Review article

Oral anticoagulation in the elderly: new oral anticoagulants - innovative solution for an old problem?

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Abstract

The direct oral anticoagulants emerge as the most innovative and promising drugs towards preventing and treating cardiovascular disease, raising great interest among the scientific community.

Numerous studies and meta-analysis generated many data clarifying clinicians' doubts; however, there are remaining uncertainties regarding their use in particular groups such as patients with prosthetic valves, in valvular atrial fibrillation (defined as atrial fibrillation related to mitral rheumatic heart disease or prosthetic heart valves), among the elderly, in paraneoplastic thromboembolism, in pulmonary embolism with hemodynamic compromise, and the scarcity of specific antidotes.

This review article intends to condense the vast scientific production addressing new oral anticoagulants by focusing on their advantages and disadvantages when used on the elderly.

Introduction

The increase in lifespan created what probably is the greatest challenge in modern medicine: to prolong the quantity of life years while maintaining the quality of life. This challenge determines that invasive diagnostic and therapeutic methods should be implemented, as well as the latest technology in individuals once called "elderly". Ageing, as a result of better healthcare, has motivated important social changes that led to a paradigm change in medical practice: advanced aged now represents just another individual characteristic and not a limiting factor for clinical investment.

Bearing this in mind, the authors address the use of new oral anticoagulants in the elderly, stressing its advantages and disadvantages, and putting it into context with the singularities of this age group.

The complexity of anticoagulating the elderly

The decision of anticoagulating an individual with advanced age (a person over 80 years of age according to the World Health Organization)[1] is quite complex, since important factors should be taken into consideration in this particular group, for instance impaired cognition that limits drug adherence and potentiates the risk of falls.

The high prevalence of comorbidities that increase the hemorrhagic risk (cancer, hepatic, hematological and gastrointestinal diseases) and diseases that simultaneously constitute an indication for anticoagulation but also a risk factor for bleeding (arterial hypertension and ischemic stroke, according to the risk scores CHA_2DS_2VASc[2,3] and HASBLED[4]) are to be considered.

Chronic kidney disease (CKD) as well as low body weight, frequently involve dosing adjustments.

Another singularity in this population is polymedication which significantly contributes to the increased risk of pharmacological interactions.

Advanced age *per se* is, paradoxically, an independent risk factor for thromboembolism and hemorrhagic dyscrasia, impairing the delicate hemostatic balance.[5,6]

According to the thromboembolic risk score CHA_2DS_2VASc (anticoagulate if score ≥ 2 points), age ≥65 years scores 1 point and the score is doubled if ≥75 years old.[2,3,7] As such, it is evident that age plays a key role in this score, and being ≥75 years old is by itself a formal indication for anticoagulation considering that no contraindications are present.

Nevertheless, age ≥65 years is a risk factor according to the hemorrhagic risk score HASBLED.[4]

As clinicians, it is our responsibility to evaluate the benefit of anticoagulating and to judiciously decide which drug suits best each patient. How can we overcome this dilemma?

New oral anticoagulants (NOAC) seem to be an appealing alternative to traditional anticoagulation.

The discovery of these molecules had such an impact that it justified the review, in 2012, of the European Society of Cardiology non valvular atrial fibrillation (defined as atrial fibrillation not associated with rheumatic valvular disease nor prosthetic heart valves) guidelines.[8]

Pharmacokinetics and pharmacodynamics

Physiological factors like age, body weight, nutritional status and renal function, and clinical factors such as acute illnesses and drug interaction are well known determinants of the pharmacokinetics/ pharmacodynamics balance of a drug.

Medicating the elderly, often a group characterized for being frail, for suffering from multiple comorbidities, polymedicated and prone to clinical decompensation requires a stricter surveillance than the general population as the metabolism and elimination of many drugs are impaired, requiring dose adjustment in order to avoid toxicity.

NOACs directly and selectively inhibit a coagulation pathway enzyme (thrombin/factor IIa or factor Xa)[8] in opposition to coumarins that inhibit vitamin K-dependent coagulation factors (II,VII, IX and X)[9] and heparins that act primarily by activating antithrombin.[10]

Due to this mechanism of action, these drugs are also called direct oral anticoagulants (DOAC) or target-specific oral anticoagulants (TSOAC).

Dabigatran is a direct thrombin inhibitor (DTI), while rivaroxaban, apixaban and edoxaban inhibit factor Xa.

These drugs present predictable pharmacokinetics (PK), characterized by a fast onset of action, a short half-life and a wide therapeutic window, allowing a safe use without frequent monitoring.[9,11]

In the elderly with drug compliance limitations, the need for regular monitoring of anticoagulation levels due to the narrow therapeutic window of coumarin anticoagulants, in addition to the need of achieving a time in the therapeutic range (TTR) >70% to ensure appropriate efficacy, represents a major disadvantage for vitamin K antagonists (VKA) comparing to NOAC.[7,12]

In individuals with a TTR <70% or labile INR values, despite a good compliance, it may be pertinent to start a NOAC as long as the patients do not belong to the previously

described groups. The SAMe-TT_2R_2 score allows an estimation of the anticoagulation quality with coumarins in atrial fibrillation (AF), considering values between 0 and 1 to be adequate.[13]

Transition between anticoagulants

NOACs reach peak concentrations 1-4 hours after administration, which means that no bridging period with heparins is needed while transitioning from VKA to these new drugs.[14]

In the clinical trial ROCKET AF, the patients that stopped VKA and started rivaroxaban when the INR dropped <3, had similar outcomes as the group that started rivaroxaban *de novo*.[15,16]

Regarding dabigatran[17] and apixaban[18] it is recommended to start these drugs when the INR drops <2 after discontinuing the VKA. It is suggested to start edoxaban when INR ≤ 2.5.[19]

Considering that NOACs have a short half-life (12-14 hours for dabigatran[20,21], 5-13 hours for rivaroxaban[22], 8-15 hours for apixaban[10] and 6-10 hours for edoxaban[10]) compared to warfarin, which can reach a terminal half-life of up to 160 hours[9], it is speculated that an increased thromboembolic risk may be present during the transition to VKA.

The increased stroke risk verified in the ROCKET AF trial when patients were switched to VKA in the end of the trial, supports this suspicion.[23]

The scarce available evidence regarding the transition from NOACs to VKAs[10], suggests the start of VKA three days before suspending dabigatran if creatinine clearance (CrCl) > 50 mL/min, two days before if CrCl between 30-50 mL/min and one day before if CrCl between 15-30 mL/min.[24]

For rivaroxaban it is recommended to start the VKA four, three or two days before suspending the factor Xa inhibitor, respectively, considering the above mentioned CrCl intervals.[24]

Both for apixaban and edoxaban it is recommended to start the VKA and maintain the co-administration of the NOAC until the INR reaches values ≥ 2.[18,19]

The paucity of robust data addressing the transition between anticoagulants is furthermore complicated by the fact that the PK of the NOACs is altered and their half-life is prolonged in the elderly (the area under the concentration-time curve of dabigatran is increased twofold[20], for apixaban[18] there is a 33% increase and concerning rivaroxaban the half-life sets around 11-13 hours[22]).

Chronic kidney disease and low body weight

Renal excretion is a major elimination route for NOAC.[9,10] In CKD the half-life of these drugs is prolonged, therefore the European Heart Rhythm Association (EHRA) contraindicates the use of dabigatran if CrCl<30mL/min and in end-stage renal disease (CrCl<15mL/min) regarding the factor Xa direct inhibitors.[25]

The prevalence of CKD in the elderly may pose a limitation to NOACs use in this population.[26]

The pro-drug dabigatran etexilate is converted to the active drug dabigatran in the liver, presenting a longer clearance in CKD and in the elderly.[17] Considering this, the European Medical Agency (EMA) suggests a dose reduction (110 mg BID instead of 150 mg BID) in individuals over 80 years old, contraindicating this drug if the glomerular filtration rate (GFR) is below 30 ml/min.[20,26]

Regarding rivaroxaban, it is suggested a dose reduction from 20 mg/day to 15 mg/day if GFR 15-49 mL/min, and it is contraindicated if the GFR is below 15 ml/min.[22,26]

For apixaban, a dose reduction from 5 mg BID to 2.5 mg BID is suggested if at least 2 of the 3 following criteria are present: age ≥ 80 years, body weight ≤ 60 kg, serum creatinine ≥ 1.5 mg/dl. The same dose is suggested if GFR is between 15–29 mL/min. Patients with a creatinine clearance < 15 ml/min should not take this drug as mentioned before.[18,26]

With edoxaban, the standard dose is 60 mg/day and a dose reduction to half is recommended in patients with GFR between 50 and 15 mL/min or with a body weight ≤ 60 kg. It is contraindicated if GFR is < 15 ml/min.[19,27]

Betrixaban, a factor Xa inhibitor mainly excreted in bile is still undergoing phase III trials and could overcome some of the limitations of NOACs in severe CKD.[28]

Pharmacological interactions

The elderly are usually polymedicated and could therefore benefit from NOACs since they present a reduced pharmacological interaction potential compared to VKA.[9,10,29] Despite this, one must consider certain aspects.

Drugs that simultaneously inhibit CYP-3A4 and P-glycoprotein (systemic imidazole derivatives, tacrolimus, cyclosporine and ritonavir) increase apixaban and rivaroxaban bioavailability, and therefore its concomitant use is not recommended.[18,22]

Regarding edoxaban, its co-administration with rifampicin is contraindicated and a dose reduction to 30 mg/day is recommended if taken concomitantly with drugs that interfere with P-glycoprotein (including weak competitors such as amiodarone, diltiazem, verapamil, dronedarone, quinidine and macrolides).[19,27,30]

Since dabigatran is not metabolized by CYP450, it has a limited potential for pharmacological interactions; nonetheless, its PK may vary due to the concomitant use of drugs that modulate the action of the efflux transporter P-glycoprotein. It is recommended a dose reduction to 110 mg twice daily if taken simultaneously with verapamil.[20]

In a patient population prone to infections it may be preferable to use a NOAC instead of a VKA, since the effect of the latter may be potentiated by antibiotics that eliminate intestinal vitamin K-producing bacteria.[9,31]

Although quinolones are considered as the antibiotics that most frequently interfere with VKAs, exposure to other classes of antibiotics (penicillins, cephalosporins, macrolides, cotrimoxazole) and inclusively antimycotics (imidazole derivatives) encompasses an augmented hemorrhagic risk.[9,32]

The overestimation of the hemorrhagic risk

A variable that weighs in the risk-benefit equation of anticoagulating the elderly is their increased sensibility to coumarins. It is speculated that a reduced clearance of the VKAs and/or a greater inhibition of vitamin K-dependent coagulation factors may justify this.[33]

Furthermore, the elderly sometimes have nutritional deficits, namely a poor vitamin K diet that also enhances the coumarins' hemorrhagic risk.[9] Alcohol consumption also affects VKAs' efficacy.[9] Regarding the NOACs, rivaroxaban should be taken along with food as food ingestion influences its absorption and bioavailability by increasing its area under the curve plasma concentrations by 39%.[25]

Moreover, there is also the idiosyncratic variation of these drugs, based on the genetic polymorphism of CYP-2C9, which is responsible for VKA metabolization.[9]

The overall hemorrhagic risk (the sum of major and non-major bleedings) in clinical trials comparing NOACs and warfarin was similar, or even inferior in the NOACs' arm, as demonstrated in a meta-analysis that included over 70 000 patients.[34]

In these studies, the major bleeding risk (defined as an hemoglobin drop $\geq$ 2g/dl, need for $\geq$ 2 units of whole blood or packed red blood cells, and/or bleeding in a critical location) was about 2-3% per year, and was comparable to the risk of warfarin-treated patients.[15,27,30,35,36]

A meta-analysis that included 10 studies with dabigatran, rivaroxaban or apixaban in stroke prevention in atrial fibrillation and acute venous thromboembolism (VTE) prevention, specifically in patients $\geq$ 75 years, showed a greater efficacy in favor of NOACs (vs traditional anticoagulants) with a comparable risk for major or non-major clinically relevant bleeding.[37]

Considering deep vein thrombosis (DVT), a meta-analysis documented a reduction by half in the risk of fatal bleeding in patients treated with a NOAC.[38]

In patients aged < 75, dabigatran presented a dose-independent inferior bleeding risk, while in patients > 75 years the risk of major extracranial bleeding was similar between the 110 mg BID dose and warfarin, and greater with the 150 mg BID dose due to the increased risk of gastrointestinal (GI) bleeding.[39]

Concerning apixaban the bleeding risk was inferior independent of age.[36]

The risk of major GI bleeding was also greater with rivaroxaban[15] and edoxaban.[30]

It should be pointed out that the annual incidence of intracranial bleeding with NOACs ranged from 0.1-0.5%, which is quite lower than the incidence with coumarins, and that the reduction in fatal bleeding is intimately correlated with the decrease in intracranial bleeding.[34]

Considering that the major and most feared complication of anticoagulation is intracranial bleeding, which accounts for 90% of all warfarin-related deaths, this should be the strongest argument in favor of NOACs use.[40,41]

Advanced age is, aside from arterial hypertension, the major risk factor for spontaneous intracranial bleeding.[42,43]

The incidence of spontaneous intracranial bleeding in elderly aged 70-80 years is about 0.15% per year, increasing to 0.3-0.8% per year if these individuals are anticoagulated; nonetheless, the benefit of stroke reduction due to anticoagulation outweighs that risk.[44,45,46]

The risk of fall-related subdural haematoma is so low that an anticoagulated AF patient with an average stroke risk (estimated to be 5% per year) would have to fall 300 times per year so that the risk of bleeding outweighed the benefit of being under antithrombotic treatment.[33]

The scarcity of specific antidotes

Bearing in mind that the major complication for anticoagulation is hemorrhagic dyscrasia, the scarcity of available antidotes for NOACs, unlike coumarins and heparins (that can have their effect reverted with phytomenadione/vitamin K or protamine sulphate, respectively) may pose a limitation to its use.[10,14, 26,47,48, 49]

Activated charcoal and prothrombin complex appear as alternatives to a specific antidote, while antagonists to these molecules still undergo further development.[10,20] Fresh frozen plasma and phytomenadione, on the other hand, have revealed lack of efficacy neutralizing NOACs.[10]

In patients on dabigatran presenting with major bleeding, hemodialysis eliminated about 60% of the circulating DTI.[9]

The only available antidote, recently approved by the Food and Drug Administration (FDA) based on the RE-VERSE AD trial, is the human antibody fragment idarucizumab that inhibits dabigatran.[50]

A factor Xa analogue that reverses the effect of its inhibitors is still under development.[51]

The anticoagulant effect of NOACs cannot be monitored precisely with routine laboratory tests.[10,52] There are very specific analysis such as thrombin and ecarin clotting time which accurately estimate the effect of dabigatran, and the decrease of anti-Xa activity (that evaluates the Xa inhibitors' effect), however, its availability is scarce and only few centers have it by routine.[52]

Although NOACs present stable PK and PD, enabling the use of fixed doses without frequent monitoring, their use requires vigilance bearing in mind their potentially severe complications. The EHRA advocates regular follow-up based on the patient profile, such as periodical renal function evaluation in the elderly and frail patients.[25]

Some particular circumstances may also demand laboratory re-evaluation, namely the introduction of drugs that may interfere with their effect and acute clinical conditions that may alter the CrCl.[25]

This Association also recommends systematic laboratory testing and thorough examination of dyscrasia signs in the specific setting of patients with cancer submitted to chemotherapy and radiotherapy.[25]

Besides these situations it is reasonable to perform coagulation tests in emergency scenarios such as an overdose suspicion and patients undergoing an urgent surgical procedure.[25]

It should be emphasized that in this less compliant population regular laboratory testing could be justifiable given the short half-lives of the NOACs.

An undertreated high-risk population

Despite all the evidence about the benefit of anticoagulating the elderly with AF, particularly regarding stroke reduction, this population continues to be undertreated.[44,45,46]

Some series estimate that only 30 to 50% of the elderly without contraindication for anticoagulation are effectively under treatment.[53,54]

Advanced age is an independent risk factor for developing AF, and it is likely that 5-15% of individuals aged > 80 suffer from this arrhythmia. It is estimated that by 2050

half of the patients with AF will be over 80 years old.[55] According to a Framingham study 23.5 % of strokes in patients that age are due to AF.[56]

Currently about 70% of patients with AF are aged between 65 and 85 years.[57]

In individuals with AF, age ≥ 75 is the main risk factor for the development of stroke and thromboembolism[58], carrying a 3-fold increased risk of stroke and mortality compared to arterial hypertension.[59] An age-proportional ischemic stroke risk in non-valvular AF patients has also been found.[58,59]

Approved indications

1- Stroke prevention in non-valvular atrial fibrillation

Among anticoagulation indications, stroke prevention as a complication from AF is the widest and with greatest impact on public health.

Concerning this, the non-inferiority clinical trial ROCKET AF[15] demonstrated the efficacy of rivaroxaban vs warfarin in the prevention of the composite endpoint of stroke and systemic embolism in patients with non-valvular AF.

A secondary analysis of the ROCKET AF study that compared the efficacy and safety results between warfarin and rivaroxaban in patients aged ≥75 vs <75, found that the positive benefit-risk profile of rivaroxaban relative to warfarin did not vary with age.

In elderly patients on rivaroxaban there was a trend to increase the combined bleeding end point due to non-major bleeding, namely GI bleeding. Nevertheless the risk of intracranial hemorrhage was reduced, allowing us to conclude that the net clinical benefit of rivaroxaban compared with warfarin is more pronounced in elderly patients than in younger patients.[60]

In the ARISTOTLE clinical trial apixaban was proved to be superior to warfarin in terms of efficacy and safety.[36]

In the RE-LY study, 150 mg BID of dabigatran was superior to warfarin, with a similar overall major bleeding risk, despite the above mentioned increase in GI bleeding. The 110 mg BID dose had similar efficacy, with the advantage of reducing by 20% the risk of major bleeding.[35] An FDA Medicare analysis of a population over 65 years of age assigned to 150 mg BID or 75 mg BID (approved in the United States for patients with GFR between 15–30 mL/min) corroborated the RE-LY study results in terms of efficacy and safety.[61]

A 20% reduction on ischaemic strokes, a threefold lower rate of intracranial hemorrhagic complications and a 14% survival benefit were found. Although the major bleeding risk was equivalent to VKAs, a 28% increased risk of GI bleeding was associated to dabigatran. These findings were not extensible to the 16% of patients who

received dabigatran 75 mg BID, since in this group the outcomes were similar to warfarin's, except for a lower rate of intracranial hemorrhage with dabigatran.
Subgroup analyses stratified by age and gender showed that risk of major GI bleeding with the DTI was increased for women aged ≥ 75 and for men aged ≥ 85 vs warfarin.
Surprisingly in women aged ≥ 85 there was a trend for a higher risk of death with dabigatran compared to warfarin, questioning the efficacy of the DTI in this subset of patients. [61] This specific group was barely represented in RE-LY and analyses of age and mortality were not reported.

The positive efficacy and safety profile, namely a 28% prevention in stroke risk and a 26% reduction in major bleedings, was also confirmed by another real world general practice study.[62]

A cohort study enrolling routine care patients also achieved better outcomes with the DTI and found a greater stroke reduction particularly among the subgroup of patients aged 75 or older.[63]

A Danish nationwide registry studied patients started on dabigatran, rivaroxaban or apixaban for stroke prophylaxis in atrial fibrillation vs warfarin. It was concluded that VKA initiation has declined consistently since the introduction of the NOACs. Older age, female gender and personal history of stroke were features associated with the use of NOAC, while CKD (which was the factor most strongly linked to warfarin use), myocardial infarction and heart failure were related to VKA utilization. The predicted thromboembolic risk and hemorrhagic risk was similar between users of NOACs and warfarin.
The study inferred that treatment with NOACs is being consentaneous with guidelines recommendations.[64]

The international GLORIA-AF registry also addressed this issue, showing that there is a widespread use of oral anticoagulation in North America and in Europe, predominantly NOACs.[65]
This analysis highlighted that a significant amount of high-risk patients in North America and in Asia still receive antiplatelet treatment or have no antithrombotic therapy at all, albeit the percentage of treated patients with an indication for anticoagulation has risen comparing to previous registries.[66,67]

Edoxaban, initially introduced in Japan, received clearance from the FDA in January 2015, based on the non-inferiority trial ENGAGE-AF TIMI-48.[30]

It should be mentioned that patients with a GFR >95 ml/min (normal GFR according to the Kidney Disease Outcomes Quality Initiative criteria), presented an increased risk for ischemic stroke vs warfarin, therefore an alternative anticoagulant should be used. This finding may be explained by the fact that half the clearance of edoxaban is made by the kidney, which means that in patients with normal renal function the serum level of the drug, and consequently the efficacy, is inferior to that of patients with renal impairment.[19]

Dabigatran was the only NOAC to be studied in AF patients with mechanical valvular prosthesis.[18,19,22] The RE-ALIGN trial compared dabigatran (in doses that ranged from

150, 220 or 300 mg BID according to the GFR, aiming serum levels >50 ng/ml) with warfarin (adjusted to the target INR) in a population that underwent mechanical mitral/aortic valvuloplasty. The trial was stopped prematurely due to an increased risk of stroke, valvular thrombosis and bleeding (including major bleeding, namely hemopericardium) in the dabigatran arm.[68]

2- Cardioversion in non-valvular AF

X-VeRT was the first prospective randomized trial to compare a NOAC and VKA in patients with non-valvular AF undergoing elective electrical/chemical cardioversion. Rivaroxaban 20 mg/day (or 15 mg/day if GRF was 30-49 mL/min) reduced by 50% the risk of cardiovascular events (composite endpoint of stroke, transitory ischemic accident, systemic embolism, myocardial infarction and cardiovascular death), and by 24% the risk of bleeding.[69] Although the trial was not powered to achieve statistical significance, as it was designed to complement data from the ROCKET AF clinical trial, this indication was approved by the EMA.

Dabigatran and apixaban are also approved for this indication, based on *post hoc* analysis of the RE-LY[70] and ARISTOTLE[71] trials, respectively. A recent meta-analysis corroborated these findings.[72]

3- Treatment and prevention of venous thromboembolism

DVT, its prevention and treatment, as well as its major complication pulmonary embolism (PE), both commonly referred to as VTE, are an indication to anticoagulate.[10,73]

Aging is considered to be one of the most important and prevalent risk factors for developing VTE.[74]

The trials that compared NOACs with conventional drugs for VTE treatment and prevention (heparin followed by VKA) were designed for non-inferiority.

These trials included clinically stable PE patients and therefore there is no scientific evidence to support the use of NOACs in hemodynamically unstable PE.[28,75,76,77,78,79,80,81]

The EINSTEIN-DVT[75] and EINSTEIN-PE[76] trials included patients with acute DVT or PE and compared rivaroxaban 15 mg BID for 3 weeks followed by 20 mg/day up to 3, 6 or 12 months of treatment, with conventional treatment. The efficacy endpoint defined as recurrent DVT or PE and safety endpoint (bleeding) were similar between groups.

An extrapolation of the EINSTEIN-DVT trial was made, and the patients completing 6–12 months of treatment with the factor Xa inhibitor or VKA would continue to receive

additional 6–12 months of rivaroxaban or placebo. Compared to the placebo group, patients treated with rivaroxaban had fewer recurrences of DVT but presented an increased risk of non-major bleedings.[75]

Subgroup analysis from the EINSTEIN-DVT and EINSTEIN-PE pooled data found that fragile patients (defined as those aged > 75 years, CrCl < 50 ml/min or body weight ≤ 50 Kg) treated with rivaroxaban had a substantial net clinical benefit and major bleeding reduction compared to traditional treatment.[82]

In the RE-COVER trial, patients with acute VTE were initially treated with heparin for 5 to 10 days and afterwards received dabigatran 150 mg BID or warfarin. The rate of VTE recurrence and VTE-related mortality was similar in both arms. The overall bleeding risk and major bleeding rates were also comparable.[78]

The RE-COVER II trial, with the same design as RE-COVER, confirmed the non-inferiority of dabigatran.[79]

In the RE-MEDY trial, a sample of RE-COVER patients that received a minimum of 3 months of anticoagulation was selected and received additional treatment with warfarin or dabigatran for 6 to 36 months. The VTE recurrence rate was similar among groups but with less major bleedings in the dabigatran arm.[80]

The RE-SONATE trial had a similar design but compared dabigatran with placebo. The VTE recurrence rate was similar among groups but there were more major bleedings in the dabigatran arm.[80]

Additional data from the RE-COVER, RE-COVER II, RE-MEDY and RE-SONATE trials assured that age had no impact on recurrent VTE or hemorrhage outcomes.[79, 83]

The use of apixaban in VTE patients was evaluated in the AMPLIFY[80] and AMPLIFY-EXT[81] trials.

The AMPLIFY trial evaluated apixaban 10 mg BID during the first week followed by 5 mg BID for 6 months *vs* standard of treatment (enoxaparin followed by warfarin) for a total of 6 months in the treatment of VTE. The risk of major bleeding was significantly inferior in the arm of the factor Xa inhibitor, with a 69% reduction.[80]

In AMPLIFY-EXT two doses of apixaban, 2.5 mg BID and 5 mg BID were compared to placebo in patients previously treated for 6-12 months with conventional VTE anticoagulant treatment. By the end of the 12-month follow-up, the incidence of VTE, VTE-related, non VTE-related and overall mortalities were reduced with both doses of apixaban. Subgroup analysis found similar effectiveness with both doses of apixaban, nevertheless an increased risk of major and non-major bleeding was identified with both doses in patients aged > 75 years compared with placebo. [81]

The HOKUSAI-VTE trial included patients with acute DVT or PE and compared edoxaban to warfarin, after initial treatment with low molecular weight heparin

(LMWH) or unfractionated heparin. The duration of the treatment was 3-12 months and the VTE recurrence and VTE-related death rates were comparable between groups. In the group treated with the factor Xa inhibitor there was 19% less clinically relevant non-major bleedings. No difference in the outcomes was found in the subgroup of patients aged > 75 years.[27]

In paraneoplastic thrombosis there is a high VTE recurrence rate, as well as hemorrhagic complications.[84]

Monotherapy with LMWH is the most effective treatment in paraneoplastic VTE, despite the inconvenience of the parenteral administration, weight and GFR related dose adjustments and bleeding complications.[84]

In EINSTEIN-DVT and -PE trials approximately 5% of patients in each group had active cancer; the efficacy and safety results were comparable to the overall population.[75,76]

In AMPLIFY and AMPLIFY EXT, only 2.6% and 1.7% of the patients (respectively) had active cancer.[80,81] A subgroup analysis of the AMPLIFY trial demonstrated a reduction of VTE recurrence and a lower rate of bleeding with apixaban.[81]

In the dabigatran trials the percentage of patients with active cancer was about 4%, and a reduction of VTE recurrence was seen in the DTI group but the rate of bleeding complications was not reported.[77,78,85]

The HOKUSAI-VTE trial included 2.5% of patients with active cancer, a reduction of VTE recurrence as well as major/non-major bleedings was reported in the edoxaban arm.[27]

4- Secondary prevention of acute coronary syndrome

Recently EMA has recommended rivaroxaban 2.5 mg BID for secondary prevention of acute coronary syndrome (ACS) based on the ATLAS ACS 2-TIMI 51 trial, in which the combination of the factor Xa inhibitor with dual antiplatelet therapy (acetylsalicylic acid and clopidogrel) *vs* placebo for patients with recent ACS reduced the composite primary efficacy endpoint of cardiovascular death, myocardial infarction and stroke, while increasing the risk of intracranial hemorrhage from 0.2 to 0.4%. The 5 mg BID dose triplicated that risk and therefore was not approved by the above mentioned Agency.[86]

Conclusion

Despite the extensive evidence on the benefit of anticoagulating the elderly, this risk group is still undertreated.

Predictable pharmacokinetics and pharmacodynamics, a rapid onset of action, significantly less food and pharmacological interactions, the absence of routine laboratory monitoring, as well as an improved efficacy/safety ratio, are clear advantages of NOACs compared to VKAs in this polymedicated and less compliant group.

Considering that the main complication associated with antithrombotic treatment is intracranial hemorrhage and that NOACs have demonstrated to be superior to VKA in this endpoint, this probably is the strongest argument in favor of its use on a population prone to both thrombotic and bleeding events.

Notwithstanding its large applicability, NOACs are contraindicated in valvular AF and there is no scientific evidence that support its use in hemodynamically-unstable PE.

In paraneoplastic VTE the available evidence is insufficient to support its use, therefore further studies with follow-up periods greater than 6 months (as treatment is usually *ad aeternum*) are needed to address specifically patients with cancer and to compare NOAC with LMWH monotherapy.

In a society where the elderly have an increasingly significant role, there is an urge to redefine social and therapeutic concepts, in order to invest in a non-prejudiced and evidence-based *modus*.

Conflict of Interests

The authors declare no conflict of interests.

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