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Review

Antithrombotic treatment for stroke prevention in atrial fibrillation: The Asian agenda

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ABSTRACT

Atrial fibrillation (AF) is the most common heart arrhythmia. Untreated AF incurs a considerable burden of stroke and associated healthcare costs. Asians have AF risk factors similar to Caucasians and a similarly increased risk of AF-related stroke; however, with a vast and rapidly ageing population, Asia bears a disproportionately large disease burden. Urgent action is warranted to avert this potential health crisis. Antithrombotic therapy with oral anticoagulants is the most effective means of preventing stroke in AF and is a particular priority in Asia given the increasing disease burden. However, AF in Asia remains undertreated. Conventional oral anticoagulation with warfarin is problematic in Asia due to suboptimal control and a propensity among Asians to warfarin-induced intracranial haemorrhage. Partly due to concerns about intracranial haemorrhage, there are considerable gaps between AF treatment guidelines and clinical practice in Asia, in particular overuse of antiplatelet agents and underuse of anticoagulants. Compared with warfarin, new direct thrombin inhibitors and Factor Xa inhibitors are non-inferior in preventing stroke and significantly reduce the risk of life-threatening bleeding, particularly intracranial bleeding. These agents may therefore provide an appropriate alternative to warfarin in Asian patients. There is considerable scope to improve stroke prevention in AF in Asia. Key priorities include: early detection of AF and identification of asymptomatic patients; assessment of stroke and bleeding risk for all AF patients; evidence-based pharmacotherapy with direct-acting oral anticoagulant agents or vitamin K antagonists for AF patients at risk of stroke; controlling hypertension; and awareness-raising, education and outreach among both physicians and patients.

Abbreviations: AF, atrial fibrillation; ASA, acetylsalicylic acid; $CHADS_2$, congestive heart failure, hypertension, age ≥75, diabetes, prior stroke/transient ischaemic attack (doubled); CHA_2DS_2-VASc, congestive heart failure or left ventricular dysfunction, hypertension, age ≥75 (doubled), diabetes, prior stroke/transient ischaemic attack (doubled)-vascular disease, age 65–74, and sex category (female); GI, gastrointestinal; ICH, intracerebral haemorrhage; INR, international normalised ratio; NOAC, non-vitamin K oral anticoagulant; ESC, European Society of Cardiology; EHRA, European Heart Rhythm Association; VKA, vitamin K antagonist; ACS, acute coronary syndrome; CrCl, creatinine clearance; PCC, prothrombin complex concentrate; DES, drug eluting stent; PCI, percutaneous coronary intervention; US, United States of America.

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1. Introduction

1.1. Pathophysiology

Atrial fibrillation (AF) is characterised by disorganised electrical signals that disrupt cardiac function. Erratic transmission of atrial impulses through the atrioventricular node, leads to ventricular contractions that are irregular in both time and volume [1]. Structural remodelling of the atrium over time, drives AF progression from transitory (usually ≤48 h) self-limiting episodes (paroxysmal), to persistent (>7 days or requiring corrective intervention), long-standing persistent (>1 year) and permanent forms [2]. Stalled atrial mechanical contraction is associated with blood stasis in the atria, which can precipitate thrombus formation and subsequent embolism that causes a stroke or systemic arterial infarction [3]. All types of AF substantially increase the risk of stroke [4], which emerging evidence indicates nearly doubles as AF progresses from paroxysmal to permanent forms [5].

1.2. Epidemiology & burden

AF is the most common sustained heart rhythm abnormality [2]. The principal risk factors include: advancing age, especially above 50 years, and male gender [6–8]; hypertension [9]; structural heart disease, especially heart failure [10]; and obesity [11]. Increasing prevalence of AF worldwide reflects the growing proportions of individuals affected by these risk factors; prevalence in the United States (US) is projected to double from 2000 to 2050 [7]. Despite AF being relatively less prevalent in Asians than Caucasians, Asia bears a far greater overall burden of disease, because of its much larger absolute aged population [12]. Moreover, rapid population ageing in Asia, coupled with rising incidence of cardiovascular disease, hypertension, obesity and diabetes is predicted to drive escalating prevalence of AF even faster than projected in western populations [12,13], such that by 2050, 72 million AF patients in Asia will outnumber the combined total in Europe and the US by more than two to one [14].

Untreated AF incurs a considerable risk of stroke, in particular ischaemic stroke which is approximately five-fold more common in patients with AF [6]. An estimated 15% of ischaemic strokes are attributable to AF [15,16]. Prior stroke or transient ischaemic attack, hypertension, structural heart disease, advanced age, congestive heart failure, female gender atherosclerotic disease and diabetes, independently increase the likelihood of stroke in AF [17]. AF-induced strokes are more severe and have worse prognosis than those of other aetiologies [18–20], and incur considerable corresponding burdens of mortality, morbidity and healthcare expenditure. Stroke kills 20% of such patients and disables 60% of survivors [21]. Furthermore, stroke survivors with AF are more likely than those without to have another stroke [20,22]. The adverse impact of AF is underscored by excess mortality in both men and women with AF [23]. In the US, the total cost of healthcare for AF patients is estimated to be approximately US$16 billion/year [24]. The economic burden associated with stroke accounts for approximately 3% of total healthcare expenditure in the US, Canada and countries in Europe [25], and is likely to be enormous across Asia; although there are no regional data, the total cost of treating stroke is estimated to be US$2 billion in Australia [26], US$3 billion in Korea [27], US$ 3,787 billion in China [28], and US$22 billion in Japan [29].

In general Asians and Caucasians share similar major risk factors for AF and associated comorbidities [12], with hypertension the most common risk factor worldwide [30]; however, there are significant differences between countries/regions in Asia and other parts of the world in the relative predominance of different risk factors and concomitant diseases, as well as large global variations in how AF is treated (Fig. 1) [30]. Notwithstanding these differences, epidemiology data from Japan and Taiwan show similar or even greater increased relative risk of AF-related stroke to that in predominantly Caucasian populations [6,31–33]. Without appropriate thromboprophylaxis, some 2.9 million Asians in 2050 will have an AF-related stroke [14]. It follows that treating AF to prevent stroke is no less urgent a priority in Asia than elsewhere.

Antithrombotic pharmacotherapy is acknowledged to be the most important measure for preventing stroke in AF, with anticoagulation the most effective intervention for patients at high risk. Yet contrary to international guidelines, AF continues to be untreated or undertreated globally, and especially so in Asia [34]. In North America and Western Europe, more than 60% of AF patients with non-rheumatic heart disease who are at high risk of stroke receive oral anticoagulant therapy, compared with around 40% in South East Asia and India and just 11% in China (Fig. 1) [30,35]. At a hospital in Hong Kong 45% of AF patients were prescribed acetylsalicylic acid (ASA), 31% an oral anticoagulant, but 24% received no antithrombotic pharmacotherapy [36]. Similarly, in Taiwan, although nearly 90% of AF patients were at high or very high risk for thromboembolic events, only 24.7% overall received guideline-recommended therapy: 50.6% of high risk patients received ASA and 29.0% no antithrombotic medication whatsoever [37]. Such regional variation in implementation reflects differences in healthcare systems, resources and access, and physician expertise and preferences. Improving patient outcomes in AF requires not only more assiduous implementation of current guidelines, but also greater understanding of regional variations in aetiology, epidemiology and treatment of AF in different socioeconomic settings [30,38].

1.3. The evolving AF management landscape

Stroke risk in AF is stratified by assigning weighted point values to various contributory risk factors to compute individual risk scores; the schema in most widespread current use are $CHADS_2$ (congestive heart failure, hypertension, age ≥75, diabetes, prior stroke/transient ischaemic attack [doubled]) [39], and CHA_2DS_2-VASc (congestive heart failure or left ventricular dysfunction, hypertension, age ≥75 [doubled], diabetes, prior stroke/transient ischaemic attack [doubled] - vascular disease, age 65–74, and sex category [female]) [40]. Both risk scores correlate well with annual stroke rates in Caucasian populations [39–41]; and have been endorsed by international guidelines; however, $CHADS_2$ performs poorly in discerning patients at genuinely low risk who do not require antithrombotic therapy, whereas by integrating additional risk factors CHA_2DS_2-VASc is better at distinguishing such patients from those at intermediate risk [38]. Both schemes have been validated in a small Japanese cohort [42,43] and although more data are needed to confirm their utility in larger Asian populations [12], the most urgent priority is to encourage physicians to use contemporary risk assessment tools, which may then be refined in particular ethnic groups if necessary. Updated 2012 guidelines from the European Society of Cardiology (ESC) recommend using only CHA_2DS_2-VASc rather than $CHADS_2$ for assessing stroke risk, with no treatment rather than ASA for CHA_2DS_2-VASc = 0, oral anticoagulant rather than ASA for CHA_2DS_2-VASc = 1 and oral anticoagulants for CHA_2DS_2-VASc ≥2, with new direct Factor Xa inhibitors or thrombin inhibitors preferred over vitamin K antagonists (VKA) [44].

Bleeding is the major complication of anticoagulant therapy and the ESC also recommends routine assessment of bleeding risk using the HAS-BLED score [45] in all patients before commencing anticoagulation [2]. Crucially, high bleeding risk should not preclude anticoagulation; however, it may influence the choice of anticoagulant therapy and also highlights modifiable risk factors, such as hypertension and medication use, thereby providing an opportunity for interventions that may minimise the bleeding risk. Judicious use of these predictive scoring systems to balance a patient's risks of thrombosis versus bleeding and manage anticoagulation accordingly, is a key aspect of the current trend towards individualised AF therapy.

The escalating burdens of AF-related stroke in Asia make urgent action imperative to bridge existing gaps between guidelines for stroke prevention and current clinical practice. Given the rapidly changing AF treatment paradigm and as new pharmacotherapies become available,