT: 62.0%	Stroke: 15.2% Male: 12.1%–15.2% Female: 14.7%–17.6%
Malaysia*	2000-2003	Hospital-based Prospective N = 1 435	Warfarin: 20%	

ASA = Aspirin, ATT = Antithrombotic therapy, TE = Thromboembolism, TIA = Transient ischemic attack.
[a] Source: Lip GY, et al. *Chest*. 2012.

and used risk stratification scheme. The limitations of the $CHADS_2$ score have been recognized (14,15). Based on a nationwide cohort study, for example, those with a $CHADS_2$ score = 0 were not truly "low risk", with one-year event rates ranging from 0.84 (CHA_2DS_2-VASc score = 0) to 3.2 (CHA_2DS_2-VASc score = 3) (9).

In 2010, the CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥ 75 years [doubled], diabetes mellitus, stroke [doubled], vascular disease, age 65–74 years, sex category [female]) was recommended for the assessment of risk of thromboembolism in patients with AF. Various validation studies

Table 4: Stroke and bleeding risk score

$CHADS_2$	Stroke rate (%/year)	CHA_2DS_2-VASc	Stroke rate (%/year)	HAS-BLED	Points awarded
0	1.9	0	0	H	1
1	2.8	1	1.3	A	1 or 2
2	4.0	2	2.2	S	1
3	5.9	3	3.2	B	1
4	8.5	4	4.0	L	1
5	12.5	5	6.7	E	1
6	18.2	6	9.8	D	1 or 2
		7	9.6		
		8	6.7		

$CHADS_2$ and CHA_2DS_2-VASc score: Low risk = 0, Intermediate = 1, High risk = ≥ 2. HAS-BLED score: Low risk = 0–1, Intermediate risk = 2, High risk = ≥ 3. Abbreviations: $CHADS_2$ = Cardiac failure, hypertension, age, diabetes, and stroke (doubled), CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes mellitus, stroke (doubled), vascular disease, age 65–74 years, sex category (female), HAS-BLED = Hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly.

have shown that the CHA_2DS_2-VASc score can better identify truly low risk AF patients, who are unlikely to benefit from antithrombotic therapy (8,16).

Bleeding risk needs to be balanced against stroke and systemic embolism risk when making decisions for thromboprophylaxis. The HAS-BLED (Hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly) score has been proposed to use in conjunction with CHA_2DS_2-VASc, with which clinicians might make a simple and informed judgment to the benefits and risks of anticoagulation (Table 4). A high HAS-BLED score is not a means to stop oral anticoagulation, as such patients have an even greater net clinical benefit (17).

In conclusion, the importance of oral anticoagulation in the management of AF has been beyond any doubt documented. With the exception of real low risk patients (CHA_2DS_2-VASc = 0), every patient with AF will benefit from oral anticoagulation. This rule seems to apply irrespective of age, gender, or ethnicity. It is crucial to fill the gap between clinical trial and clinical practice in the management of AF. The simplicity and efficacy of risk stratification tools and the advantages of new oral anticoagulants are expected to significantly contribute to the improvement of our practice. With respect to the AF population in the Far East and South East Asia, the limited data have showed that the rates of AF-related stroke are high, representing a great healthcare burden. Things can only improve.

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