

## Anticoagulation Needs in Asians with Atrial Fibrillation: A Mythbuster

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### Abstract

Atrial fibrillation (AF) has long been known to increase the risk of stroke. As a result, relevant international guidelines recommend that measures to reduce the risk of thrombus formation should be considered in all patients presenting with AF. Based on risk assessment scores, patients would then receive either thrombocyte aggregation inhibitors or oral anticoagulants. Despite this advice, compliance rates with the recommendations are poor across all countries surveyed. Evidence from the Global Anticoagulant Registry in the Field (GARFIELD) registry shows that major deviation from guidelines is due in large part to physicians' decision-making. In this brief narrative review, we address some of the frequent reasons cited by physicians why the guidelines are disregarded for Asian patients.

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**Key words:** Bleed, Elderly, Falls, Patient preference, Stroke prevention

### Introduction

Atrial fibrillation (AF) increases the risk of stroke 5-fold in Caucasians. While the relative risk for stroke is somewhat lower in Asia, estimated at 3.6% in Singapore,<sup>1</sup> total AF and stroke-associated mortality rates are reported to be similar.

The pathophysiology of stroke in patients with AF is usually multifactorial. However, cardiogenic embolism due to the lack of organised atrial contraction is ultimately the root cause. AF-associated stroke carries a heavy disease burden as more such patients become bedridden than patients whose stroke has a different underlying cause.<sup>2</sup>

Anticoagulation in AF has been known to reduce the incidence of stroke events since the early 1990s. The most recent international guidelines are those of the American College of Chest Physicians (ACCP, published in 2012), European Society of Cardiology (ESC, published in 2010 and updated in 2012), Canadian Cardiovascular Society (CCV, published in 2012) and by the American Academy of Neurology (AAN, 2014). Table 1 shows an overview

of current guidelines.

In Eastern Asia, the overall guidance follows that of Western societies. In fact, Chinese guidelines are translated from the American Heart Association guidance. Only the Japanese guidelines, which are not evidence- but consensus-based, give mildly different advice in that they recommend lower international normalised ratio (INR) targets of 1.6 to 2.6 in patients over 70 years of age.

To aid decision-making in the prescription of anticoagulation, several scoring tools have been developed. Of these, CHA<sub>2</sub>DS<sub>2</sub>-VASc<sup>3</sup> and HAS-BLED<sup>4</sup> are the currently recommended tools. There is no clear numerical evidence for balancing bleeding risk against the risk of stroke. The most recent ACCP guidelines have assessed evidence related to patients' preferences and recommend that a ratio of stroke versus gastrointestinal (GI) bleeding risk in the range of 2:1 to 3:1 should prompt the physician to recommend oral anticoagulation.

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Table 1. Current Guidelines on Anticoagulation in AF from America, Europe, and the Far East

Organisation	Year	Country	Reference
ACCP	2012	USA	Guyatt et al. <i>Chest</i> 2012;141:48S-52S
AHA	2011	USA	Goldstein et al. <i>Stroke</i> 2011;42:517-584
AAN	2014	USA	Culebras et al. <i>Neurology</i> 2014;82:716-724
CCVS	2012	Canada	Skanes et al. <i>Can J Cardiol</i> 2012;28:125-136
ESC/ESH	2012	EU	Camm et al. <i>Eur Heart J</i> 2012;33:2719-2747
China	2011	PRC	Anon. <i>Chinese J Neurol</i> 2011;44:282-286
JCS	2010	Japan	Group JCSJW. <i>Circ J</i> 2010;74:2479-2500
CRCS	2013	Korea	<a href="http://www.stroke-crc.or.kr">http://www.stroke-crc.or.kr</a>

ACCP: American College of Chest Physicians; AHA: American Heart Association; AAN: American Academy of Neurology; CCVS: Canadian Cardiovascular Society; ESC: European Society of Cardiology; ESH: European Society of Hypertension; JCS: Japanese Cardiology Society; CRCS: Clinical Research Centre for Stroke; AF: Atrial Fibrillation; USA: United States of America; EU: European Union; PRC: People's Republic of China

Until very recently, oral long-term anticoagulation was exclusively done using dicoumarol derivatives. Although the dicoumarol derivative warfarin reduces stroke risk by 65% in patients with non-valvular AF, its complex dose-response relationship, manifold food and drug interactions, regular blood monitoring requirements and risk of haemorrhage are serious disadvantages which may have contributed to the low rate of effective anticoagulation in patients with AF. With the recent approval of several new drugs, often referred to as the novel oral anticoagulants (NOACs), therapeutic options have increased. As of January 2014, 3 such drugs have been licensed in Singapore: dabitrigan, rivaroxaban and apixaban.

In Singapore, anticoagulation use in AF is “strongly recommended in most circumstances without reservations”, according to the Ministry of Health Clinical Pharmacy Guideline on Anticoagulation published in 2006. Regardless of this recommendation, a recent local study<sup>5</sup> showed that 40.7% of the study population (n = 1826) were discharged without any anticoagulation despite high thromboembolic risk. This is an international phenomenon, evident both in Western countries, and in the Far East.

The reasons for this are multifactorial. Physician's decision, patient's refusal, previous bleeding history are some of the common reasons stated for not choosing the appropriate anticoagulation therapy. However, it is striking that in a recent analysis of data from the GARFIELD registry, Kakkar et al noted that ineffective anticoagulation in 48% of the cases could be attributed to decisions made by physicians.<sup>6</sup>

This paper addresses some of the objections to anticoagulation therapy frequently voiced by physicians. The topical subheadings quote these as we typically encounter them in daily practice when we try to establish why our patients' anticoagulation is not in line with the available guidance. For each topic, we first reviewed the evidence provided in the guidelines cited above. We then submitted suitable search terms to PubMed and Google Scholar to look for relevant newer studies addressing these questions, as well as specifically looking for studies in patients with an Asian background. We present the information in the form of a narrative literature review.

### “This Patient is too Old for Anticoagulation”: Anticoagulation in Elderly Patients

“Old age” is often cited as a reason why physicians opt not to anticoagulate. In fact, however, the risk of stroke increases from 1.5% in patients aged 50 to 59 years to 23.5% in patients aged 80 to 89 years and is inversely correlated to the prognosis.<sup>7</sup>

Wolf et al, analysing data from the Framingham study, saw an incremental rise of AF as a main contributor to stroke in patients with increasing age.<sup>8</sup> Wolf's reports on the link between AF and stroke led to studies suggesting the use of warfarin to reduce stroke risk in patients with AF. While these early studies on the link between AF and stroke were conducted in Caucasian patients, the situation appears to be similar in Asian populations. In a prospective cohort of 302 stroke patients older than 80 years of age, Wang et al found the risk factors for stroke in very elderly Chinese to be similar to those reported in Western countries.<sup>9</sup> Similar prevalence is reported in Japan and Korea.

A recent meta-analysis showed that physicians are less likely to opt for anticoagulation therapy in patients over 70.<sup>10</sup> Several possible reasons for this decision have been cited.

Physicians often fear that elderly patients, who are frequently on poly-pharmacological treatments, cannot maintain therapeutic INR due to various interactions of medications and compliance issues. Yet the patients (mean age 83.9 years) studied in The Warfarin versus Aspirin for Stroke Prevention in Octogenarians with Atrial Fibrillation study (WASPO) achieved the therapeutic INR range in 69%, expressed as a percentage of time patients spent in the target INR range from 2.0 to 3.0.<sup>11</sup> Even taking into account the closer monitoring of study patients, WASPO emphasises that good quality anticoagulation control can be achieved in elderly patients receiving poly-pharmacological treatment and hence, age alone should not be the deciding factor as to whether effective anticoagulation control can be achieved.

Since the early 2000s, several studies have specifically looked at the safety of anticoagulation in the very elderly.

For instance,

- The Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA)<sup>12</sup> study assessed the annual risk of primary events of 973 elderly patients (mean age 81.5 years). The risk of primary events, which included ischaemic stroke, systemic embolus or intracranial haemorrhage, was lower for patients on warfarin as opposed to those on aspirin (1.8% of patients vs 3.8%). Warfarin efficacy was similar in elderly patients (aged  $\geq 85$  years) and younger patients.
- WASPO<sup>11</sup> showed that elderly patients (mean age 83.9 years) taking aspirin had more incidents of adverse events when compared to patients taking warfarin (33% of patients vs 6%,  $P = 0.002$ ).
- A large Italian study<sup>13</sup> specifically looked at bleeding risk in very old patients on vitamin K antagonists. In their population of 4093 patients with a median age of 84 years (range, 80 to 102 years) at the start of the study, major bleeding events were rare at 1.87 events per 100 patient years.

Physicians treating elderly patients tend to use anti-platelet agents such as aspirin, because of the perceived increased risk of bleeding associated with anticoagulation therapy. Contrary to this common perception, however, the risk of significant bleeding in patients receiving warfarin and aspirin is similar (1.5% vs 1.4%),<sup>14</sup> so that elderly patients would benefit most from anticoagulation.

Average life expectancy is predicted to increase over the next few years. But with an ageing population, the incidence of stroke too will increase and elderly patients, particular those with AF will eventually form the majority of stroke patients. This calls for urgent action as the prevalence of AF has been estimated to triple by the year 2050.<sup>15</sup>

#### **“My Patient is Likely to Bleed on Anticoagulation”: Risk of Haemorrhage**

Perhaps the most feared complication of anticoagulation therapy is intracranial haemorrhage. The absolute risk of warfarin-associated intracranial haemorrhage in AF patients is relatively low at 0.2% per year. A recent meta-analysis of 39 studies looked at major bleeding events as a function of indication for anticoagulation.<sup>16</sup> It concluded that no significant difference in bleeding rates could be found between contemporary indications AF, ischaemic heart disease, venous thromboembolism and prosthetic heart valves. The meta-analysis also showed that the rate of ICH increases by 9% every year of age ( $P = 0.0001$ ) in the patient population ( $n = 22,415$ ) but is increased by 72% with each 1.0-point increase in target INR. This emphasises the importance of anticoagulation within the target range.

A number of bleeding risk scoring tools exists, but they are often not pragmatic in clinical settings as they require access to a laboratory, money and time. Without taking recourse to established scoring systems, physicians tend to underestimate stroke risk by 22%, while they overestimate the bleeding risk by as much as 670%.<sup>17</sup>

The most readily available scoring tool is HAS-BLED.<sup>4</sup> It takes into account presence of hypertension, abnormal renal or liver function, history of stroke, history of bleeds in the past, labile INR, age (aged  $\geq 65$  years), drug history and alcohol use. A score of  $\geq 3$  would alert the physician to closely monitor patients. It is however not an absolute exclusion criterion from anticoagulation therapy.<sup>18</sup> Rather, physicians must ensure that the patients with HAS-BLED  $\geq 3$  are regularly monitored and that the target INR range is reached.

While intracranial haemorrhage is potentially fatal, both patients and physicians usually primarily think of GI haemorrhage when considering the risks of anticoagulation therapy. A recent meta-analysis looking at the increase of bleeding rates comparing aspirin with placebo showed an absolute increase of 0.12% per year. Use of warfarin along with other drugs does not further increase the bleeding risk. Direct comparison of monotherapy with warfarin versus aspirin showed no significant differences.<sup>19</sup>

#### **“My Patient Falls too Often to be Safely Put on Anticoagulation Therapy”: Anticoagulation and Falls**

Elderly patients who are thought to be likely to fall are often not started on anticoagulative therapy because of perceived risk of bleeding complications. The risk for anticoagulation related bleeds in falling patients cannot be measured in a controlled study. Hence, all published data are estimates. Based on a Markov decision analytic model to determine the ideal treatment for elderly patients with AF who are at increased risk of falling, a patient with an average risk of 5% of AF-associated stroke would be required to fall about 300 times per year for the risks of anticoagulation (intracranial bleeding) to outweigh the benefits. The most current available guidance by the AAN, published in 2014, thus advises not to withhold anticoagulation because of perceived risk of falls.

#### **“My Patient Does not Want Anticoagulation”: The Role of Adequate Education**

A study which investigated the impact of patient preference for anticoagulation treatment in AF showed that 47% of the 97 randomly selected AF patients (age range, 70 to 85 years) were not being prescribed warfarin by the physicians although they wanted to be on warfarin treatment.<sup>20</sup> It is important that physicians educate patients on the various

anticoagulant agents and explain the importance, the risks and the benefits of being on anticlot therapy.<sup>17</sup> Preliminary data from an ongoing study shows that 49% of the patients were unaware of the reasons why they were treated with either aspirin or anticoagulants.

The most recent ACCP guidelines have specifically addressed the issue of patient preferences. They found that most patients would regard a stroke versus bleeding risk ratio ranging from 3:1 to 2:1 as an argument to sway them towards anticoagulation, and recommends that physicians should take the same approach.

**Conclusion**

The perceived risks of anticoagulation are barriers, which hinder physicians from prescribing appropriate treatment to local patients. Table 2 lists the raised concerns and evidence refuting them. Anticoagulation therapy has proven to be beneficial to all patients with AF, and the benefit of adequate anticoagulation typically outweighs the risk. Anticoagulation is especially important in the elderly population as they have an increased risk of stroke due to AF. This would ultimately ensure that AF-associated strokes can be reduced with appropriate and effective use of anticoagulation.

Table 2. Summary of the Myths on Anticoagulation in Asians and Evidence Disputing such Myths

Myth	Evidence
“Patient is too old for anticoagulation.”	WASPO trial reports that 69% of patients (mean age, 83.9 years) achieved therapeutic INR range of 2.0 to 3.011. BAFTA trial reports that similar efficacy of warfarin was seen in elderly (aged > 85 years) and younger patients. <sup>12</sup> Poli et al showed bleeding events amongst elderly patients (with a median age of 84 years) were rare at 1.87 events per 100 patient years. <sup>13</sup>
“Patient is likely to bleed on anticoagulation.”	Hansen et al showed no significant differences in bleeding rates between warfarin monotherapy and aspirin monotherapy thus perhaps implying that warfarin is not more likely to cause bleeding. <sup>19</sup> Hansen et al also showed that incidence rate of GI bleeding on monotherapy is lower than for aspirin monotherapy. <sup>19</sup>
“My patient falls too often to be safely put on anticoagulation therapy.”	Markov decision model showed that with an average risk of 5% of AF-associated stroke, patients would be required to fall about 300 times a year for the risks of anticoagulation (i.e intracranial haemorrhage) to outweigh the benefits (AAN guideline 2014).
“My patient does not want anticoagulation.”	Protheroe et al showed that 47% of the 97 randomly selected AF patients (age range, 70 to 85 years) were not being prescribed warfarin by the physicians although they wanted to be on warfarin treatment. <sup>20</sup>

WASPO: Warfarin versus Aspirin for Stroke Prevention in Octogenarians with AF; BAFTA: Birmingham Atrial Fibrillation Treatment of the Aged; AAN: American Academy of Neurology; AF: Atrial fibrillation

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