

Anticoagulation in Patients Aged ≥ 75 years with Atrial Fibrillation: Role of Novel Oral Anticoagulants

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ABSTRACT

Atrial fibrillation (AF) is an important cause of preventable, disabling stroke and is increasingly prevalent with advancing age. As life expectancies increase around the world, AF-related stroke is a growing global public health concern. Most AF patients are elderly (≥ 75 years old) and increasing age is a consistent independent risk factor for AF-associated stroke. Warfarin anticoagulation is highly effective for stroke prevention in AF patients, but is underutilized especially in the elderly. Although elderly patients are at increased risk of hemorrhage with oral anticoagulants, the benefit for ischemic stroke reduction exceeds

the risk of hemorrhage for most elderly patients. Consequently, age alone should not be considered a contraindication for anticoagulation. Novel oral anticoagulants such as dabigatran, rivaroxaban and apixaban are at least as effective as warfarin in preventing strokes in patients with AF. Relative to warfarin, these novel agents reduce the risk of intracranial hemorrhage, the most devastating complication of anticoagulation therapy in elderly AF patients. The novel oral anticoagulants are especially appealing for stroke prevention in elderly patients with AF.

Keywords: Age; Anticoagulation; Apixaban; AF; Bleeding; Dabigatran; Novel oral anticoagulants; Rivaroxaban; Stroke; Stroke prevention; Warfarin

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INTRODUCTION

Atrial fibrillation (AF) is a major risk factor for disabling ischemic stroke due to embolism from the left atrial appendage. The prevalence of AF increases with increasing age (Fig. 1) [1]. The true prevalence of AF is difficult to assess, as

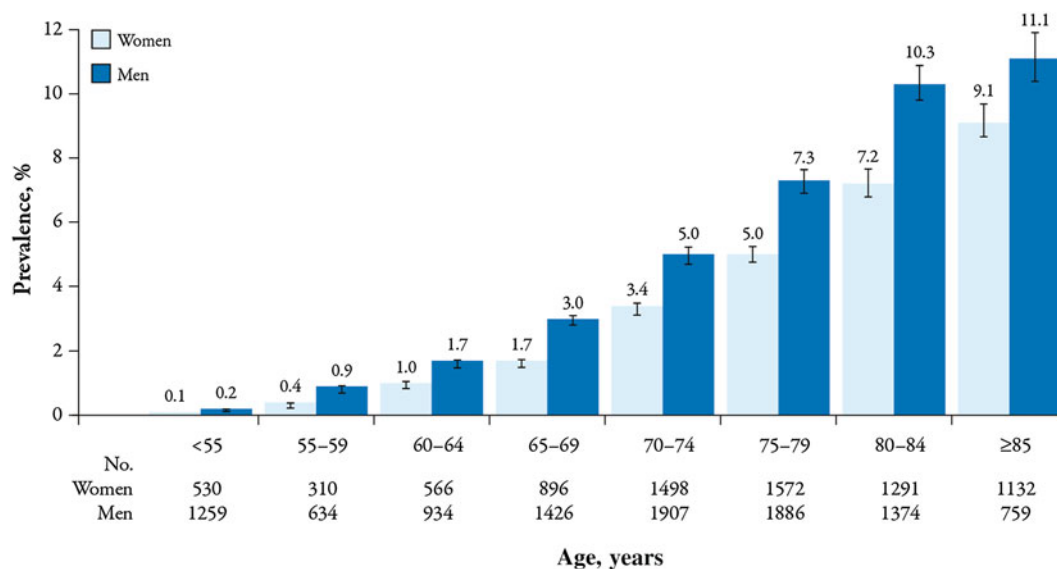


Fig. 1 Prevalence of AF with increasing age [1]. Error bars indicate 95% confidence intervals. Numbers indicate number of men and women with atrial fibrillation in each category. Adapted from Go et al. [1]

a significant proportion of patients will be asymptomatic or have subclinical disease; however, it is estimated that at least 10% of elderly people (≥ 75 years old) have AF [2] and 56% of people with the condition are elderly [3, 4]. The influence of AF on health increases with age, and 71% of strokes that occur in patients with AF are in those aged over 70 years [5]. The outcome of patients following stroke due to AF is worse, on average, compared with non-AF-related strokes [6].

Antiplatelet agents and oral anticoagulants are effective in reducing the risk of stroke in AF patients, with oral anticoagulants being more effective in reducing the risk of ischemic strokes than antiplatelet agents [7]. However, increasing age is associated with underutilization of warfarin [8]. Clinical data on elderly patients are limited as they are often underrepresented in randomized controlled trials (RCTs). Furthermore, older patients have an increased risk of hemorrhage and often have

multiple comorbidities including chronic kidney disease (CKD), anemia, hypertension, diabetes and an increased risk of falls.

In recent years, novel selective oral anticoagulants have become available. All undergo substantial renal excretion [9], but are at least as effective as adjusted-dose warfarin in reducing the risk of stroke. They are also associated with a decreased risk of intracranial hemorrhage in patients with AF [10–12]. While it is likely that the new generation of novel oral anticoagulants will eventually replace warfarin, the role of these agents in the elderly remains to be fully defined. This review examines the use of novel oral anticoagulants in patients aged ≥ 75 years with AF, focusing on information from randomized trials. In addition, the relationship between age, AF and stroke risk, as well as the current evidence for oral anticoagulants and antiplatelet agents for stroke prevention in the elderly, will be considered.

METHODS

This review article incorporates data from observational studies, review articles, available guidelines and RCTs on the use of anticoagulants and antiplatelet agents for stroke prevention in elderly patients. Relevant literature was obtained with a MEDLINE search. The literature was chosen based on their inclusion and influence on current practice.

DISCUSSION

Age and AF

AF is the most common clinically significant arrhythmia and is associated with significant mortality and morbidity [13]. The number of patients with AF is forecast to increase as will the proportion of elderly patients [1]. Adjusting for age, risk factors for AF include valvular heart disease, congestive heart failure, diabetes and hypertension, all of which are more common in the elderly.

AF independently increases stroke risk by fivefold in the general population and accounts for a greater proportion of strokes with increasing age [5]. The risk of thromboembolism in AF increases sharply with age over 65 years, with the relative risk increasing approximately 1.45-fold per decade [7]. Age is a strong and consistent predictor of stroke in patients with AF and is included in all stroke risk stratification schemes for AF [14, 15]. While increasing age as a risk factor for AF and stroke is continuous, age ≥ 75 years is arbitrarily used to dichotomize risk in cohort analyses and systematic reviews [16].

Other independent risk factors for stroke include previous transient ischemic attacks or stroke, heart failure, hypertension and diabetes.

The Congestive cardiac failure, Hypertension, Age ≥ 75 , Diabetes and previous Stroke or transient ischemic attack (CHADS₂) score is a simple, commonly used stroke risk stratification scheme for patients with AF [17]. It was developed by incorporating the Stroke Prevention in AF (SPAF) and AF Investigators (AFI) risk schemes and was validated in a cohort of patients with AF admitted to hospital [18–20] (Table 1). Most guidelines now recommend the use of vitamin K antagonists in patients with a CHADS₂ score of 1 or greater. However, the recommendations have to be balanced against the risk of hemorrhage, which is higher during anticoagulation in the elderly.

Table 1 Comparison of CHADS₂ and HAS-BLED scores [18–20]

CHADS ₂ score		HAS-BLED score	
Congestive heart failure	1	Hypertension	1
		Age >65 years	1
Hypertension	1	Stroke	1
Age >75 years	1	Bleeding history	1
Diabetes	1	Labile INRs	1
Previous stroke	2	Drugs or ethanol abuse	1 each
		Abnormal renal or liver dysfunction	1 each
Score	Risk of stroke (%/year)	Score	Risk of hemorrhage (%/year)
0	1.9	0	1.13
1	2.8	1	1.02
2	4.0	2	1.88
3	5.9	3	3.74
4	8.5	4	8.70
5	12.50	5	12.50
6	18.2	6–9	>12.5

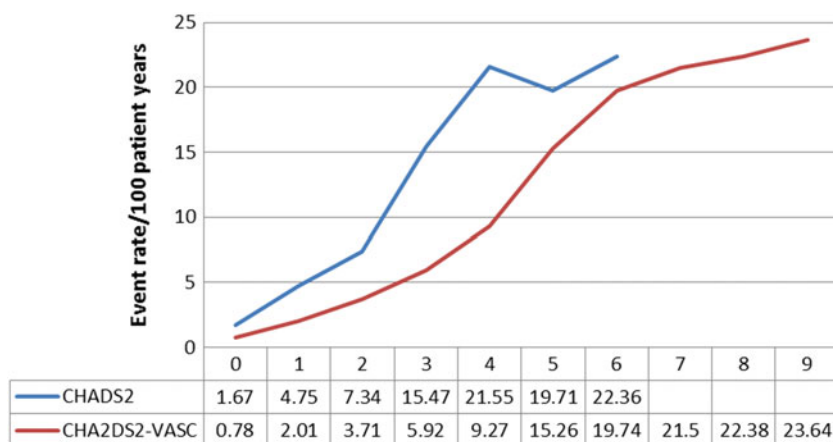


Fig. 2 Comparative rate of death, stroke and systemic embolism between CHADS₂ versus CHA₂DS₂-VASc [15, 22]

The Congestive cardiac failure, Hypertension, Age ≥ 75 , Diabetes and previous Stroke or transient ischemic attack, Vascular disease, Age 65–74 and Sex score (CHA₂DS₂-VASc) has been proposed as an improvement over CHADS₂, specifically for stratifying risk in patients under the age of 75 years, who do not have any of the CHADS₂ risk factors for stroke [21, 22]. In addition to the risk factors identified in the CHADS₂ score, CHA₂DS₂-VASc incorporates one point each for sex, history of vascular disease and age ≥ 65 years. Age ≥ 75 years will incur an extra point.

Female sex is incorporated into CHA₂DS₂-VASc as an independent predictor of stroke in AF despite the absence of a clear biologically plausible explanation for the underlying etiology. Large differences in stroke risk between the sexes were noted in the AFI meta-analysis in 1990 [23] and were consistent with large observational studies [24–26]. The difference in stroke risk between the sexes was greatest with increasing age. Elderly women had a significantly higher risk of stroke compared with similarly aged men [24].

The additional components within CHA₂DS₂-VASc compared with CHADS₂ was

shown to improve discrimination in patients with a CHADS₂ score of 1 by identifying patients aged < 75 years with sufficiently low absolute stroke risk who may not be expected to benefit from anticoagulant therapy [15, 22] (Fig. 2). Conversely, all patients aged ≥ 75 years would be considered for anticoagulation, as the additional point for older age would give a CHA₂DS₂-VASc score of at least 2 [27, 28].

Renal function declines gradually with age and CKD is common in patients with AF. One-third of all outpatients with AF and over 50% of elderly patients with AF have CKD (estimated glomerular filtration rate (eGFR) < 60 ml/min) [29, 30]. CKD is an independent predictor of stroke risk in patients with AF (HR 1.5) [29, 31, 32] and the impact of Stage 3 CKD on stroke risk is similar to other predictors used in the CHADS₂ score [14]. However, the precise mechanisms underlying increased stroke risk in CKD are unclear and have not been incorporated into any of the commonly used risk stratification scores. There are less data stratifying stroke risk in Stage 4 CKD and end stage renal failure, but AF remains an independent risk factor for ischemic stroke [33].

Warfarin in Elderly Patients with AF

Most ischemic strokes in patients with AF are due to cardiogenic embolism from thrombi originating from the left atrial appendage; however, up to 25% of cases may be caused by intrinsic small vessel cerebrovascular disease with co-existing vascular risk factors such as coronary artery disease, hypertension and diabetes [34]. Aspirin appears to exert most of its effect via prevention of non-cardiogenic embolic events, while warfarin is far superior to aspirin in preventing cardio-embolic ischemic strokes [34]. At most, aspirin reduces the relative risk of stroke by about 25% in patients with AF. Most of the reduction in stroke risk with aspirin leads to a reduction in transient ischemic attacks and non-disabling strokes [35]. Dose-adjusted warfarin reduces the relative risk of stroke by about 60% in patients with AF compared with placebo [3, 28, 36]. With increasing age, the benefit of aspirin in preventing stroke decreases and appears to be ineffectual when patients enter their eighth decade, whereas the risk reduction derived from warfarin anticoagulation is preserved with age [7].

The most serious side effect of warfarin is bleeding, including intracranial bleeding. Age is an independent risk factor for bleeding on anticoagulant therapy [37, 38] and warfarin is associated with an increased risk of bleeding compared with aspirin therapy (HR 1.71) [39]. The absolute risk reduction of all strokes and cardiovascular events is not substantially offset by the proportionally smaller increased risk of hemorrhage in the general population. Elderly patients are likely to derive the greatest benefit from warfarin therapy, but have the highest risk of hemorrhage. Elderly patients are underrepresented in most RCTs assessing the use of warfarin in AF, with patients aged

≥ 75 years representing only 20% of patients in most RCTs involving oral anticoagulants in AF [40]. The exception is the Birmingham AF Trial in the Aged (BAFTA), which was restricted to AF patients ≥ 75 years old with no contraindications to hemorrhage. BAFTA participants were randomized to warfarin versus aspirin, and there was no increased risk of major hemorrhage with anticoagulation. The rates of hemorrhage in BAFTA were lower when compared with a previous subgroup meta-analysis of anticoagulation in patients aged ≥ 75 years. 40% of patients in BAFTA had already been established on warfarin and probably underestimated bleeding risk compared with warfarin-naïve patients [41].

Prediction of Hemorrhage in Elderly Patients on Warfarin

Several risk stratification scores have been developed to help predict hemorrhage during warfarin anticoagulation. The Hypertension, Abnormal liver/renal function, Stroke, Bleeding history or disposition, Labile International Normalized Ratio, Elderly, Drugs/alcohol (HAS-BLED) score has been incorporated in European and Canadian guidelines on the management of patients with AF [19, 20]. The score is relatively easy to use and provided modest predictive value for major hemorrhage in patients on oral anticoagulants (C-statistic 0.69) in the Euro Heart Survey cohort [42]. However, HAS-BLED requires validation in other patient populations such as the elderly before it is adopted universally. Other bleeding risk prediction scores for warfarin anticoagulation have been proposed, but none have been adequately validated in our view [38, 43]. Many of the factors that predict hemorrhage in these risk prediction scores are also risk factors for stroke.

Therefore, the use of risk stratification scores in elderly patients with AF is likely to be limited as a result (Table 1).

Based on CHA₂DS₂-VASc risk factors, men with no hypertension, diabetes or prior stroke but who had AF in the SPAF trials were at the lowest risk of stroke while on aspirin therapy, with a stroke rate of 1.6%/year (95% CI 0.7–3.9) [7]. Men aged ≥ 75 years participating in BAFTA and without other CHA₂DS₂-VASc risk factors had a stroke rate of 2.1%/year (95% CI 0.77–4.6) during aspirin therapy [27]. The margin of error for these rates is wide and includes rates that would warrant anticoagulation. Elderly women with AF carry a higher risk of stroke than elderly men [28]. It is unclear whether patients aged ≥ 75 years with AF who are at low risk can be reliably identified.

Randomized Trials Comparing Warfarin Versus Aspirin in Patients with AF Aged ≥ 75 years

A meta-analysis of randomized trials, including 29 trials involving 28,044 patients with a mean age of 71 years, confirmed the superiority of warfarin over anti-platelet agents in reducing

stroke risk. The absolute increase in major extracranial hemorrhage on warfarin compared with aspirin was overshadowed by the absolute reduction in stroke risk in patients with AF [44]. However, only 2,680 (10%) participants in these randomized trials were ≥ 75 years old despite the fact that most patients with AF were within this age group. However, based on the AFI pooled meta-analysis from six trials [39] and the results of BAFTA [45], it is clear that warfarin anticoagulation reduces the risk of stroke to a greater extent than aspirin in elderly patients with AF (Table 2) [46, 47].

In BAFTA, elderly patients on oral anticoagulants had a 52% relative risk reduction in all strokes or systemic embolism compared with aspirin and had no significant increase in intracranial or extracranial hemorrhage [45]. The risk of major hemorrhage was lower than that noted in the AFI pooled meta-analysis [39]. This may be explained by the use of a contemporary International Normalized Ratio (INR) target range of 2–3. In addition, 40% of patients in BAFTA were not warfarin naïve and were already established on warfarin prior to enrollment compared with the warfarin-naïve

Table 2 Absolute stroke rate in AF patients ≥ 75 years old and effect of anticoagulation

Trial	<i>N</i> , aspirin	Stroke rate on aspirin (%/year)	Anticoagulant	Relative risk reduction by anticoagulant	NNT for 1 year
AF Investigators (2002) [39]	855	5.9%/year ^a	Warfarin	0.37 [#]	46
BAFTA (2007) [45]	485	4.9%/year	Warfarin	0.52 [#]	40
ACTIVE A (2009) [46]	~1,550	4.4%/year	NA	NA	NA
AVERROES (2011) [47]	~950	6.1%/year	Apixaban	0.67 [#]	24

N number of participants, *NNT* number needed to treat, *NA* not applicable

In addition, the observational cohort ATRIA study reported an ischemic stroke rate of 3.2%/year among 2,313 AF patients ≥ 75 years who were not taking warfarin [1]

^a Restricted to ischemic strokes

[#] Statistically significant reduction with *p* value <0.05

cohorts in the other studies included in the AFI pooled meta-analysis. This observation is supported by other recent warfarin inception studies in which elderly patients had an increased risk of hemorrhage in the first year of treatment [41, 48]. Once established on treatment and monitored closely, warfarin is safe in elderly patients with AF.

Current guidelines support the use of oral anticoagulation therapy in all patients ≥ 75 years for the prevention of ischemic stroke [3, 28]. Despite this, the uptake of oral anticoagulants among patients ≥ 75 years remains low. In our view, all patients with AF ≥ 75 years old (and especially women) should be considered for anticoagulation prophylaxis to prevent stroke in the absence of any clear contraindications, provided it can be initiated and monitored safely [7]. From the data summarized above, the risk of stroke for these patients is sufficiently high and the efficacy of warfarin is established.

Challenges with Warfarin Anticoagulation in Elderly Patients with AF

While all patients aged ≥ 75 years should be considered for warfarin anticoagulation, the decision to prescribe warfarin for an individual patient should take into consideration risk of stroke versus hemorrhage, practicalities for monitoring anticoagulation and patient preference [49, 50]. Furthermore, patients with AF aged ≥ 75 years are more likely to experience significant co-morbidities on multiple medications.

Time in Therapeutic Range on Warfarin Anticoagulation

Limitations of vitamin K antagonists for stroke prevention include their narrow therapeutic window, which requires regular blood

monitoring for assessment of INR and dosage adjustments. The optimal therapeutic range for anticoagulation with warfarin in non-valvular AF is between 2 and 3. Higher intensity anticoagulation with INRs of greater than 3 are associated with double the risk of intracranial hemorrhage compared with patients who are not on warfarin [51–53]. The risk of intra-cerebral hemorrhage is higher with advancing age [54]. Conversely, a target INR of less than 2 confers no further reduction in hemorrhage risk compared with an INR of 2–3 [52]. Attaining an INR >2 is associated with not just lower risk of stroke, but also reduced stroke severity and fewer deaths [51].

Older patients are more sensitive to warfarin and require lower dosages to achieve a target INR range [55]. In addition, older patients are more likely to be on multiple medications with frequent INR fluctuations due to ill health, poor diet and issues with compliance, which may ultimately result in less time within the therapeutic INR range compared with younger patients. Closer monitoring of anticoagulation may be merited in elderly patients. The highest risk of major bleeding during warfarin anticoagulation is in the first 12 months after treatment initiation. Subsequently, warfarin-experienced patients are at lower risk of hemorrhage and stroke compared with warfarin-naïve patients [45].

Risk of Falls

Other risk factors for intracranial hemorrhage in the elderly are an increased risk of falls and associated neuropsychiatric disease [38, 56]. Risk of falls and intra-cerebral hemorrhage with warfarin are often quoted as a reason to avoid anticoagulation. However, if a patient has a 5% annual risk of stroke from AF, it has been estimated that the patient would need to fall over 295 times to offset the benefit of oral

anticoagulants [57]. The association between intracranial hemorrhage and neuropsychiatric disease is multifactorial in nature and may be more a reflection of impairment of functional status. Psychotropic medications, poor compliance with medication and associated alcohol use may all contribute to the increased risk of falls in patients with neuropsychiatric disease. Patients with Alzheimer's dementia may be predisposed to intracranial hemorrhage if they have amyloid angiopathy or apolipoprotein E polymorphisms. However, quantification of the risk and application to decision-making regarding anticoagulation in this setting have not been clearly defined.

Chronic Kidney Disease and Anemia

The prevalence of renal disease increases with advancing age [30]. Patients with CKD have three times the risk of AF compared with patients without CKD and are likely to be on warfarin anticoagulation. However, stage 3 CKD is associated with twice the rate of major bleeding during warfarin anticoagulation [12, 58]. These higher rates of major bleeding were not adjusted for age. In a longitudinal cohort analysis, stage 3 CKD was not an independent predictor of hemorrhage during warfarin anticoagulation [59]. While the Anticoagulation and Risk Factors In AF (ATRIA) dataset showed CKD with an estimated creatinine clearance (eCrCl) of <30 ml/min was an independent predictor of major hemorrhage (HR 4.3, $p < 0.001$), it has not been sufficiently validated for general clinical use [43]. While patients with CKD are at increased risk of anemia, the same ATRIA dataset concluded anemia (hemoglobin <13 g/dl in men; <12 g/dl in women) was an independent predictor of hemorrhage (HR 4.2, $p < 0.001$) [43]. Anemia is prevalent in the elderly and is estimated to affect 23.9% of patients over the age of 70 years [60, 61].

Patient Preferences for Anticoagulation

The decision to take anticoagulation for AF requires consideration of the potential risks and benefits. Physicians and patients can differ in how they weigh up these factors when arriving at a decision to take oral anticoagulants. Patients at risk of developing AF, who have no previous history of stroke, place more value on the avoidance of stroke and less value on the avoidance of bleeding than physicians [62].

There is significant underuse of antithrombotic drugs in elderly patients with AF. Physicians may make strong recommendations for or against warfarin as a treatment, but patient preferences should be considered before making decisions about anticoagulation.

Novel Selective Oral Anticoagulants for Elderly Patients with AF

While warfarin has been established as the mainstay treatment for SPAF, novel anticoagulants have been introduced in the past few years, which are more selective in their anticoagulant mechanisms and easier to administer. Four novel anticoagulants (two direct thrombin inhibitors, ximelagatran and dabigatran, and two factor Xa inhibitors, apixaban and rivaroxaban) have been evaluated in large phase III randomized trials. Ximelagatran was withdrawn from the market in 2006 due to rare, but serious, hepatotoxicity. The other novel anticoagulants have not shown the same adverse effect. The four recent randomized trials testing the novel oral anticoagulants in AF patients included 21,062 participants ≥ 75 years old and provide substantial evidence for their efficacy in this age group [10–12, 47] (Table 3).

Dabigatran, apixaban and rivaroxaban do not require regular anticoagulation monitoring

Table 3 Comparison of novel oral anticoagulants in patients ≥ 75 years

Novel agent	Trial	Intervention versus warfarin unless specified	Number of participants ≥ 75 years	Hazard Ratio for Stroke Risk	Hazard Ratio for major Hemorrhage
Dabigatran	RE-LY [10]	Dabigatran 110 mg bid	7,258	0.88 (0.66–1.17)	1.01 (0.83–1.23)
		Dabigatran 150 mg bid		0.67 (0.49–0.90)	1.18 (0.98–1.42)
Rivaroxaban	ROCKET-AF [11]	Rivaroxaban 20 mg bid (15 mg od if eCrCl 30–49 ml/min)	6,229	0.88 (0.75–1.03) ^a	1.04 (0.90–1.20) ^a
Apixaban	ARISTOTLE [12]	Apixaban 5 mg bid	5,678	0.79 (0.65–0.95) ^b	0.69 (0.60–0.80) ^b
	AVERROES [47]	Apixaban 5 mg bid (2.5 mg bid if 2 out of 3 of the following criteria; serum creatinine ≥ 133 ml/min, age ≥ 80 years or weight ≤ 60 kg) vs. Aspirin	1,897	0.46 (0.33–0.65) ^b	1.13 (0.74–1.75) ^b

^a Intention to treat analysis. Estimated from the entire group irrespective of age as no statistically significant interaction with age

^b Estimated from the entire group irrespective of age as no statistically significant interaction with age

Table 4 Key pharmacological characteristics of novel anticoagulants

Feature	Drug		
	Dabigatran	Rivaroxaban	Apixaban
Type of drug	Direct thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Half-life (h)	14–17	7–11	8–15
Bioavailability (%)	~6	80–100	34–88
Renal elimination (%)	~80	33	~22
Dosage	150 mg bid (110 mg bid if patients at risk of bleeding or >80 years of age)	20 mg od (15 mg od in patients with eCrCl 15–49 ml/min)	5 mg bid (2.5 mg bid in patients with impaired renal function and >80 years or <60 kg in weight)
Age-related dosage recommendations	110 mg bid if >80 years	None	2.5 mg bid if >80 years with serum creatinine ≥ 1.5 mg/dl (133 μ mol/l)
T_{max} after oral ingestion (h)	1.5	2–4	1.5–3.5

or frequent dose adjustments; however, a specific antidote to rapidly reverse the anticoagulant effect of these agents in the event of an acute hemorrhage is not available (other than acute hemodialysis for agents such

as dabigatran) [63] (Table 4). These novel anticoagulant agents have been approved for clinical use and have been shown to be at least non-inferior to dose-adjusted warfarin for stroke prevention.

Dabigatran

In the Randomized Evaluation of Long-term Anticoagulant Therapy (RE-LY) randomized trial, two doses of dabigatran (110 mg and 150 mg twice daily) were compared with warfarin [10]. Both doses of dabigatran in RE-LY were associated with a lower risk of major hemorrhage in patients <75 years, but this was not the case in those aged ≥ 75 years. The risk of major hemorrhage and extracranial hemorrhage rose more steeply with dabigatran than warfarin with increasing age. Dabigatran 150 mg twice daily was associated with an increased risk of major extracranial bleeding in elderly patients compared with warfarin. However, the risk of intracranial bleeding remained lower with both doses of dabigatran with no evidence of interaction with age [64]. Dabigatran 150 mg bid was associated with a lower risk of strokes or systemic embolism compared to warfarin and there was no association between dabigatran and the risk of myocardial infarctions [10]. As dabigatran is dependent on renal excretion, it is contraindicated in severe renal disease (eCrCl <30 ml/min). In the USA, only dabigatran 150 mg bid is licensed for use in the prevention of strokes in patients with AF, while in Canada and the UK dabigatran 110 mg bid is also licensed for use in patients at increased risk of bleeding (older patients >80 years, eCrCl 30–60 ml/min or low body weight).

Rivaroxaban

In contrast to the other novel anticoagulants currently on the market, rivaroxaban is dosed daily (Table 4). Rivaroxaban is less dependent on renal excretion compared with dabigatran. Rivaroxaban was compared with warfarin in the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with vitamin K

Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) study in patients at high risk of stroke and hemorrhage [11]. While patients with severe renal disease were excluded from the trial, patients with moderate renal function (eCrCl 30–49 ml/min) were recruited and received a reduced dose of rivaroxaban (15 mg daily). There was no significant difference in stroke or systemic embolism on comparing the treatment effects of rivaroxaban versus warfarin in patients with or without reduced eCrCl [58]. The risk of intracerebral and fatal hemorrhages was lower with rivaroxaban compared with warfarin. However, there was an increased risk of non-major clinically relevant bleeding in patients aged ≥ 75 years treated with rivaroxaban compared with warfarin [65].

Apixaban

Apixaban was compared with warfarin in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study [12] and with aspirin in patients deemed intolerant of warfarin in the Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for vitamin K Antagonist Treatment (AVERROES) study [47]. The dose of apixaban was reduced from 5 mg bid to 2.5 mg bid in participants who had a serum creatinine concentration ≤ 1.5 mg/dl (133 μ mol/l) and either age ≥ 80 years or a body weight ≤ 60 kg in both studies. When compared against warfarin, apixaban was more effective in reducing strokes and all-cause mortality and had a lower risk of major bleeding with no significant age interaction [12]. Those participants with at least moderate renal impairment (eCrCl 25–50 ml/min) had half the rate of major hemorrhage with apixaban (3.3%) versus warfarin (6.7%) [66].

When compared with aspirin in patients deemed unsuitable for warfarin in the AVERROES study, apixaban was superior to aspirin in preventing stroke or systemic embolism in patients with AF, including those aged ≥ 75 years [47]. There was no significant increase in risk of major bleeding in patients ≥ 75 years. In addition, there was no significant difference in the risk of major bleeding in patients with stage 3 CKD. The results of the AVERROES study have significant implications for at least 30% of patients who are considered ideal candidates for anticoagulation therapy and are at risk of stroke, but are not on warfarin [67]. This is particularly relevant in the elderly as over 50% of patients ≥ 75 years who are at risk of strokes due to AF are not on anticoagulation therapy [26, 48].

Comparisons Between Novel Oral Anticoagulants

The use of novel anticoagulants to reduce stroke risk in patients remains an exciting avenue for further study. The differences in trial populations between individual trials with differing dosing regimens and lack of head-to-head comparisons combine to prevent reliable comparisons between novel agents. Indirect comparisons may be misleading, as the populations were not homogenous. ROCKET-AF included a population at high risk of stroke compared with the RE-LY and ARISTOTLE studies. In addition, the time in therapeutic range achieved in the warfarin arm of the ROCKET-AF study was lower than in RE-LY and ARISTOTLE. Aspirin use could have affected the safety and efficacy of the novel agents and was lowest in ARISTOTLE (30.9%) [12] (vs. 39.7% in RE-LY (39.7%) [10] and 36.5% in ROCKET-AF [11]).

Based on our analysis of available evidence, apixaban (ARISTOTLE dosing schedule), rivaroxaban (ROCKET-AF dosing schedule) and dabigatran 150 mg bid are all superior to therapeutic warfarin anticoagulation for reduction in stroke and systemic embolism in patients with AF ≥ 75 years old. The relative risk reduction for stroke or systemic embolism with these new oral anticoagulants averages about 30%. This translates to a number needed to treat of about 150 elderly AF patients per year to prevent one stroke or systemic embolism with novel anticoagulants compared with warfarin. Major hemorrhage rates are similar or reduced by novel oral anticoagulants compared with warfarin in elderly AF patients; an exception to this is high-dose dabigatran, which is associated with a major increase in gastrointestinal bleeding, but a significant reduction in intracranial hemorrhage relative to warfarin.

CONCLUSIONS

The prevalence and importance of AF is increasing with an aging population. Oral anticoagulants are effective at reducing the absolute risk of ischemic stroke compared with antiplatelet agents in elderly patients, but are associated with increased risk of hemorrhage. However, the risk of extracranial hemorrhage is overshadowed by the absolute reduction in risk of stroke in most elderly patients. Novel anticoagulants, dabigatran, rivaroxaban and apixaban, are at least as effective as warfarin in reducing the risk of stroke and are safer in elderly patients than warfarin. These agents are also easier to use and unlike warfarin do not require frequent blood test monitoring. The use of novel anticoagulant agents will likely increase as these agents are better tolerated than warfarin in the elderly. While more

expensive compared with warfarin, the absolute economic costs remain uncertain. The greater use of anticoagulation with either warfarin or these novel agents will reduce the risk of ischemic stroke in elderly patients. As more novel anticoagulants such as edoxaban come to market, direct randomized comparisons of the novel agents will be necessary to delineate clear roles for the individual agents. Currently, recent trials of novel anticoagulants have challenged whether warfarin should be the preferred anticoagulant option for elderly patients. The novel anticoagulants are clearly effective for use in elderly patients with AF in clinical trials and should be strongly considered when anticoagulation is indicated.

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