Anticoagulation therapy in the elderly with non-valvular atrial fibrillation: a double-edged sword

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I am tomorrow what I establish today.
I am today what I established yesterday...
J. Joyce

Abstract

Prevalence of non-valvular atrial fibrillation is increasing over time. Particularly in elderly population, treatment strategies to reduce the rate of stroke are challenging and still represent an unsolved cultural question. Indeed, the risk of thromboembolism increases in the elderly in parallel with the risk of bleeding. The frequent coexistence of several morbidities, frailty syndrome, polypharmacy, chronic kidney disease and dementia strengthens the perception that risk-benefit ratio of anticoagulant therapy could be unfavorable, and explains why such treatment is underused in the elderly. Recently, the introduction of non-vitamin K oral anticoagulants (NOACs) has allowed us to overcome the large number of limitations imposed by the use of vitamin K antagonists. In this manuscript, the benefits of individual NOACs in comparison with warfarin in elderly patients are reviewed. Targeted studies on complex elderly patients are needed to test usefulness of a geriatric comprehensive assessment, besides the scores addressing risk of thromboembolic and hemorrhagic events. In the meantime, it is mandatory that use of anticoagulant therapy in most elderly people, currently excluded from randomized controlled trials, is prudent and responsible.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, with an estimated lifetime risk of 25%. Its prevalence grows with age: it is less than 0.1% in subjects aged ≤55 years and progressively increases up to 9-10% in subjects aged ≥80 years. In 2010, in the European Union, there were 8.8 million of adults with AF and such prevalence is projected to increase to 17.9 million cases in 2060.1,2 AF is associated to a four to five-fold increased risk of embolic stroke: this risk is estimated to rise to 1.45-fold per decade of age. In fact, the ischemic stroke is expected to occur in 14/1000 persons/year and 29/1000 persons/year, respectively in subjects aged between 75 and 84 years and in those of 85 years or older.3,4 Its high incidence is partly explained by the age-related prevalence of several diseases that are recognized as risk factors both for stroke and for AF, such as hypertension, heart failure and renal failure. Almost 25% of all ischemic strokes in patients over 80 years of age are attributable to AF. Oral anticoagulant therapy (OAT) with vitamin-K antagonists (VKAs) in patients with AF reduces the risk of ischemic stroke by 64%: by taking into account the higher incidence of stroke in the elderly than in younger patients, it finally results in an absolute risk reduction greater in the former than in the latter.1-5

On the other hand, aging is also associated with an increased risk of major bleedings, especially in case of OAT. The risk of hemorrhagic events related to OAT is age-dependent and increases of about 40% for decade of life. Bleeding, particularly cerebral hemorrhage, is the most feared complication of OAT. Regardless of the category of anticoagulant, aging is an independent risk factor for bleeding with anticoagulation levels both in the therapeutic range and, chiefly, outside the therapeutic range, as widely demonstrated with VKAs.2,3 The annual risk of major bleeding in patients treated with VKAs is estimated at 2-3%, while the rate of minor bleeding is 14%.2,6 Thus, concern about the bleeding risk of anticoagulants largely contributes to the underuse of VKAs in patients with AF. Surveys from Europe and North America have consistently shown that VKAs are used in only 50-60% of patients having indication to OAT.7 As noteworthy, the major challenge in the elderly receiving VKAs is to ensure adequate time in therapeutic range (TTR).

Basing on such considerations, the main goal of AF treatment in the elderly should be reaching the utmost benefit in terms of ischemic stroke reduction, by minimizing the risk of harmful events. As detailed below, it may stem only from adequate knowledge of conditions in which OAT in the elderly represents a real advantage.

Oral anticoagulants in the elderly: is there a net clinical benefit?

As risk of stroke grows with aging, efficacy of OAT in reducing ischemic cerebrovascular events increases in the elderly. Several comorbidities, which are known to occur more frequently in the last decades of life, further enhance the progressive risk of cardio-embolic stroke related to aging. Enlightening data from real world registries point out that the prevalence of frailty and multimorbidity (>3 diseases) accounts for 50% and 71%, respectively, in elderly patients hospitalized for AF. Consequently, as showed by Atrial Fibrillation Investigators’ data, the coexistence of comorbidities enhances the benefits of OAT, especially in patients aged ≥75 years.8

On the other hand, advanced age is also associated with a progressive increase in the risk of major bleeding, with a hazard ratio that is more than tripled in subjects aged ≥85 years, compared to those aged <60 years, particularly if treated by OAT.9,10 Indeed, although Warfarin is widely regarded as the cornerstone of therapy for cardio-embolic stroke prevention, the related risk of bleeding is not negligible: a meta-analysis on antithrombotic therapy to prevent stroke in patients with non valvular atrial fibrillation (NVAF) showed that Warfarin therapy is associated to an annual incidence of major bleedings which varies from 1.7 to 3% in patients aged <75 years and from 4.2 to 5.2% in those aged ≥75 years.11

The increased risk of bleedings and

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other safety concerns, about frailty, multidrug therapy, pharmacological interactions, dementia and tendency to falls, overall represent the main reasons why physicians are reluctant to undertake anticoagulation or prone to discontinue such therapy in the elderly. This behavior explains why only a low percentage of elderly patients with NVAF takes OAT.8-10 Indeed, it has been demonstrated that the use of OAT in patients with AF decreases progressively with age, from a prevalence of about two-thirds in patients aged ≤75 years to about 50% in those aged >75 years.13 Notably, a prospective cohort study has unequivocally confirmed that OAT is frequently denied to frail patients.14 Frailty and dementia are major determinants in the exclusion of elderly patients from OAT, but observational findings suggest that paradoxically the frail patient may take the utmost advantage from anticoagulation. Indeed, in the previously cited study, frail patients have been clearly shown at higher risk of stroke (HR 3.5) and mortality (HR 2.8) at six-month follow-up, when compared to non-frail patients.13

As confirmation of the advantage of OAT in the elderly, despite concerns to prescribe it, literature data actually support a net clinical benefit in the use of warfarin, especially in this age group. Results from the Swedish AF Cohort Study, indeed, clearly demonstrate that the benefit of anticoagulation with warfarin in terms of reduction of ischemic stroke, intracranial hemorrhage (ICH) and overall mortality, when compared to antplatelet therapy or no antithrombotic therapy, tends to increase in parallel to both thromboembolic (quantified by the Congestive Heart Failure, Hypertension, Age ≥75, Diabetes, Stroke doubled - Vascular disease, Age 65-74 and female Sex, CHA2DS2-Vasc score) and hemorrhagic (quantified by the Hypertension, Abnormal renal/liver function, Stroke - Bleeding history or predisposition, Labile INR, Elderly ≥65 years, Drug/alcohol concomitantly, HAS-BLED score) risks.15 Furthermore, the AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) study, which involved more than 13000 AF patients, showed that the net clinical benefit of OAT raises with both age and Congestive heart failure, Hypertension, Age ≥75, Diabetes, Stroke (CHADS2) score. Adjusted net clinical benefit, indeed, was highest for patients aged ≥85 years (2.34% per year): it increased from zero in CHADS2 scores 0-1 up to 2.22% per year in CHADS2 categories 4-6. Peaking of net clinical benefit occurred from the age of 75 years, regardless of weighting factor for ICH.16 Results from several Italian registries have further confirmed the net clinical benefit of OAT in the elderly. In a retrospective cohort observational study on 980 patients with mean age 83 years, ischemic and hemorrhagic stroke occurred in 12.3% and 1.3% of patients, respectively, and major bleedings in 4.4% of patients: use of VKA was independently associated with reduced mortality and with a non-significant reduction in incidence of ischemic stroke, without excess in bleeding risk.17 No clear gender related differences have been found in elderly patients with AF about risk of major adverse events: in a large, multicenter observational study including 4093 elderly patients who started VKA treatment after the age of 80 years, elderly males showed a higher rate of bleeding complications, and females showed a slightly higher rate of stroke, thus suggesting the possibility of a higher net clinical benefit of anticoagulant treatment in females.18

Therefore, basing on literature data, it is strikingly evident that OAT is associated to a net clinical benefit, which increases with age. The elderly earn the utmost advantage from OAT, mainly when cerebrovascular dementia can be supposed deriving from multiple cardio-embolic ischemic strokes. Nevertheless, all conditions predisposing to increasing bleeding risk of OAT in the elderly should be adequately acknowledged in order to promote a conscious use of anticoagulation in such special population, which, in other words, means a careful tailoring of OAT on the individual patient. Particularly, the age-related safety profile of different anticoagulants, which is described below, should be taken into account in order to address the best individual treatment strategy.

### Non-vitamin K antagonist oral anticoagulant in the elderly

For decades, the VKA Warfarin has traditionally represented the cornerstone for stroke prevention in AF patient, thanks to its undoubted efficacy, despite important limits (Table 1).19 Such limits, which are more obvious in the elderly, in relation to changes in body composition, pharmacokinetics, as well as the frequent polypharmacy and frailty syndrome, unfortunately decrease Warfarin effectiveness and safety.20,21

Recently, some non-vitamin K antagonist oral anticoagulants (NOACs) have been developed, in order to overcome the main limitations of warfarin. Four randomized controlled trials (RCTs), each of them carried out with a different drug, have showed either non inferiority or superiority of NOACs in the prevention of stroke and systemic embolism (SE) in the general population, with significantly reduced risk of intracranial bleeding, determining a net clinical benefit compared with warfarin.22-25 The subgroup analysis about net clinical benefit provided similar results in patients aged ≥75 years, compared to general population, although, as expected, the absolute incidence of stroke, SE and major bleeding was higher in subjects aged ≥75 years than in the younger population.26 Taking together, the NOACs have been proven effective and safe in comparison with warfarin in the elderly. However, incidence of major bleedings resulted heterogeneous between the different therapeutic agents, as reported in the trials described below.

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**Table 1. Main limitations of warfarin therapy in elderly patients.**

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<tr>
<th>Limitations</th>
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<tr>
<td>Unpredictable response</td>
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<td>Slow onset and slow cessation of therapeutic effect</td>
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<td>Narrow therapeutic window</td>
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<tr>
<td>Difficulties in ensuring adequate time in therapeutic range</td>
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<tr>
<td>Several interactions with food</td>
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<td>Several interactions with drugs</td>
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<td>Need for routine monitoring of coagulation parameters with frequent dosage adjustments</td>
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Direct thrombin inhibitors

Dabigatran

The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial compared dabigatran with warfarin in 18,113 patients with NVAF, presenting a mean CHADS2 score of 2.2 and a median age of 71.2 years. Forty percent of patients in the RE-LY trial were aged ≥75 years.21 In the whole trial population, dabigatran 150 mg (but not 110 mg) twice daily (BID) vs warfarin showed better results in terms of reduction of stroke and SE (HR 0.66, P<0.001) and comparable effects in major bleeding (HR 0.93, P=0.81). The lower dose of dabigatran showed a 20% reduction of relative risk of major bleeding, compared to Warfarin, in the presence, however, of a comparable thromboembolic risk. Both doses of dabigatran reduced the rate of ICH, compared with warfarin.22,27

Specifically, in patients aged ≥75 years, Dabigatran 150 mg bid performed similarly to warfarin in reducing stroke and SE, but at the expense of an age-related increase in the risk of major extracranial bleeding. In fact, as compared with warfarin, the risk of major bleedings associated to Dabigatran 150 mg bid was lower in patients aged <75 years (HR 0.7; P<0.001) and higher in those aged ≥75 years (HR 1.18; P<0.001), whereupon an increased risk of harm outcomes with the exception of gastrointestinal hemorrhage.22 A large single-center cohort of real-life Italian population with NVAF at high thromboembolic and hemorrhagic risk has demonstrated a safety profile of both dosages of dabigatran regarding major or fatal bleeding: among patients with a mean age of 64.9±8.8 years (CHA2DS2Vasc Score ≥3 in 94.3% and HAS-BLED ≥3 in 59.7%) taking Dabigatran150 mg and among patients with mean age of 73.9±7.5 years (CHA2DS2Vasc Score ≥3 in 73.4% and HAS-BLED ≥3 in 87.4%) taking dabigatran 110 mg, no gastrointestinal bleedings occurred, but one case of subarachnoid hemorrhage in the former group and one case of ischemic stroke and one of bladder bleeding in the latter group.19 In a recently published meta-analysis on observational cohort studies, dabigatran was comparable with warfarin in preventing ischemic stroke among patients with NVAF, with a lower risk for ICH relative to warfarin, but a greater risk for gastrointestinal bleeding, particularly among the elderly. Indeed, while there was no evidence for an increased risk of gastrointestinal bleeding with dabigatran in studies of younger populations, actually there was an increased risk of ≤50% for dabigatran 150 mg versus warfarin in studies of older populations with mean/median age ≥75 years.24

Direct factor Xa inhibitors

Rivaroxaban

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) multicenter RCT compared Rivaroxaban 20 mg once/day (OD) (15 mg od in patients with creatinine clearance 15-49 mL/min) with Warfarin in 14,264 AF patients with a median age of 64.9±8.8 years (CHA2DS2Vasc Score ≥3 in 73.4% and HAS-BLED ≥3 in 87.4%) taking dabigatran 110 mg, no gastrointestinal bleedings occurred, but one case of subarachnoid hemorrhage in the former group and one case of ischemic stroke and one of bladder bleeding in the latter group.19 In a recently published meta-analysis on observational cohort studies, dabigatran was comparable with warfarin in preventing ischemic stroke among patients with NVAF, with a lower risk for ICH relative to warfarin, but a greater risk for gastrointestinal bleeding, particularly among the elderly. Indeed, while there was no evidence for an increased risk of gastrointestinal bleeding with dabigatran in studies of younger populations, actually there was an increased risk of ≤50% for dabigatran 150 mg versus warfarin in studies of older populations with mean/median age ≥75 years.24

Apixaban

The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial included 18,201 NVAF patients with a median age of 70 years and a mean CHADS2 score of 2.1. This trial showed that Apixaban 5 mg bid (2.5 mg bid if any two of three conditions were present: age ≥80 years, serum creatinine ≥1.5 mg/dL or ≥133 μmol/L and body weight <60 kg) was non-inferior and maybe superior to warfarin in preventing stroke/SE (HR 0.79, P=0.001), and in reducing major bleeding (HR 0.69; P=0.001) and ICH.24

In patients aged ≥75 years (31% of the whole study population), apixaban was associated with a reduction of both incidence of stroke/se and rate of major bleedings similarly to warfarin (HR 0.64, P=0.6; HR 0.71, P=0.11, respectively).26 The advantage of apixaban, regarding to major bleedings, was even greater in patients with renal dysfunction. Furthermore, this drug

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has been proven more beneficial than warfarin in decreasing the risk of digestive bleedings. By summarizing, the efficacy and safety of apixaban was consistent across all subgroups, including elderly patients.38,39

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) trial, apixaban (5 mg bid or 2.5 mg bid, basing on criteria already established for the ARISTOTLE) was compared with aspirin (81-324 mg od) in AF patients unsuitable for Warfarin. Such design stemmed from previous findings showing that aspirin was able to promote a 20% reduction of stroke, compared to placebo. AVERROES included 5,599 AF patients with a median age of 70 years and a mean CHADS2 score of 2. In this study, the rate of stroke/SE was significantly reduced with apixaban, compared to aspirin (HR 0.45 P<0.001), with similar effects on major bleedings or ICH. These results were not influenced by age and suggest that apixaban should be considered a viable alternative, especially for elderly patients unsuitable for warfarin therapy.40 A sub-group analysis of the AVERROES trial indicates that older patients with AF are at particularly high risk of stroke if given aspirin and have substantially greater relative and absolute benefits from apixaban compared with younger patients with no greater risk of hemorrhage. Particularly, apixaban was more efficacious than aspirin for preventing strokes and systemic embolism in patients ≥85 years (HR 0.14, 0.02-0.48) compared with younger patients (HR 0.50, 0.35-0.69).

Major hemorrhage was higher in patients ≥85 years compared with younger patients but similar with apixaban versus aspirin with no significant treatment-by-age interaction.41 In a large cohort of patients with non-valvular AF, assessing the real-world effectiveness and safety of dabigatran, rivaroxaban, and apixaban, in comparison with warfarin, apixaban was associated with better effectiveness and safety than warfarin. Particularly, while dabigatran 150 mg and rivaroxaban were both related to a higher risk of gastrointestinal bleeding, apixaban was related to a not significant numerically lower risk of gastrointestinal bleeding. Such finding may explain why apixaban was found to be prescribed for many elderly patients in such cohort.42

**Edoxaban**

Among all RCTs on NOACs, the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation (ENGAGE AF) trial involved the largest number of elderly patients. In fact, out of the 21,105 patients enrolled in this study, 8474 (40.2%) were aged ≥75 years. In this trial, patients were randomized in 1:1:1 fashion at edoxaban 60 mg od, edoxaban 30 mg od or warfarin, the latter up-titrated to a target INR between 2 and 3. The dosage of edoxaban was halved to 30 mg if any of the following determinants were present at enrollment or happened during the study: creatinine clearance ≤50 mL/min; body weight ≤60 kg; concomitant use of potent P-glycoprotein inhibitors.25 Twenty-five percent of enrolled patients met criteria for dose reduction with higher prevalence in the ≥75 years subgroup (10.4%, 18.2% and 41.2% of patients, respectively, in <65, 65-74 and ≥75 year age groups). Moderate renal dysfunction was the main determinant of dose reduction in patients aged ≥75 years. Data analysis of ENGAGE-AF showed that, in patients aged ≥75 years, the incidence of stroke/SE was similar, regardless of treatment with edoxaban or warfarin (HR 0.83 P=0.84), while major bleeding and ICH were significantly reduced with edoxaban (HR 0.83 and 0.4, respectively).

Although in the whole trial population the reduced edoxaban regimen, compared to warfarin, was associated with higher rates of ischemic stroke but lower incidence of gastrointestinal bleeding, in the subgroup of elderly, edoxaban 30 mg od (corresponding to average plasma concentrations of the drug and of the mean anti FXa activity decreased by 30-40% and 20-40%, respectively) showed similar efficacy to warfarin in preventing stroke/SE with the advantage of greater reduction in major bleeding (P<0.001).45 In the elderly, particularly in those with renal dysfunction, the need to individualize the dosage should be taken into due consideration, since Edoxaban presented a wider therapeutic window for thromboembolism than for major bleedings in this class of age.

### Knowledge gaps and discussion

Anticoagulant therapy in the elderly is commonly considered a double-edged sword, because the simultaneous presence of frailty, comorbidity, polypharmacy and dementia reduce the residence of the patient, with a greater vulnerability to hemorrhagic events. Thus, the higher the risk of thromboembolism the lower the percentage of patients undergoing anticoagulant therapy: this might be claimed the therapeutic paradox of the elderly. Nevertheless, retrospective observational studies have highlighted that in old patients the use of VKA is associated with a reduction in overall mortality, regardless of health conditions and functional state.45 Particularly, in elderly AF patients, even if cognitively impaired and/or functionally dependent, OAT is associated with reduced mortality and lower occurrence of ischemic stroke.46 Thus, the overall benefit of OAT seems to outweigh the risks, even in elderly patients at increased risk of bleeding or death.47 The NOACs emerged as an attractive alternative to Warfarin in elderly patients: the evidence of a net clinical benefit, mainly determined by the reduction in ICH, has lead recent international guidelines to suggest their use as first choice in patients with NVAF.38,48,49

However, some conceptual and practi-
Table 2. Summary of efficacy and safety data of NOACs vs warfarin expressed as O.R.66

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<th>Stroke</th>
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<th>Gastroint. Bleeding</th>
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<td>0.46</td>
<td>0.49</td>
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References

5. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European


