

Efficacy and safety of oral anticoagulation in elderly patients with atrial fibrillation

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ABSTRACT

Elderly patients with atrial fibrillation are at a higher risk of both ischemic and bleeding events compared with younger patients; therefore, balancing risks and benefits of antithrombotic strategies in this population is crucial. Recent studies have shown that because the risk of stroke increases with age more than the risk of bleeding, the absolute benefit of oral anticoagulation is the highest in elderly patients in whom it outweighs the risk of bleeding. Direct oral anticoagulants (DOACs) have been developed as a treatment for the prevention of cardioembolic stroke to overcome some limitations of warfarin, such as the need for frequent monitoring, labile INR values requiring frequent dose adjustment, dietary and drugs interactions, and increased risk of intracranial bleeding. Despite the better safety profiles of DOACs compared with warfarin, elderly patients often remain undertreated because of the fear of bleeding complications. This review summarizes current evidence regarding the risks of thromboembolisms and bleeding in different antithrombotic strategies in elderly patients (aged ≥ 75 years) with atrial fibrillation, including data from the warfarin-controlled phase 3 DOACs trials. (*Anatol J Cardiol* 2018; 19: 67-71)

Keywords: atrial fibrillation, elderly, anticoagulation

Introduction

Atrial fibrillation is the most common cardiac arrhythmia, and its prevalence increases with age, ranging from approximately 0.1%–0.16% in adults aged < 49 years to 9%–17% in elderly people aged > 80 years (1, 2). Atrial fibrillation is associated with substantial mortality and morbidity, including a five-fold increase in the risk of stroke (3, 4).

The incidence of stroke increases with age; indeed, age is included as a significant risk factor for thromboembolism in the commonly used CHA₂DS₂-VASc score (age between 65 and 74 years contributes 1 point and ≥ 75 years contributes 2 points) (5). Advanced age is also a risk factor for bleeding. Elderly patients (defined as those aged ≥ 75 years) are at a high risk of falling and usually have a low body mass index, altered body composition of muscle and fatty tissue, and age-related decline in renal function. Therefore, balancing risks and benefits of antithrombotic strategies in this population is crucial.

In light of the projected increase in the worldwide prevalence of atrial fibrillation in the near future, there is an urgent need for effective stroke preventive strategies, especially in the elderly (6, 7).

Oral anticoagulation represents the cornerstone of treatment to reduce the risk of cardioembolic stroke in patients with atrial

fibrillation (class of recommendation I, level of evidence A) (8). Of note, a large meta-analysis by Hart et al. (9) showed that well-managed warfarin is associated with a 64% relative reduction in the risk of ischemic stroke compared with placebo or no treatment. On the other hand, antiplatelet therapy, being associated with a non-significant 19% relative risk reduction, is not recommended for the prevention of cardioembolic stroke in atrial fibrillation (class of recommendation III) (8).

Table 1 summarizes available data on clinical outcome of elderly patients with atrial fibrillation treated with different antithrombotic strategies [antiplatelet therapy, vitamin K antagonists, direct oral anticoagulants (DOACs)] (10-21).

Vitamin K antagonists

Previous historical studies have compared outcomes of patients with atrial fibrillation aged ≥ 75 years treated with anticoagulant versus antiplatelet agents. In particular, the randomized Birmingham Atrial Fibrillation Treatment of the Aged Study (BAFTA) trial, performed in the setting of primary care, demonstrated that the use of warfarin (target INR 2-3) compared with aspirin 75 mg daily resulted in a significant 52% relative reduction of the composite primary endpoint including stroke, systemic embolism, and

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Table 1. Main descriptors and results of studies specifically evaluating clinical outcome with different antithrombotic strategies in elderly/very elderly patients with atrial fibrillation

Studies	Type	N. patients	Age	Treatment comparison	Follow-up (yrs)	Primary outcome	Results on primary outcome	Major bleeding
Antithrombotic strategies								
VKA vs. antiPLT								
BAFTA (10)	CRT	973	≥75 yrs	Warfarin vs. aspirin 75 mg	2.7	Stroke/SEE/ICH	RR 0.48 (0.28-0.80)	1.9% yr vs. 2.0% yr P=0.90
WASPO (11)	CRT	75	≥80 yrs	Warfarin vs. aspirin 300 mg	1	Death, thromboembolism, serious bleeding,	25% vs. 44% P=0.11 withdrawal from the study	0 vs. 7.7%
Wolff et al. (12)	Retrospective	561	≥85 yrs	VKA (36% of patients) vs. antiPLT (49%) vs. none (15%)	1	Stroke	OR with VKA: 0.53 (0.22-1.28)	-
Perera et al. (13)	Prospective	207	≥70 yrs	Warfarin (40%) vs. antiPLT (47%) vs. none (13%)	6 months	Stroke	3.6% vs. 8.2% vs. 30.8%	22.9% vs. 22.4% vs. 7.7%
SPAF II (14)	Post-hoc from CRT	385	≥75 yrs	Warfarin (INR 2-4.5) vs. aspirin 325 mg	2.7	Stroke	3.6% yr vs. 4.8% yr P=0.39	-
Patti et al. (15)	Retrospective	505	≥85 yrs	VKA (78% of patients) vs. antiPLT (15%) vs. none (7%)	12 months	Stroke/TIA/SEE	OR of VKA vs. antiPLT or no therapy 0.64 (0.24-1.69) P=0.37	VKA vs. antiPLT or no therapy 4.0% yr vs. 4.2% yr P=0.77
NOAC vs Antiplatelet								
AVERROES (16)	Post-hoc from CRT	2.264	≥75 yrs	Apixaban 5 mg vs. aspirin 81-324 mg	1.1	Stroke/SEE	≥75 yrs: HR 0.33 (0.19-0.54) ≥85 yrs: HR 0.14 (0.02-0.48)	≥75 yrs: 2.6% yr vs. 2.2% yr; P=0.50 ≥85 yrs: 4.7% yr vs. 4.9% yr P=0.93
NOAC vs VKA								
RE-LY (17)	Post-hoc from CRT	7.258	≥75 yrs	Dabigatran 110 mg/150 mg vs. warfarin	Median 2.0	Stroke/SEE	D110 vs. W: HR 0.88 (0.66-1.17) D150 vs. W: HR 0.67 (0.49-0.90)	D110 4.4% yr / D150 5.1% yr vs. W 4.4% yr D110 vs. W: P=0.89 D150 vs. W: P=0.07
ROCKET AF (18)	Post-hoc from CRT	6.229	≥75 yrs	Rivaroxaban 20 mg vs. warfarin	2	Stroke/SEE	HR 0.80 (0.63-1.02)	4.9% yr vs. 4.4% yr HR 1.11 (0.92-1.34)
ARISTOTLE (19)	Post-hoc from CRT	5.678	≥75 yrs	Apixaban 5 mg vs. warfarin	1.8	Stroke/SEE	HR 0.71 (0.53-0.95)	3.3%yr vs. 5.2%yr P<0.05
ENGAGE AF (20)	Post-hoc from CRT	8.474	≥75 yrs	Edoxaban 60 mg vs. warfarin	2.8	Stroke/SEE	HR 0.83 (0.66-1.04)	4.0% yr vs. 4.8% yr P<0.05
Graham et al. (21)	Real world registry	39.208	75-84 yrs and ≥85 yrs	Dabigatran vs. warfarin	-	Ischemic stroke	-75-84 yrs: 12.7 vs. 13.7 per 1000 patients/yr; P>0.05 -≥85 yrs: 16.0 vs. 23.5 per 1000 patients/yr; P>0.05 for men, P<0.05 for women	-75-84 yrs: 4.4 vs. 10.9 per 1000 patients/yr; P<0.05 -≥85 yrs: 4.8 vs. 13.5 per 1000 patients/yr; P>0.05 for men, P<0.05 for women
AntiPLT, antiplatelet; CRT, controlled randomized trial; HR, hazard ratio; NOAC, non-vitamin K antagonist oral anticoagulant; OR, odds ratio; RR, risk reduction; SEE, systemic embolic event; VKA, vitamin K antagonist								

intracranial hemorrhage (yearly risk, 1.8% vs 3.8%; relative risk, 0.48; 95% CI, 0.28–0.80; p=0.003) (10). The occurrence of major bleeding complications in the warfarin and aspirin arms was similar (yearly risk, 1.9% vs. 2.0%; p=0.90), but the study may have been

underpowered for the evaluation of safety outcome measures and the high percentage of crossovers in the warfarin arm (approximately 30%) might have led to an underestimation of the bleeding risk. A post-hoc analysis of the Stroke Prevention in Atrial Fibrilla-

tion II study including 385 patients aged ≥ 75 years confirmed the efficacy of warfarin for preventing stroke compared with aspirin 325 mg daily (3.6% vs. 4.8% per year; RR, 0.73; $p=0.39$), with an absolute risk reduction of 1.2% per year (14). A recent analysis from the European PREvention of Thromboembolic Events-European Registry in Atrial Fibrillation (PREFER in AF) registry indicated that even in very elderly patients (aged ≥ 85 years), the use of anticoagulant therapy (essentially warfarin) was associated with a 36% risk reduction of thromboembolic events compared with no antithrombotic or antiplatelet therapy (15). Because of the higher baseline risk profile of very elderly patients, the utilization of anticoagulant therapy here translated into more pronounced absolute event reductions than in younger patients (2.0% vs. 0.3% per year; number needed to treat for 1 year=50), with the greatest net clinical benefit in the elderly. Of note, in this study, the incidence of major bleeding complications in patients aged ≥ 85 years on anticoagulant therapy was not different from that in patients treated with antiplatelet agents. In the setting of very elderly patients, similar efficacy of vitamin K antagonists were observed in a retrospective, population-based study from the United Kingdom and similar net clinical benefit was demonstrated in an observational study of 13,559 patients with atrial fibrillation (12, 22).

However, the bleeding risk associated with warfarin in the elderly remains a matter of debate. A subgroup analysis on patients aged ≥ 75 years from six randomized clinical trials indicated a doubling of rates of major hemorrhages during follow-up in patients taking warfarin compared with those taking aspirin (23). However, three of those six trials had a higher upper limit of target INR (4.0–4.5 instead of 3), and this may have increased the propensity to bleeding in the warfarin group.

Altogether, available evidence suggests that in the elderly population, the benefits of the traditional vitamin K antagonist are considered to outweigh the risks. Nevertheless, therapy with vitamin K antagonist is underutilized in elderly patients because of the perception of healthcare professionals that such a treatment is not safe (24, 25). However, 25%–65% of elderly patients with atrial fibrillation in the real world are not prescribed oral anticoagulation (12, 13, 15). The most frequent reasons for this underutilization include the risk of falling (26.7%), poor prognosis (19.3%), bleeding history (17.1%), participant or family refusal (14.9%), older age (11.0%), and dementia (9.4%). Unfortunately, within 1 year, 42% of elderly patients not receiving oral anticoagulation at discharge die compared with 19.1% of those receiving oral anticoagulation ($p<0.001$) (26).

DOACs

Since 2010, the regulatory approval of four DOACs, dabigatran, rivaroxaban, apixaban, and edoxaban, has provided an alternative to the use of warfarin for the prevention of cardioembolic stroke. Phase III randomized clinical trials have shown that DOACs have at least equal efficacy, with lower rates of intracranial hemorrhage compared with warfarin. In addition, apixaban and edoxaban were found to reduce major bleeding events in the overall trial popula-

tion compared with warfarin (27). Despite the availability of these safer drug alternatives to warfarin, oral anticoagulation use remains suboptimal in elderly patients with atrial fibrillation.

An analysis of the Randomized Evaluation of Long-Term Anticoagulant Therapy (RELY) trial found that among patients with atrial fibrillation aged ≥ 75 years, lower dabigatran dose (110 mg twice daily) was associated with major bleeding rates similar to warfarin (4.43% vs 4.37%; $p=0.89$; p for interaction <0.001), whereas higher dose (150 mg twice daily) showed a greater risk of major bleeding (5.10% vs 4.37% in the warfarin arm; $p=0.07$; p for interaction <0.001) (17). This risk was limited to extracranial bleeding; in fact, the risk of intracranial bleeding was lower with both doses of dabigatran regardless of age. A recent substudy of the RELY trial suggested that the effects of dabigatran on extracranial major bleeding are age-dependent, thereby supporting the use of dabigatran 110 mg twice daily in patients aged ≥ 80 years (28).

An analysis of the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) study demonstrated that patients aged ≥ 75 years had higher stroke/systemic embolism (2.57% vs 2.05%/100 patient-years; $p=0.0068$) and major bleeding (4.63% vs 2.74%/100 patient-years; $p<0.0001$) rates than younger patients (18). However, the efficacy and safety of rivaroxaban relative to warfarin did not differ with age. Overall, there was no difference in the major bleeding rates between rivaroxaban and warfarin, whereas older patients in the rivaroxaban group had higher occurrence of the combined endpoint including major or clinically relevant non-major bleeding (interaction, $p=0.009$); however, this was restricted to extracranial bleeding and driven primarily by gastrointestinal bleeding, which was more frequent among elderly patients in the rivaroxaban than in the warfarin arm.

An analysis of the Apixaban for the Prevention of Stroke in Subjects with Atrial Fibrillation (ARISTOTLE) study included 39% of patients aged 65–74 years, 18% aged 75–79 years, and 13% aged ≥ 80 years. The use of apixaban was associated with less major bleeding, less total bleeding, and less intracranial hemorrhage regardless of age (19). As the risk of stroke, death, and major bleeding increased significantly with age and apixaban consistently prevented these events irrespective of age, the absolute benefits of apixaban were greater in the older population.

In the Effective aNticoagulation with factor Xa next GEneration in Atrial Fibrillation-Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF-TIMI 48) trial, 8,474 of the 21,105 participants were aged ≥ 75 years, the largest number of elderly patients enrolled in a randomized controlled trial of DOAC to date (20). The incidence of stroke/systemic embolism in patients aged ≥ 75 years was similar with edoxaban and warfarin, whereas major bleeding complications were significantly reduced with the use of edoxaban. In particular, the occurrence of intracranial hemorrhage increased only gradually with increasing age in the edoxaban group, whereas the elevation in the rates of intracranial hemorrhage was steeper with warfarin as age increased. As a result, the absolute risk difference in both major and intracranial bleeding in older populations was

greater for edoxaban than for warfarin; further subgroup analyses revealed that these benefits of edoxaban relative to warfarin were maintained in the setting of patients aged ≥ 80 and ≥ 85 years (20) and were prominent in the subgroup of patients at a high risk of fall (29). Of note, in the ENGAGE AF-TIMI 48 trial, (20) the risk of major bleeding markedly increased with increase in age, highlighting the need for safe anticoagulation treatment strategies.

Real-world data assessing the safety of DOACs in elderly patients indicated that over a mean of 2.6 years, the incidence of major bleeding while taking DOACs was 1.37 per 100 person-years (30). An increased risk of bleeding was associated with a decline in glomerular filtration rate compared with baseline. Therefore, the authors conclude that DOACs appear to be a safe type of anticoagulation in elderly patients with atrial fibrillation, but emphasize the need for regular monitoring of renal function. In a meta-analysis of randomized controlled trials comparing DOACs (rivaroxaban, apixaban, and dabigatran; insufficient data was available for edoxaban) with conventional therapy in patients aged ≥ 75 years, DOACs did not cause excessive bleeding and were associated with equal or greater efficacy than conventional therapy (31). However, data from phase III clinical trials on atrial fibrillation overall indicate that apixaban and edoxaban in elderly patients are associated with the highest reduction of extracranial bleeding events versus warfarin. In the ENGAGE AF-TIMI 48 and ARISTOTLE trials, the absolute major bleeding rates were consistently lower with DOAC than with warfarin across all age groups. The major limitation of individual studies on DOACs use in elderly patients are that they represent subgroup analyses, although pre-specified, of larger trials and had relatively low number of patients (2,436 patients were aged ≥ 80 years). In addition, elderly patients in clinical trials are generally relatively healthy and adhere to medication; conversely, discontinuation of and non-adherence to DOACs in the older populations are commonly reported in real-world studies (32, 33).

However, while there is a need for more real-world data, available evidence till date suggests that DOACs are effective alternatives to warfarin in elderly patients with atrial fibrillation with a better safety profile.

Conclusion

Treatment of elderly patients affected by atrial fibrillation presents numerous challenges; the most important is balancing the benefits of antithrombotic strategies against the possible increased risk of a potentially serious bleeding event, such as recurrent gastrointestinal bleed or intracerebral hemorrhage. In the past, the fear of bleeding has led to underuse of anticoagulation in older populations, but the introduction of DOACs may offer a safer alternative to warfarin, particularly in this setting of patients.

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