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Age as a Risk Factor for Stroke in Atrial Fibrillation Patients: Implications in Thromboprophylaxis in the Era of Novel Oral Anticoagulants

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Abstract

Atrial fibrillation is associated with significant morbidity and mortality. There is a strong relationship between atrial fibrillation and aging, thromboembolism, stroke, congestive heart failure and hypertension. In addition, advanced age is a powerful risk factor for stroke and thromboembolism in patients with atrial fibrillation.

For many years, vitamin K antagonists were the only approved anticoagulants for the management of atrial fibrillation. Lately new anticoagulants made their appearance and large trials have already shown their superiority against vitamin K antagonists. Since the arrhythmia is encountered frequently in the elderly, it is crucial to identify the beneficial effects of the novel oral anticoagulants in this particular patient population.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia with an incidence markedly increasing with advanced age. The prevalence of AF is 2.3% in people older than 40 years and 5.9% in those older than 65 years. 10% of people over 80 years suffer from AF.[1] Epidemiological studies such as Framingham emphasized the strong and consistent association between the incidence of AF and age.[2]

Stroke and thromboembolism are major adverse events in patients with AF. The risk of ischemic stroke is 5-fold higher among patients with AF.[3] This risk is not consistent amongst various age groups. The elderly are at an increased risk of stroke even in the absence of AF. Previous studies and meta-analysis have shown that AF confers additional risk for stroke in elderly patients.[4]

This review article is an overview of the impact of age on the prognosis and managements of AF.

Key Words:
Atrial Fibrillation, age, stroke, systemic embolism, risk prediction

Disclosures:
Dr Lip has served as a consultant for Bayer, Astellas, Merck, Sanofi, BMS/Pfizer, Daiichi-Sankyo, Biotronik, Portola and Boehringer Ingelheim and has been on the speakers bureau for Bayer,BMS/Pfizer, Boehringer Ingelheim, and Sanofi Aventis

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Age as a Risk Factor for Stroke in Atrial Fibrillation

AF represents a major risk factor for stroke, systemic embolism and heart failure. Age is a well known independent and consistent risk factor for adverse outcomes in patients with AF. In the Framingham Study, the percentage of stroke attributable to AF increased steeply from 1.5% at 50–59 years of age to 23.5% at 80–89 years of age.[5]

More recent studies and 'real world' registries established advanced age as an independent risk factor for stroke.[6-10] For example, in a cohort of 409 patients with non-rheumatic AF, Stollberger et al identified age and previous stroke as the most powerful predictors of stroke/embolism on a multivariate analysis.[6] In the Stroke Prevention in Atrial Fibrillation I-III trials, a multivariate logistic regression analysis in 2012 participants given aspirin alone or in combination with low, inefficacious doses of warfarin, found age to be independently associated with increased stroke risk.[8] In a more recent meta analysis of the AF investigators, including 8932 patients and 17 685 years of observation from 12 randomized trials on stroke prevention in AF, patients' age significantly increased the risk of ischemic stroke (adjusted hazard ratio [HR] per decade increase 1.45; 95% confidence interval (CI) 1.26 to 1.66).[10] However one study failed to confirm age as an independent risk factor for stroke in AF.[11]

Age and Stroke Risk Prediction Schemes

Multiple risk stratification schemes have been proposed to assist with stroke risk estimation in patients with non-valvular AF. Despite the substantial differences among them comorbidities such as

Table 1: Risk of stroke and (a) CHADS2 and (b) CHA2DS2VASc score

a.	CHADS2 score	Adjusted stroke rate (% year)1
	0	1.9 (1.2-3.0)
	1	2.8 (2.0-3.8)
	2	4.0 (3.1-5.1)
	3	5.9 (4.6-7.3)
	4	8.5 (6.3-11.1)
	5	12.5 (8.2-17.5)
	6	18.2 (10.5-27.4)
b.	CHA2DS2-VASc score	Stroke and thromboembolism event rate at 1 year follow up (%)[2]
	0	0.78
	1	2.01
	2	3.71
	3	5.92
	4	9.27
	5	15.26
	6	19.74
	7	21.50
	8	22.38
	9	23.64

previous stroke/TIA, age, hypertension and diabetes are consistently included features.[12] Age ≥75 years is the most commonly used cut off point when age is introduced as a dichotomous variable in the schemes

In the $CHADS_2$ [cardiac failure, hypertension, age, diabetes, stroke (doubled)] score and NICE (National Institute for Health and Care Excellence) guidelines the significant role of age>75years as a risk factor for stroke in AF is well appreciated.[13,14] Nevertheless, stroke risk in AF is a continuum; and so is the impact of age on individual's risk. Thus, the latest European Society of Cardiology (ESC) guidelines proposed the use of the CHA_2DS_2-VASc [cardiac failure, hypertension, age≥75 years(doubled), diabetes, stroke (doubled)-vascular disease, age 65-74 and sex category (female)] score for risk stratification of patients with AF.[3] In the CHA_2DS_2-VASc score, age 65-74 adds one point in the score and age ≥75 adds two points and classifies a patient at high risk for stroke, even in the absence of other risk factors (Table 1). CHA_2DS_2-VASc includes more clinically relevant variables compared to older schemes, but it is still limited by lack of consideration of important factors such as frailty, cognitive and functional decline, or adherence to therapy. [15,16]

Age as a Risk Factor for Bleeding in Patients with Atrial Fibrillation

Age also represents an important well established risk factor for major hemorrhage in patients on antithrombotic therapy. From a meta-analysis of the Atrial Fibrillation Investigators database contained data from 12 trials, advanced age increased the risk of serious bleeding (HR 1.61; 95% CI 1.47 to 1.77). Compared with placebo, oral anticoagulation increased the risk of serious bleeding by more than 50% (HR 1.56; 95% CI 1.03 to 2.37) in these older trials.[10]

The HAS-BLED [(hypertension, abnormal liver/renal function (1 point each), stroke, bleeding history or predisposition, labile INR, elderly (>65), drugs/alcohol concomitantly (1 point each)] score (Table 2) was developed to identify AF patients of greater bleeding risk. This calculates bleeding risk using 9 clinical variables including age (as a dichotomous variable). A HAS-BLED score ≥3 indicates high risk and a need for careful review and follow up, as well as to address correctable bleeding risk factors, namely uncontrolled blood pressure (the H in HAS-BLED), labile INRs if on warfarin (the L in HAS-BLED) and concomitant medication (the D in HAS-BLED).[17]

Eventhough elderly people are more prone to bleeding when on anticoagulation therapy, an INR target below 2.0 does not preclude bleeding nor offers adequate protection from thrombotic events.[1718,1819] Moderate anticoagulation (2.0-3.0 INRs), with a high (individual) average time in therapeutic range (TTR, eg >70%) in elderly patients with AF seems to be the safest approach.[20,21]

Falls have been a major concern when oral anticoagulation is considered for elderly patients. This was based on the assumption that elderly are more prone to falls and thus more prone to post-traumatic bleeding. Nevertheless, the only study that prospectively investigated the impact of falls on the outcome of patients on oral anticoagulation concluded that patients at high risk of falls did not have a significantly increased risk of major bleeds. The authors concluded that being at risk of falls is not a valid reason to avoid oral anticoagulants in medical patients, eventhougheven though the need for further research is warranted.[21,22]

Age and Stroke Prevention in Atrial Fibrillation: Vitamin K Antagonists

Data based on historical randomized controlled trials demonstrated that oral anticoagulation significantly reduces the risk of ischemic strokes and all cause mortality compared with placebo in all age groups.[10] Anticoagulants have been also proven more effective than antiplatelet agents at reducing stroke risk in AF patients. Nevertheless, whether this benefit outweighs the increased risk of bleeding in elderly patients was uncertain until recently.

The HAS-BLED [(hypertension, abnormal liver/renal function (1 point each), stroke, bleeding history or predisposition, labile INR, elderly (>65), drugs/alcohol concomitantly (1 point each)] score (Table 2) was developed to identify AF patients of greater bleeding risk. This calculates bleeding risk using 9 clinical variables including age (as a dichotomous variable). A HAS-BLED score ≥3 indicates high

Table 2: Clinical characteristics comprising the HAS-BLED bleeding risk score.

Letter	Clinical characteristic	Points awarded
H	Hypertension (ie uncontrolled blood pressure)	1
A	Abnormal liver or kidney function	1 or 2
S	Stroke	1
B	Bleeding tendency or predisposition	1
L	Labile INRs	1
E	Elderly (age>65yrs, frail condition)	1
D	Drugs (eg. aspirin or NSAID concomitantly) or alcohol excess/abuse (1 point each)	1 or 2
		Maximum 9 points

risk and a need for careful review and follow up, as well as to address correctable bleeding risk factors, namely uncontrolled blood pressure (the H in HAS-BLED), labile INRs if on warfarin (the L in HAS-BLED) and concomitant medication (the D in HAS-BLED).[17]

More recent data underlined the observations from the BAFTA (Birmingham Atrial Fibrillation Treatment of the Aged) investigators. For example, Singer et al reported results from the ATRIA (An-Ticoagulation and Risk factors in Atrial fibrillation) registry showing that the adjusted net clinical benefit of warfarin was greatest for patients 85 years or older (2.34% per year; CI 1.29% to 3.30%).[25]

In addition, the small WASPO (Warfarin versus Aspirin for Stroke Prevention in Octagenarians with AF) trial revealed that dose-adjusted warfarin was significantly better tolerated with fewer adverse events (including bleeding) compared to aspirin 300 mg in a study of octogenarians with AF - although aspirin 75 mg may had been better tolerated, there has been no evidence for efficacy in AF at this dose although this trial was too small and underpowered for thromboembolic endpoints.[26]

In 2009, the Atrial Fibrillation Investigators database reported the effect of age on the relative efficacy of oral anticoagulant and antiplatelet therapy on ischemic stroke, serious bleeding, and vascular events in patients with AF. The study concluded that as age advanced, the relative efficacy of antiplatelets to prevent ischemic stroke decreased, whereas it does not change for oral anticoagulants. So the absolute benefit of oral anticoagulants increases as patients get older, as stroke risk increases with age. Neither oral anticoagulation nor antiplatelet treatment interacted significantly with patients age for either serious hemorrhage or cardiovascular events. This analysis modeled patients age as a continuous variable rather than arbitrary cutting patient age at 75 years.[10] These results are in agreement with more recent data from the ATRIA registry.[27]

Utilization of Oral Anticoagulation in Elderly Patients with AF

It is well established that AF is associated with significant morbidity and mortality and large randomized controlled trials have already demonstrated that long-term oral anticoagulation therapy can reduce the risk of stroke by approximately 64% per year in patients with nonvalvular AF. Nevertheless only 15% to 44% of AF patients at risk of stroke are prescribed warfarin. This clinical evidence-clinical practice gap is more pronounced in advanced age groups; so that elderly people with AF are less likely to receive OAC therapy.

Why is this so? This is mostly due to the fact that the risk for major bleeding is also increased in advanced age.[28] Moreover elderly people with AF more commonly present with comorbidities associated with increased risk for major hemorrhage. The risk for hemorrhagic events seems to be greater in the first three months in patients newly initiated on warfarin. Even though crucial, optimal INR control is most of the times not feasible in advanced age. Advanced age is known to be a barrier to anticoagulation therapy. Even physicians who decide to prescribe anticoagulation therapy for older patients, aim for a lower intensity than the one established by the literature [29] Polypharmacy in the elderly also contributes to low utilization of oral anticoagulant therapy and suboptimal compliance.[30,31,32]

Whilst the elderly may have an increased risk of major bleeding, the absolute gain in stroke reduction with OAC in most elderly patients with AF would outweigh the small absolute increase in serious bleeding by OAC.[10]

Age and Stroke Prevention in Atrial Fibrillation: New Oral Anticoagulants

Until recently, vitamin K antagonists such as warfarin were the only available OACs for stroke prevention in patients with AF. The advent of new OACs gave hope for a more effective management of patients with AF. They can be administered in fixed doses and are characterized by few food or drugs interactions, simplifying the long-term therapy.[33] There is still need of monitoring and follow-up of patients on new OACs as contraindications to new OACs might develop or their dose might require adjustment. Renal impairment and concomitant medication should be regularly assessed in patients on new OACs. Table 3 presents phase III completed or ongoing trials with new oral anticoagulants, with emphasis on the interaction of efficacy and safety with regard to age.[34]

In the RE-LY trial (Randomized Evaluation of Long-term anticoagulant therapY with dabigatran etexilate) , which included 18111 patients aged 71.5±8.7 years, dabigatran, an oral direct thrombin inhibitor, given at a dose of 110 mg bid was associated with rates of stroke and systemic embolism similar to those associated with warfarin, as well as 20% lower rates of major hemorrhage. With the higher dose of 150 mg bid, dabigatran was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage. The study did not report any significant interactions between treatment efficacy and age.[35] A sub-analysis of the RE-LY data demonstrated that both doses of dabigatran compared with warfarin had lower risks of both intracranial and extracranial bleeding in patients aged <75 years, but in those aged ≥75 years, intracranial bleeding risk was lower but extracranial bleeding risk was slighly higher with the 150mg bid dose of dabigatran compared with warfarin.[36] Thus, there was an important age interaction for major bleeding in the RE-LY trial.

Rivaroxaban, an oral factor Xa inhibitor, when tested in 14264 patients with a median age 73 (interquartile range [IQR] age 65-78) years at a dose of 20mg once daily was non-inferior to warfarin for the primary end point of stroke and systemic embolism. Rivaroxaban did not reduce mortality and ischaemic stroke, but reduced significantly hemorrhagic stroke and intracranial bleeding. Even though rivaroxaban reduced significantly fatal bleeding, gastrointestinal bleeding and bleeding requiring transfusion increased.[37] In 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), elderly AF patients were well represented as 43% of the study population was ≥75 years. No significant interaction between rivaroxaban's efficacy or safety and age was present in the ROCKET-AF trial (Table 3).

Apixaban is an oral Xa inhibitor that has already demonstrated its superiority towards warfarin. The ARISTOTLE trial (Apixaban versus Warfarin in Patients with Atrial Fibrillation) compared apixaban with dose adjusted dose warfarin in a cohort of 18201 patients with a median age 70 (IQR 63-76) years. Apixaban reduced the primary efficacy endpoint of stroke or systemic embolism by 21% compared with warfarin. Apixaban further reduced major bleeding by 31% and all cause mortality by 11%. Eventhough gastrointestinal bleeding was

Table :3 Landmark studies on new oral anticoagulants in stroke prevention in atrial fibrillation

Study	n	Primary outcomes		Event rates (per 100 patient years)			Age interaction
				Age group	VKA or ASA	NOAC	
RE-LY [31, 32]	18113	Efficacy	Stroke and SE	Event rates not reported			No interaction reported
			Major bleeding	<65	2.43	0.82	p=0.0003
			110mg bid	65-74	3.25	2.29	
		Safety		≥75	4.37	4.43	
				<65	2.43	0.89	p=0.0001
			150mg bid	65-74	3.25	2.6	
				≥75	4.37	5.1	
ROCKET-AF [33]	14264	Efficacy	Stroke and SE	<75	3.7	3.6	No interaction
				≥75	5	4.06	
		Safety	Major and non major	<65	15.83	14.64	No interaction
			clinically relevant	65-74	19.99	19.48	
			bleeding	≥75	23.43	25.78	
ARISTOTLE [34]	18201	Efficacy	Stroke and SE	<65	0.9	1.0	No interaction
				65-74	1.7	1.3	
				≥75	2.2	1.6	
		Safety	Major bleeding	<65	1.5	1.2	No interaction
				65-74	2.8	2	
				≥75	5.2	3.3	
AVERROES [35]	5599	Efficacy	Stroke and SE	<65	2	0.7	No interaction
				65-74	2.7	2	
				≥75	6.1	2	
		Safety	Major bleeding	<65	0.5	0.7	No interaction
				65-74	1	0.9	
				≥75	2.2	2.6	
ENGAGE-AF [36]	20500	Efficacy	Stroke and SE				Ongoing study
		Safety	Major bleeding				

similar for patients treated with apixaban and warfarin, the rate of intracranial hemorrhage and hemorrhagic stroke was significantly lower in the apixaban group. The ARISTOTLE population was younger than the ROCKET AF population and patients above 75 years represented 31% of the cohort. The ARISTOTLE investigators did not report a significant interaction between age groups and either apixaban's efficacy or safety.[38] In the AVERROES trial (Apixaban versus Acetylsalicylic Acid to Prevent Strokes), apixaban was tested against aspirin in 5599 patients with AF who were at increased risk for stroke and for whom vitamin K antagonist therapy was considered unsuitable. There was no significant interaction between age and apixaban's efficacy or safety compared to aspirin.[39] The results of the another ongoing Phase 3 clinical trial testing the oral Factor Xa inhibitor, edoxaban against warfarin, are awaited.[40]

Newer anticoagulants have established their superiority against warfarin in reducing rates of stroke in clinical trials. Time will tell if this is so in a real world population.[41-44] Nevertheless, all landmark trials were not designed to assess net clinical benefit in age subgroups and they are unlikely to be sufficiently powered to detect differences in these populations. Thus, all post-hoc analysis should be interpreted with caution. It is obvious from the sub-analysis of the RE-LY that bleeding risk differs among age groups and caution is recommended when new agents are prescribed in the elderly.[36]

Furthermore, practical aspects of the everyday use of these new OACs should be considered. Given that these drugs do not have a specific antidote, management of life threatening bleeding is problematic. This limitation is partially counterbalance by their short half-life which in turn makes compliance an important issue as missing a dose exposes the patient to thromboembolic risk. [42-44] Post marketing surveillance data are required to evaluate the long term safety of new oral anticoagulants in the elderly. The net clinical benefit of these drugs generally seems in favor for its widespread use.[45,46]

Conclusions:

Age has an independent effect on the stroke risk, with age ≥75years being recognized as a strong risk factor. It is well established that elderly AF patients will receive the greater net clinical benefit from oral anticoagulants considering the greater stroke risk. Careful prescription of oral anticoagulation after careful stroke and bleeding risk stratification and tight control of INR levels is strongly advised for elderly AF patients. One challenge is how to identify those elderly patients who could potentially do well if started on warfarin, with a high percentage time in therapeutic range (rather than need a novel oral anticoagulant). The new SAMe-TT2R2 score could help here, by predicting those who could potentially do well on warfarin (SAMe-TT2R2 score 0-1) or alternatively, those who are likely to have poor anticoagulation control if warfarin is used (SAMe-TT2R2 score ≥2) where a novel oral anticoagulant could be a better treatment option [47]. Age has an independent effect on the stroke risk, with age ≥75years being recognized as a strong risk factor. It is well established that elderly AF patients will receive the greater net clinical benefit from oral anticoagulants considering the greater stroke risk. Careful prescription of oral anticoagulation after careful stroke and bleeding risk stratification and tight control of INR levels is strongly advised for elderly AF patients. In several instances age per se might be a misleading risk factor and additional parameters such as comorbidities, frailty, and cognitive faction should be considered. Despite the more stable pharmacokinetic profile and fewer inherent problems than warfarin, the net clinical benefit of novel oral anticoagulants in elderly AF patients will require further evaluation in real world practice.

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