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…
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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 of 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.[2,5] 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.

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Key words: Atrial fibrillation; non-vitamin K antagonist oral anticoagulation; warfarin; elderly; stroke; hemorrhage; frailty.

Conflict of interest: the authors declare no potential conflict of interest.

Received for publication: 4 November 2016.
Revision received: 22 April 2017.
Accepted for publication: 15 June 2017.

Geriatric Care 2017; 3:6371
doi:10.4081/gc.2017.6371

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.[8] Consequently, as showed by Atrial Fibrillation Investigators' data, the coexistence of comorbidities enhances the benefits of OAT, especially in patients aged ≥75 years.[9]

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.[10,11] 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.[12]

The increased risk of bleedings and

other safety concerns, about frailty, multidrug therapy, pharmacological interactions, dementia and tendency to falls, overall represent the main reasons why physician 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.[11]

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 antiplatelet therapy or no antithrombotic therapy, tends to increase in parallel to both thromboembolic (quantified by the *Congestive Heart Failure, Hypertension, Age ≥ 75 doubled, Diabetes, Stroke doubled - Vascular disease, Age 65-74 and female Sex*, CHA_2DS_2-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* ($CHADS_2$) score. Adjusted net clinical benefit, indeed, was highest for patients aged ≥85 years (2.34% per year): it increased from zero in $CHADS_2$ scores 0-1 up to 2.22% per year in $CHADS_2$ 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 increase 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.

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

Unpredictable response
Slow onset and slow cessation of therapeutic effect
Narrow therapeutic window
Difficulties in ensuring adequate time in therapeutic range
Several interactions with food
Several interactions with drugs
Need for routine monitoring of coagulation parameters with frequent dosage adjustments

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 $CHADS_2$ 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.[22] 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), whereas the reduction in major bleeding, evident in the overall population treated by Dabigatran 110 mg bid, was lost in the subgroup aged ≥75 years. The risk of ICH was steadily reduced by dabigatran *vs* warfarin, irrespectively of drug dose and patient's age. On the contrary, Dabigatran 150 mg bid was associated with increased gastrointestinal bleeding in patients aged ≥75 years.[28,29] Since about 80-85% of dabigatran is eliminated by kidneys and elderly patients often have impaired renal function, it is advisable to pay attention to the drug dosage: indeed, a moderate kidney failure (creatinine clearance 30-50 mL/min) determines an increase of approximately twice in exposure to this drug. Notably, Dabigatran is contraindicated when creatinine clearance is <30 mL/min. The FDA, but not EMA, suggests prescribing Dabigatran 75 mg bid if creatinine clearance is 30 mL/min and the patient is contemporarily taking dronedarone or systemic ketoconazole. A lower dose of dabigatran (*i.e.*, 110 mg instead of 150 mg bid) should be considered for patients aged 75-79 years. The same dosage is recommended by EMA, but not by the FDA, for patients aged >80 years.[30,31] Data from real world registries have demonstrated a similar effect of dabigatran *vs* warfarin across the age subgroups: decreased risk of SE, ischemic stroke and myocardial infarction, without evidence of an increased risk of harm outcomes with the exception of gastrointestinal hemorrhage.[32] 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 (CHA_2DS_2Vasc 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 (CHA_2DS_2Vasc 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.[33] 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.[34]

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 73 years and a mean $CHADS_2$ score of 3.5. Enrolled patients were older and with a higher degree of comorbidities than all other trials on NOACs. Thirty-eight percent of patients in the trial were aged ≥75 years.[23] Rivaroxaban was found non-inferior to warfarin in terms of efficacy (reduction of stroke/SE) and safety (reduction of major bleeding), with the exception of gastrointestinal bleedings, that resulted higher with rivaroxaban. In patients aged ≥75 years, Rivaroxaban has fostered a reduction of stroke and SE similarly to warfarin (HR 0.8; P=0.3), with a comparable risk of major bleeding. The risk of ICH was lower with rivaroxaban (HR=0.67), in absence of significant age-related modifications.[35] In 2015, real world data presented at the American Geriatrics Society Annual Scientific Meeting showed that the rates of major bleeding and fatal outcomes in elderly patients treated in routine clinical practice generally are consistent with those reported in Phase 3 clinical trials. Particularly, of the 31,883 patients using rivaroxaban, an incidence of major bleeding was observed at 2.85 per 100 person-years, with 74.1 percent of these events occurring in those 75 years of age and older. Gastrointestinal bleeding was the most common bleeding event in all age groups, followed by ICH. Fatal outcomes as a result of major bleeding were low (mean age of death was 82.1 years) and mainly occurred in patients with comorbidities.[36] In the non-interventional study of Rivaroxaban for the prevention of stroke in patients with AF (XANTUS) study, which assessed the safety and efficacy of rivaroxaban in routine, *real-world* clinical practice, the percentage of patients aged ≥75 years was 37%, comorbidities were common and the mean $CHADS_2$ score was 2.0, while the mean CHA_2DS_2-VASc score was 3.4. In such study, incidence of major bleedings was lower than in ROCKET AF trial (with similar rate for ICH), although the event rate increased with age, reaching 3.2 events per 100 patient-years in patients aged >75 years. Similarly, the rates for symptomatic thromboembolic events was lower than in ROCKET AF, but increased with age, reaching 2.3 events per 100 patient-years in patients aged >75 years.[37]

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 $CHADS_2$ 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).[38] The advantage of apixaban, regarding to major bleedings, was even greater in patients with renal dysfunction. Furthermore, this drug

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 $CHADS_2$ 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).[43] 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.

Head-by-head comparison

A recent meta-analysis of eleven RCTs, that included all four NOACs and analyzed data of patients aged >75 years, both in the setting of AF and venous thromboembolism, has shown that every NOAC was at least comparable to VKA in terms of effectiveness in reducing the risk of stroke/SE. In the elderly, the risk of stroke/SE was significantly lowered by dabigatran 150 mg bid (OR 0.66) and apixaban (OR 0.7). Likewise, in this meta-analysis, a relevant reduction in the risk of major bleeding was found with apixaban (OR 0.63) and edoxaban 60 mg and 30 mg (OR 0.81 and 0.46, respectively), in comparison with VKA. As noteworthy, the risk of major bleeding was characterized by only a non-significant increase with dabigatran 150 mg in this age group (OR 1.18), while the risk of digestive bleeding has been proven greater with dabigatran 150 mg (OR 1.78) and 110 mg (OR 1.4), in the absence of corresponding data for the other NOACs. Regarding to ICHs in elderly patients, a significant risk reduction was noticed, in comparison with VKA, in case of use of dabigatran 150 mg (OR 0.43) and 110 mg (OR 0.36) and Apixaban (OR 0.38). Finally, as compared to VKA, Rivaroxaban has been found effective to reduce fatal bleedings (OR 0.53) and Apixaban to lower clinically relevant bleedings (OR 0.64). With the remaining NOACs, the rate of fatal or clinically relevant bleedings was similar to that of VKA.[44]

In Table 2, comparative data about efficacy and safety of the four NOACs *vs* warfarin, as a function of patient's age, are reported. It should be pointed out that data about gastrointestinal bleedings in the elderly are only available for dabigatran and edoxaban and not for other NOACs.

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 resilience 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 fall.[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.[10,48,49]

However, some conceptual and practi-

Table 2. Summary of efficacy and safety data of NOACs *vs* warfarin expressed as O.R.[46]

	Stroke		SE		Major Bleeding		Gastroint. Bleeding		ICH		Fatal Bleeding	
Age	≥75	<75	≥75	<75	≥75	<75	≥75	<75	≥75	<75	≥75	<75
RE-LY												
Dabigatran 150 mg *vs* VKA	0.66	0.64	1.2	0.73	1.78	1.19	0.43	0.43	0.92	0.55		
Dabigatran 110 mg *vs* VKA	0.88	0.93	1.03	0.65	1.4	0.83	0.36	0.34	0.73	0.5		
ROCKET AF												
Rivaroxaban *vs* VKA	0.8	0.95	1.15	0.92	-	-	0.88	0.52	0.53	0.48		
ARISTOTLE												
Apixaban *vs* VKA	0.71	0.85	0.65	0.73	-	-	0.38	0.5	0.8	0.67		
ENGAGE-AF TIMI 48												
Edoxaban 60 mg *vs* VKA	0.81	0.93	0.81	0.76	1.32		0.4	0.42	0.46	0.62		
Edoxaban 30 mg *vs* VKA	1.12	1.17	0.46	0.49	-	-	-	-	-	-		

cal aspects merit to be pointed out. Bleeding risk is one of the most feared consequences of OAT in the elderly (due to changes in body composition, with a reduction in lean body mass, renal dysfunction, frailty, comorbidities, polypharmacy, dementia and risk of falls) and, in case of NOACs, is exacerbated by the difficulty of monitoring their anticoagulant activity[48] and by the concerns about availability of antidotes. The recently introduced idarucizumab neutralizes the effects of dabigatran, thus permitting the use of such NOAC even in patients at higher risk of bleeding. On the contrary, no antidotes for Factor Xa inhibitors are available yet, although andexanet alpha is very promising in this regard. Fortunately, NOACs have a short half-life (between 5 and 17 hours), much lower than that of Warfarin (36-42 h).[50-52] ICH are one of the most devastating hemorrhagic complications, given the high risk of mortality and severe disability. All NOACs are very beneficial in reducing the ICH risk, when compared to Warfarin, and interestingly this benefit is maintained in the elderly, in spite of their increased susceptibility to falls and head trauma.[10,53]

Despite the absence of food limitations, some possible pharmacological interactions can promote adverse events by NOACs.[45] For example, the association with drugs, which are strong inducers, or inhibitors of P-gp can significantly reduce or enhance the plasma concentration of NOACs. As demonstrated by post-hoc analyses of the major RCTs, polypharmacy was frequent in the population included in the ARISTOTLE trial, and was associated with a higher comorbidity and mortality, as well as a higher rate of thromboembolic and major bleeding events. Although apixaban was more effective and at least as safe as warfarin, regardless of the number of other medications, its benefits tended progressively to reduce in function of the number of concomitantly prescribed drugs.[54] Similarly, in the re-analysis of the ROCKET-AF trial, patients taking more than 10 drugs showed a non-significant trend of increased risk of major and minor bleeding, in the absence of stroke/SE modifications, compared to patients taking up to 4 drugs.[55]

Moreover, patients on multidrug therapy have been shown to adhere less to therapy regimen than patients on little drug therapy. Contrary to Warfarin, for which about 36% of the patients have been shown not taking more than 20% of the planned doses,[56] all NOACs have demonstrated a good therapeutic adherence in over 85% of patients in real world clinical practice.[57,58] This is particularly important in patients with dementia,[59] which are known to poorly adhere to therapy and require additional treatment strategies, involving also caregivers, in order to ensure adequate surveillance of both adherence and side effects.[10,53] In this setting, NOACs should be preferred to warfarin.

In conclusion, current knowledge favors the use of NOACs in elderly patients. However, available data mainly derive from RCTs, whose main limitation is not having enrolled the most sick patients, such as those with frailty, important changes in functional status and serious comorbidities. Future studies on NOACs involving this type of patients should be encouraged. In the meantime, benefits and risks of NOACs have to be carefully weighted, always bearing in mind that elderly patients are at higher risk of thromboembolism. By such point of view, it would be advisable that a comprehensive geriatric assessment is carried out. No current studies have specifically implemented a comprehensive geriatric assessment in verifying safety and efficacy of NOACs. However, it seems conceivable that several already validated functional, cognitive and frailty scales can be employed at such purpose. Together with assessment of renal function and evaluation of specific clinical context, they should address the NOAC with the best efficacy and safety profile for a particular old patient. In such a double-edged sword, a multi-dimensional evaluation might improve patients' and care givers' compliance.

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