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REVIEW

Direct oral anticoagulants use in elderly patients with non valvular atrial fibrillation: state of evidence

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ABSTRACT

Non-valvular atrial fibrillation (NVAF) increases the risk of stroke by three- to five-fold, especially in elderly patients, creating a huge burden on medical system as well as a negative impact on patients' lives. Balancing efficacy and bleeding risk is a challenge when considering anticoagulation therapy in elderly patients, because of their frequent high risk of both stroke and bleeding. Real world data reveal the underuse of anticoagulation in the elderly, especially due to physicians' fear of bleeding, often neglecting the thromboembolic risk. Care of elderly patients with NVAF is often complicated by factors including adherence, cognitive impairment, health literacy, risk of falling, adverse effects, involvement of caregivers, and patient-physician relationship. Therefore, shared decision making and conversations between clinicians and patients are crucial. In addition, elderly patients often suffer from multiple comorbidities, requiring multiple concomitant medications, with an increased risk of drug interactions. Four non-vitamin K antagonist oral anticoagulants, the so-called direct oral anticoagulants (DOACs) — dabigatran, rivaroxaban, apixaban and edoxaban — have been approved for reducing the risk of stroke and systemic embolism in patients with NVAF. Clinical trials and real-world data show the advantages of this class of drugs compared to conventional anticoagulation in the treatment of elderly patients with NVAF and identify subgroups of older patients who may be more suitable candidates for particular agents. However, there are conflicting opinions on the absolute benefit of DOACs use in elderly patients. A key factor to consider is that elderly patients frequently suffer from renal impairment and therefore dose adjustments according to creatinine clearance are mandatory for DOACs. As each DOAC comes with its own unique advantages and safety profile, a personalized case by case approach should be adopted to decide on the appropriate anticoagulation regimen for elderly patients after weighing the overall risks and benefits of therapy.

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Key words: Anticoagulants - Atrial fibrillation - Aged.

Atrial fibrillation (AF) is the most frequent type of cardiac arrhythmia and it is due to disorganized electrical signals causing irregular contractions of the atria.

It is estimated that nowadays 1 million people in Italy suffer from AF and that 25% of the middle-aged adults in Europe and USA will develop AF. By 2030, 14-17 million AF patients are anticipated in the European Union, with 120,000-215,000 newly diagnosed patients per year.[1] AF prevalence is approximately 1.5-2% in the general population in developed countries. It increases as the population age grows, being 0.1% in individuals younger than 55 years, 3.8% among those 60 years and older, and 9% in those 80 years and older.[2, 3] Hence, it is a common disease in the elderly. In detail, data from ATRIA (USA) and VAL-FAAP (Europe) studies have shown that 9% of patients aged 80 years and 17.6% of patients older suffer from this disease.[4, 5] AF is associated with substantial mortality and morbidity. It also

independently increases the risk of congestive heart failure and of death by 1.5-2-times compared with patients in sinus rhythm.[6, 7] Finally, AF increases the incidence of dementia in patients with a history of stroke.[8] Ischemic stroke is the most feared complication of AF, and the risk of occurrence also increases with age, from 1.5% at age 50-59 years to 23.5% at age 80-89 years. As AF increases the risk of stroke by three- to five-fold, it creates a huge load on medical system as well as a negative impact on patients daily life.[9] With the ageing of the population, atrial fibrillation is becoming a growing global public health problem, with a burden impacting on patients, families and healthcare resources. Steming the risk of stroke and its resulting complications is critically important in the management of patients with AF. The most effective weapon the modern medicine has got to face the challenge to prevent stroke is the use of anticoagulants.

On the basis of a general agreement, "elderly" patients are the ones ≥75 years. These patients are usually frail: they suffer from important chronic comorbidities (hypertension, renal disease, coronary artery disease, heart failure, diabetes mellitus, chronic obstructive pulmonary disease, dementia) and frequent acute illnesses. Moreover, they have an increased risk of fall, they are often polymedicated, with an increasing risk of drug interactions, and their adherence to prescriptions is reduced, also because of their cognitive impairment. Hence, it is fundamental to take into account also the involvement of caregivers, as well as other factors including the patient-physician relationship. Thus, conversations between clinicians and patients, as well as shared decision making, are important. There are also changes in organ functions with the aging.[10] In elderly patients, increasing levels of fibrinogen and alterations of other coagulation factors create a prothrombotic environment with reduced fibrinolytic efficiency. Inflammation, endothelial dysfunction and an imbalance between oxidative stress and antioxidant defense accelerate the age-related atherothrombosis. In older people, antithrombotic therapy is complicated by physiological organ changes: kidney function and blood flow are reduced, hepatic size and architecture change, and body water and lean mass decline with age. Chronically reduced renal function and intercurrent illnesses, as pneumonia or heart failure, may cause an acute decline of creatinine clearance (CrCl) with impact on antithrombotic drugs primarily cleared by the kidney. In fact, renal function in the elderly should be estimated by equations that include age and weight, rather than by serum creatinine alone, which overestimates renal function in this population. Overall, the above changes may upset interindividual variability of response, increase drug toxicity, and potentially attenuate net therapeutic benefits, especially for drugs with a narrow therapeutic index such as warfarin.

The challenge of anticoagulation becomes even more difficult managing elderly patients, because they are at high risk of both thrombosis and bleeding.[11] In fact, age is not only an independent predictor of stroke in AF patients, but also of bleeding risk and this generates fear among physicians. For all these reasons, elderly patients can be clearly classified as "frail" individuals and they need to be treated paying attention to different aspects connected to their clinical and social conditions and taking into account their frailty. For more, clinical trials rarely include frail patients; therefore, deciding who would really benefit from anticoagulation can be difficult. Hence, in order to determine the best therapeutic approach in individuals with non-valvular atrial fibrillation (NVAF), the risk of both stroke and bleeding should be estimated in every patient, especially in the elderly population aged ≥75 years, which have an individual yearly risk of stroke >4%, but also an increased hemorrhagic risk. There are numerous strategies for estimating stroke risk in individuals with NVAF.[1] Hence, the critical conundrum is whether, in the older patient, the benefits of anticoagulation outweigh the bleeding risks. Scores help by providing more robust measures of risks and potential benefits compared with single measures like age alone. The most used scores are CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥65, diabetes, prior stroke/TIA, vascu-

TABLE I.—*Scores for risk stratification in atrial fibrillation.*

CHA_2DS_2-VASc	
Congestive heart failure	1 point
Hypertension	1 point
Age ≥75 years	2 points
Diabetes	1 point
Stroke or transient ischemic attack	2 points
Vascular disease	1 point
Age 65-74 years	1 point
Female sex	1 point
HAS-BLED	
Hypertension	1 point
Abnormal liver function	1 point
Abnormal renal function	1 point
Stroke	1 point
Bleeding	1 point
Labile international normalized ratio	1 point
Age >65 years	1 point
Drugs or alcohol	1 point

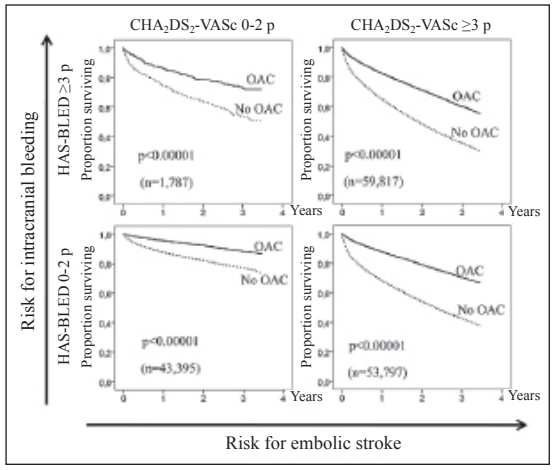

Figure 1.—All-cause mortality, ischemic stroke, and intracranial bleeds in relation to oral anticoagulant (OAC) treatment in patients with different combinations of stroke and bleeding risks on the CHA_2DS_2-VASc and HAS-BLED risk scores. From Friberg *et al.*[12]

lar disease, and female sex) and HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history/predisposition, labile international normalised ratio (INR), elderly ≥65, and drugs/alcohol abuse) for estimating, respectively, thromboembolic and bleeding hazards with anticoagulants [12] (Table I). These scores can be useful in guiding clinicians when weighing up the risk of stroke against the risk of bleeding. In fact, guidelines do not provide specific advice on anticoagulation decisions for frail older people who are more susceptible to adverse outcomes. The use of such integrated systems to estimate the benefits and the risks of anticoagulation should avoid undertreatment based on perceived bleeding risk alone.[13] In fact, lower rates of anticoagulant use are seen, especially in older patients, with up to half not being anticoagulated.[14] It is clear that, unless the risk of bleeding is exceedingly high, anticoagulation is required for most elderly subjects. Figure 1 illustrates how the benefit associated with anticoagulants grows together with the increase of the embolic risk, even in patients with HAS-BLED ≥3, of which age ≥65 is a key determinant.[12]

Bleeding risk with oral anticoagulation only mildly increases after the age of 80 years, while there is a dramatic increase in the risk of thrombosis in the same age group. While it is likely that a new generation of novel direct oral anticoagulants (DOACs) will eventually replace warfarin, the role of these agents in the elderly remains to be fully defined.[15]

Oral anticoagulants

After evaluating a patient's risk for stroke, physicians must decide between various medical strategies. From previous considerations, we can deduce that elderly patients should receive anticoagulation therapy for AF. CHA_2DS_2-VASc Score give a great relief to the increased age in the evaluation of thromboembolic risk. According to the CHA_2DS_2-VASc Score, all patients ≥75 years should receive anticoagulation therapy, unless there is a strong contraindication.[16, 17] The ATRIA and BAFTA studies have shown that in elderly patients with AF, oral anticoagulants have reduced the thromboembolic risk when compared to aspirin.[2, 18] The drugs used in these studies were vitamin K antagonists (VKAs), especially warfarin.

Vitamin K antagonists

VKAs have been the pillar of oral anticoagulation for nearly 50 years for reducing the risk of stroke in patients with AF. Randomized

clinical trials, such as SPAF-I, SPAF-II, SPINAF, and AFASAK,[19-22] showed that warfarin was significantly better than placebo and antiplatelet agents (aspirin) for the prevention of stroke in patients with atrial fibrillation. In a meta-analysis of these and other randomized trials, warfarin reduced stroke in untreated patients at intermediate risk from 4.3% to 1.1% (1.4% for aspirin), and in high risk patients from 12% to 4% (10% for aspirin).[23] A meta-analysis of 29 trials across comparators confirmed these findings.[24] In the ACTIVE W Trial,[25] warfarin was also compared with newer antiplatelet regimens, including the combination of aspirin and clopidogrel. Warfarin resulted significantly better than dual antiplatelet therapy for the prevention of stroke, without a significant increased risk of bleeding.

The target for thromboembolic protection with VKAs is maintaining an international normalized ratio (INR) between 2.0 and 3.0. In fact, an INR ≥3.0 has not shown any advantage, rather, on the contrary, it raises the risk of bleeding, especially in the elderly. This may be the reason for which the revised guidelines by Japanese Circulation Society (JCS) suggest a target INR of 1.6-2.6 for patients with NVAF and aged ≥70.[26] VKAs have some disadvantages, that are even more important in elderly patients. First of all, the INR should be monitored regularly and every patient should have to keep an INR diary, which could be difficult to get in the elderly. From another point of view, having the possibility to monitor the activity of VKAs trough a laboratory parameter (INR) could be an advantage, especially in critical and frail patient. Besides, fearing that this subgroup of patients would be eventually neglected and that INR monitoring would be skipped, VKAs were traditionally and incorrectly underused by physicians. Furthermore, elderly are prone to injuries and falls, and thus the fear of bleeding is considerable. Another consideration is that VKAs are linked to serum albumin, whose levels often fluctuate due to inflammation or malnutrition and lack of protein in the diets.[27] Hence, VKAs overdose is frequent in these situations and this forces the patient to monitor closely INR, needing a narrow therapeutic range. It is also important to remember the existence of VKAs interactions with several drugs and foods, which could significantly modify their pharmacological action. All these aspects generate complexity and inconvenience in VKAs therapy, provoking nonadherence, especially in elderly patients, often suffering from cognitive impairment.[28, 29] Surveys have found physicians to be reluctant to prescribe warfarin for elderly patients, for reasons that include overemphasis of bleeding risk at the cost of thromboembolic risk, as well as the complications inherent to VKAs therapy.[30, 31] These limitations to warfarin use could leave many elderly patients with AF without coverage; this is an important issue, as this is a population at high risk for life-threatening thromboembolic events.

DOACs

In recent years, new selective oral anticoagulants have become available as an alternative to VKAs. Four products are available: the direct thrombin inhibitor dabigatran and the Xa factor inhibitors rivaroxaban, apixaban and edoxaban. They are called DOACs, because they directly inhibit coagulation factors. All the DOACs have a more predictable pharmacokinetic profile than warfarin, easier dosages, no food limitations and fewer drug interaction. They do not require any monitoring and also for this reason they are rapidly getting popular even among the elderly. Efficacy and safety of DOACs in the elderly population are discussed, particularly for the fear of bleeding. Low weight and body mass, a high prevalence of renal impairment, cognitive decline and multiple comorbidities may predispose geriatric patients to adverse effects of these drugs. Many studies have already looked at the efficacy of DOACs compared to warfarin in patients with NVAF, but there are limited studies that look solely at the elderly population.[32] DOACs have been rapidly adopted into clinical practice before their full inclusion in clinical practice guidelines,[5] due to the advantages they offer over traditional anticoagulants, such as warfarin, low molecular weight heparin and

fondaparinux.[33-35] However, DOACs require specific dosing as well as baseline and ongoing laboratory tests, such as CrCl and hepatic function, to ensure safe and appropriate use. DOACs give the opportunity of fixed dosing regimens due to a wider therapeutic index and more predictable interpersonal pharmacokinetics and dynamics. However, determining the appropriate dose for a DOAC is dependent upon some patient-specific factors such as age, weight, baseline renal and hepatic function and concurrent medications. Even if, unlike warfarin, routine testing to evaluate anticoagulation effect is not required, it is essential to correctly dose DOACs, in order to obtain effective and safe anticoagulation.

Clinical considerations for elderly patients with NVAF

In elderly patients with NVAF there are additional factors, as comorbidities, interacting with anticoagulation. The most frequent are hypertension, coronary artery disease, heart failure, diabetes mellitus, chronic obstructive pulmonary disease and renal failure. Among patients with AF, the prevalence of chronic kidney disease (CKD) increases with age, and this increases the risk of stroke or systemic embolism and bleeding.[36] DOACs metabolism is influenced by renal impairment, while renal clearance is considered to be a minor determinant of anticoagulant response to warfarin, thus warfarin dosage adjustment is not necessary in this case. Patient characteristics related to renal function and age may influence the choice of DOACs (Table II). Since DOACs are eliminated by the kidneys to different extent, decreased fluid intake, fever, diarrhea, surgery, sepsis and radiocontrast procedures may acutely affect the pharmacokinetics of these drugs.[10] Even if it is possible to prescribe lower doses of DOACs in case of renal impairment, these drugs are generally advised not to be used in severe kidney disease. Multiple comorbidities in elderly patients often require multiple concomitant medications. In general, drug-to-drug interactions with DOACs are fewer compared with those of warfarin. All DOACs are substrates for the P-glycoprotein (P-gp) excretion system and several are metabolized, in part, by the enzyme CYP3A4. Drugs that are inhibitors or inducers of these systems may cause important interactions. Dronedarone, amiodarone, verapamil, diltiazem, quinidine, clarithromycin, erythromycin, rifampicin, ketoconazole and fluconazole, HIV protease inhibitors may seriously interact with DOACs, blocking the metabolism, thus leading to excessive anticoagulation.

TABLE II.—*Dose adjustment of DOACS according to age, body weight, renal function.*

Drug	Age	Body weight	Renal function
Dabigatran	<75years: 150 mg b.i.d. 75-80 years: 150 mg b.i.d. (consider 110 mg b.i.d. if the risk of stroke is low and the bleeding risk is high) ≥80 years: 110 mg b.i.d.	No dose adjustment required (clinical follow-up if body weight <50 kg)	CrCl ≥50 mL/min: no dose adjustment required CrCl 30-50 mL/min: 150 mg b.i.d. (110 mg b.i.d. if high risk of bleeding) CrCl <30 mL/min: contraindicated
Rivaroxaban	No dose adjustment required	No dose adjustment required	CrCl ≥50 mL/min: 20 mg o.d. CrCl 15-49 mL/min: 15 mg o.d. CrCl <15 mL/min: not recommended
Apixaban	Recommended 5 mg b.i.d. 2.5 mg b.i.d. in case of at least 2 of the following: age ≥80 years, body weight ≤60 kg, serum creatinine ≥1.5 mg/dL	No dose adjustment required 2.5 mg b.i.d. in case of at least 2 of the following: age ≥80 years, body weight ≤60 kg, serum creatinine ≥1.5 mg/dL	CrCl 15-29 mL/min: 2.5 mg b.i.d. CrCl <15 mL/min: not recommended
Edoxaban	No dose adjustment required	>60 kg: 60 mg o.d. ≤60 kg: 30 mg o.d.	CrCl ≥50 mL/min: 60 mg o.d. CrCl 15-49 mL/min: 30 mg o.d. CrCl <15 mL/min: not recommended

CrCl: creatinine clearance; b.i.d.: twice daily; o.d.: once daily.

The risk of falling is the primary factor influencing physicians to avoid anticoagulants prescription in the patients over 80 years old.[37] The increase in risk corresponds to a higher CHA_2DS_2-VASc Score. Patients ≥75 years receives 2 points in the CHA_2DS_2-VASc Score, so they need anticoagulation and therefore may be at elevated mortality risk for major bleeding and intracranial hemorrhages (ICH) following falls.

Adherence to anticoagulation therapy in elderly patients is influenced by potential barriers, such as the patient disease-related knowledge, health literacy, poor cognitive function, adverse effects and polypharmacy and patient-physician relationship.[38] DOACs regular administration is particularly important because of the quick onset/offset of action, making assessment of adherence an important component of follow-up visits. Rivaroxaban and edoxaban are administered once daily, while apixaban and dabigatran are to be taken twice daily.[39-42]

Caregivers frequently play an essential active role in the care of elderly patients. They are crucial in the coordination of care for elderly patients with NVAF, with multiple comorbidities, treated by an interdisciplinary team. A caregiver may also be important in transitioning between providers, as when an elderly patient with NVAF must move from hospitalization to long-term care, requiring an accurate and complete exchange of information.[43]

The introduction of DOACs made an individualized therapy possible. As each DOAC has its own features and safety profile, it would be desirable to choose the best anticoagulant drug for the specific patient, with his comorbidities, balancing his own stroke and bleeding risks and taking into account special considerations for elderly patients, previously analyzed. Patient's preferences, shared decision-making and discussion about the risks have to be the principles on which physicians should base their decision to prescribe a specific drug for each patient. These DOACs advantages are emphasyzed by the 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines.[44]

Four DOACs, four randomized controlled trials

In four large phase III randomized trials, patients with NVAF at moderate to high risk of stroke were randomly assigned to receive DOACs or VKA treatment.

Dabigatran

A total of 18,113 patients (mean $CHADS_2$ Score 2.1; mean age 71 years; 40% of patients aged ≥75 years) were randomized to dabigatran 110 or 150 mg or adjusted-dose warfarin in the RE-LY Trial (Randomized Evaluation of Long Term Anticoagulant Therapy with Dabigatran).[45] Dabigatran 150 mg twice daily was superior to warfarin for reduction of the risk of stroke or systemic embolism (RR 0.66, 95% CI: 0.53-0.82), while dabigatran 110 mg twice daily was non-inferior to warfarin in reducing the risk of stroke or systemic embolism (RR 0.91, 95% CI: 0.74-1.11). Dabigatran 110 mg twice daily was associated with a lower risk of major bleeding compared with warfarin (2.87 *vs*. 3.57%; P=0.002), while dabigatran 150 mg twice daily was associated with a similar risk of major bleeding (3.31 *vs*. 3.57%; P=0.32). Dabigatran 150 and 110 mg demonstrated a reduction in ICH compared with warfarin. The event rates of both stroke/systemic embolism as well as bleeding were higher in elderly patients aged ≥75 years. In elderly patients, the efficacy of both doses of dabigatran for stroke prevention was similar to that observed in patients aged <75 years. The risk of bleeding with dabigatran *versus* warfarin was significantly higher for both doses of dabigatran in elderly patients (HR 1.18, 95% CI: 0.98-1.42, for 150 mg twice daily and HR 1.01, 95% CI: 0.83-1.23, for 110 mg twice daily) compared with younger patients (HR 0.70, 95% CI: 0.57-0.86, for 150 mg twice daily and HR 0.62, 95% CI: 0.5-0.77, for 110 mg twice daily). A similar increase in the incidence of dabigatran-associated bleeding was observed in very elderly patients aged ≥80 years (HR 1.35, 95% CI: 1.03-1.77, for 150 mg twice daily and HR 1.13, 95% CI: 0.85-1.5, for 110 mg twice

daily). Further analysis showed that in elderly patients aged ≥75 years, the risk of ICH was lower with both doses of dabigatran in comparison with warfarin (0.37/0.42% per year *vs*. 1%), but the risk of extracranial bleeding was higher with dabigatran (4.1/4.7% per year *vs*. 3.4%).[46, 47]

Rivaroxaban

A total 14,264 patients (mean $CHADS_2$ Score 3.5; mean age 73 years, 44% of patients aged ≥75 years) were randomized to rivaroxaban 20 mg once daily (15 mg if creatinine clearance was 30-49 mL/min) or warfarin in the ROCKET AF Trial (Rivaroxaban Once-daily oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation).[48] Rivaroxaban was non-inferior to warfarin in the intent-to-treat analysis (annual rates of stroke/systemic embolism (SE) of 2.1% *vs.* 2.4%; P,0.001 for non-inferiority) and superior to warfarin in prespecified analyses of events during treatment (annual rates of 1.7% *vs.* 2.2%; P=0.02). The event rates of both stroke/systemic embolism as well as anticoagulant-associated bleeding were higher in elderly patients aged ≥75 years. Similar to the analysis of the trial's primary outcome, subgroup analysis for elderly patients aged ≥75 years demonstrated that rivaroxaban was non-inferior to warfarin for prevention of stroke or systemic embolism (SE) (HR 0.80, 95% CI: 0.63-1.02). The rates of major bleeding were similar in both elderly and younger patients (≥75 years 4.86% rivaroxaban *vs*. 4.40% warfarin per 100 patient-years; HR 1.11, 95% CI: 0.92-1.34; <75 years 2.69 *vs*. 2.79% per 100 patient-years; HR 0.96, 95% CI: 0.78-1.19; interaction P=0.336).[49] The risk of intracranial hemorrhage was lower with rivaroxaban (HR 0.67, 95% CI: 0.47-0.93), with no significant variations noted across different age groups. Data supported the efficacy and safety of rivaroxaban (for the primary outcome of stroke/SE, nor for major and non-major clinically relevant bleeding) compared with warfarin, with no differences due to age.

Apixaban

The ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) Trial [50] enrolled 18,201 patients (mean $CHADS_2$ Score 2.1; median age 70 years, 31% of patients aged ≥75 years) randomized to apixaban 5 mg twice daily (2.5 mg doses were used in patients with two or more of the following: age ≥80 years, body weight ≤60 kg, or serum creatinine level ≥1.5 mg/dL) or warfarin. Apixaban 5 mg twice daily was superior to dose-adjusted warfarin for prevention of stroke or systemic embolism in patients with AF (HR 0.79, 95% CI: 0.66-0.95). Efficacy of apixaban was similar in patients aged ≥75 years with respect to the primary outcome (HR 0.71, 95% CI: 0.53-0.95). The rate of major bleeding was 2.13% per year in the apixaban group, as compared with 3.09% per year in the warfarin group (HR 0.69, 95% CI: 0.60-0.80). No significant variation in the rate of major bleeding was observed across different age groups. Results were consistent for the 13% of patients ≥80 years. Gastrointestinal bleeds were not more common in the apixaban group. Advantages concerning major bleeding with apixaban were amplified in patients with renal dysfunction.[51, 52]

Edoxaban

The ENGAGE AF-TIMI 48 Trial (Evaluation of Efficacy and Safety of Edoxaban *versus* Warfarin in Subjects with Atrial Fibrillation - Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation) [53] randomized 21,105 patients with NVAF (mean $CHADS_2$ Score 2.8; mean age 72 years, 40% of the patients aged ≥75 years) to once-daily edoxaban 60 or 30 mg (in either group, the dose was halved if any of the following applied: CrCl 30-50 mL/min; body weight ≤60 kg; or concomitant use of verapamil, quinidine, or dronedarone) or VKA. Both edoxaban doses demonstrated non-inferiority to VKA in reducing the risk of stroke or SE in the primary analysis; high-dose edoxaban showed a trend toward better effi-

cacy *vs.* warfarin in a prespecified superiority analysis of the intent-to-treat population during the entire study period (1.57% *vs.* 1.80%; P=0.08). Both 60 and 30 mg regimens caused significantly less overall major bleeding and ICH. Gastrointestinal bleeds were more common with higher edoxaban dose *vs.* warfarin. The 30 mg dose was associated with higher rates of ischemic stroke but lower rates of all-cause death and gastrointestinal bleeding *vs.* warfarin.

Compared with warfarin, there were lower rates of major bleeding with both high-dose edoxaban (3.43 *vs*. 2.75%) and low-dose edoxaban (3.43 *vs*. 1.61%). No significant differences in the primary efficacy endpoint of stroke/systemic embolism, or the primary safety endpoint of major bleeding was noted in elderly patients ≥75 years, compared with those ≤75 years.[32, 54]

Meta-analyses

Some relevant meta-analyses of randomized clinical trials have been focused on the efficacy and safety of DOACs in patients aged ≥75 years. The analysis made by Sardar [55] included pool data from 25,031 patients enrolled in ten randomized clinical trials with the first three approved DOACs (dabigatran, rivaroxaban and apixaban). The risk of stroke and systemic embolism resulted significantly lower with DOACs *vs.* conventional therapy and there was no significant difference in the risk of major or clinically relevant bleeding between DOACs and conventional therapy in patients ≥75 years.

A more recent meta-analysis made by Sharma [56] examined data of elderly patients (75 years and above) enrolled in eleven randomized clinical trials of all four DOACs. There was an overall efficacy of DOACs in elderly patients, similar to that of the total population. Each drug resulted to be at minimum as effective as VKA in preventing stroke or systemic embolism, in particular dabigatran 150 mg and apixaban showed significant benefit. With apixaban and both doses of edoxaban a significant reduction of major bleeding was observed in elderly patients. Dabigatran 150 mg showed a non-significant higher risk of major bleeding compared to VKA in elderly; the same risk was similar to VKA with dabigatran 110 mg. Gastrointestinal bleeding was significantly higher in elderly compared to VKA. In elderly patients, apixaban and both doses of dabigatran showed significant reduction in ICH; a non-significant reduction was observed for rivaroxaban. Apixaban showed a reduced risk of clinically relevant bleeding in elderly. Rivaroxaban reduced the risk of fatal bleeding in elderly.

A third meta-analysis made by Sadlon [57] showed the same or greater efficacy of DOACs compared with VKAs in elderly, without statistical differences between apixaban, rivaroxaban, and highdose as well as low-dose dabigatran and edoxaban. However, when major or clinically relevant non-major bleeding were considered, apixaban showed a statistically significant odds reduction compared with dabigatran 150 mg (OR 0.54, 95% CI: 0.41-0.73), dabigatran 110 mg (OR 0.63, 95% CI: 0.47-0.86) and rivaroxaban (OR 0.57, 95 CI 0.45-0.73). The latter was associated with higher odds ratios for bleeding compared with both edoxaban doses, although low dose edoxaban showed the highest odds reduction (OR 0.41, 95% CI: 0.32-0.53 for edoxaban 30 mg *vs*. OR 0.71, 95% CI: 0.57-0.89). Finally, both doses of dabigatran were associated with increased odds ratios for bleeding compared with apixaban (dabigatran 150 mg: OR 1.84, 95% CI: 1.37-2.47; dabigatran 110 mg: OR 1.58, 95% CI: 1.17-2.13), low-dose edoxaban (dabigatran 110 mg: OR 2.19, 95% CI: 1.62-2.96) and high-dose edoxaban (dabigatran 150 mg: OR 1.49, 95% CI: 1.13-1.96).

However, even if the results of these three large meta-analyses are encouraging, they should be carefully considered because of the heterogeneity of the population enrolled.

In a large cohort study [58] of 134,414 Medicare patients, dabigatran 150 mg showed a reduced risk of ischemic stroke, intracranial hemorrhage and death and an increased risk of major gastrointestinal hemorrhage compared with warfarin in elderly patients.

Management of DOAC-associated bleeding

The increased bleeding risk in elderly patients emphasizes the need of reversal agents for anticoagulant. DOAC-associated bleeding can be difficult to manage because of the absence of commonly available drug-specific antidotes. General resuscitation measures including emergency management of an unstable patient with administration of fluids and blood products should always be the first step in management of DOAC-associated bleeding.

Although the short half-life of DOACs may decrease the need for immediate reversal, specific agents are necessary. Idarucizumab, a humanized monoclonal antibody fragment, has been approved for the reversal of dabigatran.[59-61] Idarucizumab received accelerated approval based on a reduction in unbound dabigatran and normalization of coagulation parameters in healthy volunteers.

A recombinant modified human factor Xa decoy protein, Andexanet alfa, was developed as a specific reversal agent designed to neutralize the anticoagulant effects of both direct and indirect factor Xa inhibitors. Results of the ANNEXA-A (apixaban) and ANNEXA-R (rivaroxaban) trials showed that andexanet reversed the anticoagulant activity of apixaban and rivaroxaban in older healthy participants within minutes after infusion, without evidence of clinical toxic effects.[62]

Procoagulant reversal agents such as prothrombin complex concentrate (PCC), activated PCC, and recombinant factor VIIa, although not evaluated in clinical trials, may be considered for reversal of apixaban; activated PCC, recombinant factor VIIa, and/or concentrates of coagulation factors II, IX, or X may be considered for reversal of dabigatran, but have not been evaluated in clinical trials; and PCC has partially reversed rivaroxaban-induced prothrombin time prolongation in healthy volunteers. Additionally, activated charcoal reduces absorption of apixaban, and dabigatran may be removed by hemodialysis, although there is no clinical evidence supporting these strategies in response to emergent bleeding.[48, 63, 64] These results are promising and effective reversal agents for all DOACs may soon become commonly available, which will encourage more physicians to prescribe DOACs in elderly patients. However, in daily clinical practice, reversal of DOACs' effect mostly relies on the short half-lives of these novel agents (5-17 h), which ensures rapid reductions in anticoagulant levels with time in patients who do not have concomitant renal or hepatic dysfunction. Because of its high renal clearance, dabigatran is the only DOAC that can be effectively removed from circulation with dialysis. After initial resuscitation, site-specific interventions such as gastrointestinal endoscopy, computerized tomography angiography and surgery may eventually be required to achieve hemostasis.[32]

Discussion

The aims in management and treatment of AF are to prevent thromboembolic events, mainly strokes, improving the quality of life, and at the same time, to avoid fatal, major and minor bleeding. Anticoagulation therapy should be administered in elderly patients with AF. CHA_2DS_2-VASc Score emphasizes the importance of increased age in the evaluation of thromboembolic risk. According to it, all patients ≥75 years should receive anticoagulation, unless there is a strong contraindication. VKAs were traditionally and incorrectly underused in elderly patients by physicians, fearing that this subgroup of patients would be eventually neglected and that INR monitoring would be skipped. Elderly patients are prone to injuries and falls and thus the fear of bleeding is considerable. HAS-BLED Score is valid in evaluating these patients' bleeding risk. In elderly patients, VKA overdose is frequent and hence INR should be monitored closely. DOACs do not require INR monitoring and are rapidly getting popular even among the elderly. All the available data point out the differences in bleeding risk between VKAs and DOACs and in the DOACs class. Dabigatran at a dosage of 110 mg twice daily showed a reduced cerebral hemorrhage risk in patients ≥75 years, but still maintained a smaller risk

for thromboembolic events *versus* warfarin. However, at a dose of 150 mg twice daily, the risk of major bleeding was higher compared to VKAs and was found to increase with age. Because of its renal elimination, dabigatran should be managed cautiously in patients with renal impairment and should be strongly contraindicated if creatinine clearance is below 30 mL/min. Rivaroxaban in patients ≥75 years has shown non-inferiority in comparison to warfarin in thromboembolic protection, as seen in the ROCKET-AF Trial. Patients receiving rivaroxaban presented less intracranial hemorrhages and fatal bleeding. These results applied even in the subgroup with moderate renal failure (clearance 30-49 mL/min). In such patients, the dosage of 15 mg once per day is recommended. Rivaroxaban is also contraindicated if creatinine clearance is below 30 mL/min. Apixaban, administered 5 mg twice daily, was compared to warfarin in the ARISTOTLE Trial. In the subgroup of patients ≥75 years, apixaban was more beneficial than warfarin in terms of thromboembolic protection and major bleeding events. Apixaban 2.5 mg twice daily was administered to patients with two of the three following criteria: age ≥80 years, weight ≤60 kg and serum creatinine 1.5 mg/dL. Edoxaban is administered once daily and has a renal excretion of 50%. In the ENGAGE AF TIMI 48 Trial, patients ≥75 years receiving edoxaban in the highest dosage presented a reduction in strokes and other thromboembolic events, but also an increase in major bleeding events. Patients ≥75 years receiving edoxaban 30 mg showed results similar to the warfarin group, and an even greater reduction in safety events over warfarin, compared to younger patients.[54] Summarizing, the use of DOACs provided a protective effect in comparison with VKA against intracranial bleeding in the elderly, consistent with the total population. Results for clinically relevant bleeding or fatal bleeding with DOACs did not show higher risks than with VKA in the elderly. Gastrointestinal bleeding was found to significantly increase with rivaroxaban, edoxaban 60 mg and dabigatran 150 mg in comparison with VKA in the total population. This risk increased further for dabigatran in the elderly.

Notably, the populations enrolled in the four phase III trials were different for severity of clinical conditions. In fact, in the edoxaban study (ENGAGE-AF-TIMI48) and rivaroxaban study (ROCKET-AF), both had higher mean $CHADS_2$ risk scores of 2.8 and 3.5, respectively, in comparison with 2.1 in both the dabigatran (RE-LY) and apixaban (ARISTOTLE) studies. The $CHADS_2$ risk assessment tool can help predict the risk of stroke in patients with AF, and indicated the inclusion of a lower-risk population in the RE-LY and ARISTOTLE studies.[56]

Conclusions

Treating the elderly patients with NVAF presents special challenges for many reasons, including their increased risk for both stroke and bleeding, and their cognitive impairment. Despite clinical trial data and evidence-based guidelines, surveys indicate that many clinicians continue to underuse anticoagulation in elderly patients that could receive benefit from it. Undertreatment represents a paradox because older patients are at higher risk of stroke and are more likely to need anticoagulant therapy compared with younger patients. DOACs show at least non-inferiority in stroke and systemic embolism prevention in elderly patients with NVAF compared to VKAs. Subgroup analyses are now available to illustrate the relative merits of DOACs compared with standard anticoagulation. Bleeding patterns seen with DOACs are different. Rivaroxaban carried equivalent hemorrhagic risk compared to warfarin, and dabigatran, apixaban, and edoxaban were all found to have lower risk of ICH or major bleeding. Dabigatran 150 mg, in particular, shows a significantly higher risk of gastrointestinal bleeding and a non-significantly higher major bleeding risk than VKA. Direct comparative studies of the DOACs should be undertaken in order to detect possible pharmacological differences among DOACs. Taking into account multiple factors such as thromboembolic and bleeding risks, comorbidities,

drug interactions, age, body weight, and renal function could help to personalize the prescription for a particular patient. It would be desirable to have clear indications to manage the clinical decision-making, in order to make the most appropriate choices for anticoagulation of this vulnerable population.

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