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Anticoagulation in AF and Elderly Frail Patient: How to Face New Challenges

Alba María Costa Grille, Irene Criado Martín
and Roberto Petidier Torregrossa

Abstract

Aging is an important risk factor for patients with atrial fibrillation. The estimated prevalence of atrial fibrillation in patients aged ≥80 years is 9–10%, with four- to fivefold increased risk of embolic stroke and with an estimated increased stroke risk of 1.45-fold per decade in aging. Older age is also associated with increased risk of major bleeding with oral anticoagulant (OAC) therapy. In this chapter, we will focus on the role of oral anticoagulation with new oral anticoagulants, non-vitamin K antagonist, in populations with common comorbid conditions, including age; chronic kidney disease; coronary artery disease, on multiple medication; and frailty. In patients 75 years and older, randomized trials have shown new oral anticoagulants to be as effective as warfarin, or in some cases superior, with an overall better safety profile, consistently reducing rates of intracranial hemorrhages. Prior to considering oral anticoagulant therapy in an elderly frail patient, a comprehensive assessment should be performed to include the risk and benefits, stroke risk, baseline kidney function, cognitive status, mobility and falling risk, multiple medication, nutritional status assessment, and life expectancy.

Keywords: anticoagulation, atrial fibrillation, elderly, new oral anticoagulants, frailty

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia in our daily clinical practice, affecting 4.5 million people in Europe and approximately 33.5 million people globally [1]. Estimates suggest a significant increase in AF incidence with age from 4.1/1000 under 75 years to 26.3/1000 in people older than 75 years [2]; in the same way, its prevalence rises from 0.1% in people under 55 years to 9% of those older than 80 [3–5], with an average annual cost of 2.365 € for each patient [6]. Due to the increase in life expectancy, the number of elderly people over 80 years with non-valvular AF (NVAF) will be fourfold in 2050; therefore, this group will represent over the 50% of the total of patients with this arrhythmia [4, 5], and stroke risk will increase 25–36% in elderly individuals between 80 and 89 years old [2, 7, 8].

Although people over 75 years present worse prognosis, higher mortality, and more adverse effects than those with age between 65 and 74 years [8], up to 35% of octogenarians do not receive oral anticoagulant (OAC) therapy [5]. The use of vitamin K antagonists (VKA) is reduced up to 14% for each decade of increase in

age, regardless of other stroke risk factors [5, 9]. Frequent reasons for not initiating antithrombotic treatment in frail older individuals are (1) antiplatelet therapy, (2) more than 90 years, (3) falling risk, and (4) nursing home residents, even though a strong indication and evidence show that frailty increases stroke risk but not major bleeding risk [10].

In Europe, since 2011, there is an available new family of OAC with indication for stroke and venous thromboembolism prevention in patients with NVAF. This new family includes four direct oral anticoagulants (DOACs), dabigatran (an active direct thrombin inhibitor), apixaban, edoxaban, and rivaroxaban (direct factor Xa inhibitors). Different meta-analyses have proved up to 20% reduced stroke risk, 12% reduced mortality, and 50% reduced intracranial bleeding risk, in comparison with warfarin, showing fewer drugs and food interactions, with no control needed [9, 11]. The cost-utility of these drugs has been tested by cost-effectiveness analysis [6], and benefits shown are maintained regardless of age, presenting a greater reduction on all-cause mortality, stroke, and major, intracranial, and total bleedings in older individuals, the ones that present a higher risk [12–14].

Nonetheless, studies specifically designed in elderly population are not yet available, and the current evidence exclude multimorbidity patients, polypharmacy, and geriatric syndromes and just evaluate the benefit using health indicators with low clinical impact in this population [15–17]. In addition, the mean age of the patients included in clinical trials is 5–10 years lower than mean age of real-life patients with NVAF; because of that, the current guidelines are not able to make strong recommendations for individuals of 85 years or more [5, 18]. In order to solve this lack of evidence, data from sub-group phase III pivotal trials have been used, including over 30,000 patients older than 75 years, to demonstrate efficacy of DOACs in comparison to VKA, showing equal safety profile in the older ones than in younger people [9, 19, 20] (**Figure 1**).

Anticoagulation in elderly patients supposes a huge challenge because of the frequent association with health conditions that can modify not only the therapy indication but also the type and dosage of drug, tolerance, adhesion, safety profile, and the results we seek. Among these health determinants, we highlight frailty, disability, comorbidity, polypharmacy, cognitive impairment, risk of falling, nursing home residents, nutritional status, oral feeding problems, sensory disorder, and personal and social issues [2, 21]. A complete comprehensive geriatric assessment (CGA) focused in identifying all these factors, combined with aging biology knowledge, a good

	RE-LY4 Dabigatran	ROCKET5 Rivaroxaban	ARISTOTLE1 Apixaban	AVERROES2 Apixaban	ENGAGE3 Edoxaban
Total	18,113	14,264	18,201	5,599	21,105
≥75 years (%)	7,258 (40)	6,229 (44)	5,678 (31)	1,898 (34)	8,474 (40)
Old olders	≥85 a (4%) N=722	≥85 a (4.6%) N=663	≥80 a (13%) N=2,436 ≥90 a (0.5%) N=84	≥85 a (7%) N=366	≥85 a (4%)

1. Halvorsen S, et al. Eur Heart J 2014;35:1864–1872;
2. Ng KH, et al. Age Ageing 2016;45:73–77;
3. Giugliano RP, et al. New Engl J Med 2013;369:2093–2104 (Supplementary Appendix);
4. Eikelboom JW, et al. Circulation 2011;123:2363–2372;
5. Halperin JL, et al. Circulation 2014;130:138–146
6. Kato ET, et al. J Am Heart Assoc 2016; 5(5): e003432 DOI: 10.1161/JAHA.116.003432.

Figure 1.
Rates of very elderly subjects present in pivotal studies of DOAC.

calculation of global and disability-free life expectancy, and a better knowledge of elderly pharmacology and individuality side effects of OAC in this population including long time to benefit, will allow us to get a better adequacy of this therapy and to reach better health results. More clinical trials including frail aging patients and all these factors are needed in order to achieve real-life elderly population representative samples to better adjust OAC therapy in this group of age [18, 22].

2. Medication considerations in elderly patients

2.1 Thromboembolic and bleeding risk

The thrombotic risk in patients with NVAF is stratified by the CHA2DS2-VASc score: in patients with CHA2DS2-VASc score of 0, the thrombotic risk does not overweigh the risk of bleeding, so OAC is not recommended, but a CHA2DS2-VASc score of 1 or more reverses the risk/benefit balance, and anticoagulation is clearly recommended with class IA indication [23, 24].

The uncertainty arises when the score is 1; as in these patients, the stroke rate varies widely.

The thrombotic risk increase with higher CHA2DS2-VASc score. In elderly patients (75 years or older), OAC is always suitable; however, we may assess each case individually and evaluate bleeding risk, which is the most important complication in the anticoagulation treatment [24, 25].

Bleeding events are the most important complication of antithrombotic treatment, so this requires us to personalize decision-making, especially in elderly patients with multimorbidity, geriatric syndromes, frailty, or disability.

There are several scores that help us to measure bleeding risk [26], which take into account different factors associated with increasing bleeding risk, with no intention of contraindicating OAC but to modify them with our intervention, in order to increase anticoagulation therapy's security profile.

The most widespread one is HAS-BLED score, which includes different determinants, all of them potentially modifiable, except the age. Other scores, like HEMORR2HAGES score, add some aspects that are usually included in CGA (falls, cognitive impairment) susceptible to evaluation and management by a geriatrician. The ATRIA bleeding risk score takes into account five parameters and stratify the bleeding risk into three levels [27, 28]. The ORBIT risk score proposes five determinants: age, anemia, previous bleeding episodes, renal impairment, and antiplatelet therapy. This one demonstrates similar discrimination with better sizing than HAS-BLED and ATRIA scores, according to ROCKET AF trial [29]. The ABC-bleeding score includes age, previous bleeding episodes, and three serum biomarkers (hemoglobin, troponin T, and GDF15 or cystatin C/creatinine clearance) and obtains more appropriated results than HAS-BLED and the ORBIT, according to ARISTOTLE and RE-LY trials [27], but biomarkers are not standardized, and there is no defined cut point (class IIb indication).

2.2 Suitable control of anticoagulation

Antithrombotic treatment efficacy mostly depends on an adequate maintenance of anticoagulation levels, universally measured in VKA treatment by the "international normalized ratio" or INR (therapeutic range from 2.0 to 3.0).

The poor control of anticoagulation according to INR represents one of the independent predictors most related with thrombotic and bleeding complications showing in several trials [30].

Different methods have been proposed to define VKA anticoagulation quality like control percentage out of therapeutic range, control cross-sectional analysis, and time in therapeutic range (TRT), being the last one the most widely accepted and related with complication incidence (stroke, bleeding, and mortality) [30].

The INR is considered suboptimal when TRT calculated by Rosendaal method [31] (assumes a linear progression between two INR values and calculates the specific INR for each day) is fewer than 65%. Actually, labile INR is one of the items included in HAS-BLED score, and whereas an INR value above 70% is associated with an optimal efficacy and security level, lower values increase stroke risk, major bleeding, and mortality, associating even worse prognosis than patients with NVAF not receiving antithrombotic treatment.

2.3 Frailty and falls

Frail elderly patients with NVAF must be considerately able to receive anticoagulation therapy, because of their increased vulnerability and higher functional worsening risk and disability. It is necessary to properly distinguish in the differentiation between frailty (autonomous elderly with risk of functional impairment) and disability (functional impairment established with a greater or lesser degree of autonomy) of dependency (established disability). Frailty might precede by several years the development of disability and other clinical outcomes and is a major risk factor for non-catastrophic disability [32].

The comprehensive geriatric assessment (CGA) associated with performance status test, like short performance physical battery (SPPB) or gait speed measurement, is the suitable tool to assess an individualized therapeutic decision [33–35]. Once we identify a frailty elderly, we must initiate multicomponent exercise intervention that has demonstrated reduction of multimorbidity, disability, dependence, and, thus, institutionalization and death.

Oral anticoagulation has been proposed to increase intracranial bleeding risk due to traumatic brain injury related with falls, and this has been used as a contraindication to initiate anticoagulation, increasing its under prescription as the result [36]. The evidence is limited because patients with falls are excluded from trials and also there are papers that deny that patients with OAC and higher risk of falls have increased risk of severe bleedings [37].

However, the benefit in patients with high risk (CHA2DS2-VASc >3) exceeds the risk of falls [38]. It has been estimated that a patient with anticoagulation treatment has to fall 295 times in a year so that the risk exceeds benefit of treatment [39]. Between DOACs, only edoxaban was assessed in patients with atrial fibrillation judged to be at increased risk of falling. No treatment interaction was observed between either dosing regimens of edoxaban and warfarin for the efficacy and safety outcomes. Treatment with edoxaban resulted in a greater absolute risk reduction in severe bleeding events and all-cause mortality compared with warfarin [40].

2.4 Polypharmacy

Polypharmacy is defined as the chronic administration of five or more drugs, and this may determine OAC's choice, because risk of interactions is higher with a bigger number of medicines.

VKA treatments have frequent pharmacological interactions that require strict monitoring in disease exacerbating phases, treatment modifications, or hospital admission.

DOACs interact with fewer drugs and offer a more stable level of anticoagulation, being indicated in patients with polypharmacy. All of them are dependent on

P-glycoprotein (Pgp) transport for intestinal absorption. So concomitant use of inhibitors of this transport (amiodarone, ketoconazole, quinidine and verapamil) is expected to increase absorption and plasma concentration of DOACs, and inducers (rifampicin and carbamacepine) led to a decrease of its. Rivaroxaban and apixaban are partially metabolized by cytochrome P450 (CYP3A4), so agents considered inhibitors (azolic antifungals, ritonavir, and macrolides) increase the effect, and inducers (rifampicin, phenytoin, carbamazepine, and phenobarbital) reduce it [8, 41].

2.5 Nutritional status

Attention to nutrition is fundamental to good clinical practice. Nutrition care improves patient outcomes and reduces healthcare costs. The feed MEGlobal Group on Nutrition in Healthcare proposed Nutrition Care Pathway recommending the steps: screen always, intervene promptly when needed, and supervene routinely [42].

The nutritional status may affect OAC activity; thus, protein deficit and hypoalbuminemia in malnutrition patients raise plasma OAC concentration and, therefore, bleeding risk. Because of that, every elderly patient with NVAF may undergo nutritional status assessment before to initiate oral anticoagulation. As a screening tool, Mini Nutritional Assessment Short Form (MNA-SF) is the one recommended to identify malnutrition patients and the ones in risk for it [43].

2.6 Cognitive impairment

Dementia is not an anticoagulation contraindication by itself. Factors as severity, life expectancy, and adherence to therapy must be taken into account before indicating antithrombotic treatment [28].

Elderly patients with mild to moderate cognitive impairment ("Global Deterioration Scale" or GDS <5) have not increased bleeding risk and may receive OAC [2].

Labile INR in patients with VKA is related with progression of cognitive impairment; thus, we should consider to change DOACs in patients with moderate impair of cognitive function [8].

We do not know the bleeding risk or the benefit of anticoagulation therapy in patients with NVAF and severe cognitive impairment (GDS 6–7), but this phase of dementia is related with greater mortality and poor quality of life [33]. Therefore, not initiating OAC is an option if we reach an agreement with family/caregiver.

Cognitive impairment determines poor therapy adherence, so OAC should be initiated in patients with a responsible caregiver [2].

2.7 Mobility and disability

To evaluate the instrumental activities of daily life is useful to assess the independence to manage the medication, and to evaluate basic activities of daily life determines the access to INR control. These are two essential tools that may help to choose DOACs because they can improve adherence and security [2].

Although there is no evidence about OAC therapy risk/benefit ratio in patients with severe/total functional dependence, this situation is related with increase short- and long-term mortality and poor quality of life [30]; thus, it is fair to not indicate anticoagulation in these patients.

2.8 Life expectancy

The total life expectancy and free of disability may modify anticoagulation attitude in the elderly with NVAF. Currently, life expectancy varies a lot around the

world from the higher one of 84.1 years in Japan to the lowest one of 52.2 years in Sierra Leone. Because of that, different tools have been designed and validated to assess life expectancy in order to take the right decision, not only based on age but also considering function, frailty, and comorbidity, among other factors. Some of the most used ones are Schonberg index and Lee index, both of them available in http://ePrognosis.ucsf.edu, and Studentski tables of life expectancy according to gait speed published in 2011 [44].

The time that an intervention takes until it shows efficacy (lag time to benefit) may be taken into account as well. Managing anticoagulation therapy, this time to benefit is really short, so life expectancy over 6 months is enough to justify anti-thrombotic drug use.

3. Dosage and profile of anticoagulant agent

Different meta-analyses [19, 20, 45, 46] have evaluated clinical randomized trials in patients over 75 years and have shown that DOACs are as effective in ictus prevention as warfarin; however, there are differences between type of OAC and dosage in the case of ictus/thromboembolism rate, major bleeding, and intracranial bleeding [47, 48]. Apixaban and edoxaban demonstrated less incidence of major bleeding in comparison with VKA; nevertheless, rivaroxaban and dabigatran 110 mg have similar risk. Apixaban, edoxaban, and dabigatran were associated with lower rates of intracranial bleeding compared to VKA [46].

Regarding gastrointestinal bleeding, in patients over 75 years, dabigatran and edoxaban 60 mg have demonstrated increased gastrointestinal bleeding risk in comparison with VKA, and there is no enough evidence in regard to apixaban and rivaroxaban [14, 45].

A recent review establishes that in patients older than 75 years, apixaban 5 mg twice a day is a first choice and rivaroxaban 20 mg once daily, edoxaban 60 mg once daily, and dabigatran 110 mg twice a day are second choices [49]. Given the increasing complexity of drug prescription in the elderly, in 2008 "Fit fOR The Aged (FORTA) classification" was born with intent to guide clinicians to optimize it. Recently, a systematic review of scientific evidence plus the application of Delphi method and FORTA classification has been published assessing oral anticoagulation in elderly patients with AF taking into account efficacy, security, and tolerability. Among DOACs, only apixaban was included in category A (very beneficial) because it shows superiority in every endpoint, including major and intracranial bleeding, ictus prevention, and mortality [50]. Furthermore, real-life anticoagulation [51–53] use trials have been published recently showing similar results to pivotal trials.

4. Special considerations for dosing in the elderly

There are no randomized clinical trials evaluating anticoagulation effectiveness and safety of the DOACs versus VKA in the clinical situations outlined below. The following recommendations are based on pivotal analyses of each of the new anticoagulants.

4.1 Elderly patient with renal failure

Chronic renal failure is a risk factor for both stroke and systemic embolism and in patients with atrial fibrillation (AF) [54]. Some studies using VKA have

demonstrated the overall benefit of anticoagulation in patients with moderate to severe renal insufficiency (creatinine clearance 15–49 ml/min) despite the increased risk of bleeding [55].

In patients with mild to moderate renal failure, direct anticoagulants have been shown to decrease the incidence of systemic thromboembolism and major bleeding compared to VKA [56].

Regarding safety in patients with moderate renal insufficiency (CrCl 30–49 ml/min), apixaban has been shown to significantly reduce the risk of bleeding against VKA. No significant differences were found between dabigatran and rivaroxaban versus VKA [57]. Severe renal failure (CrCl <30 ml/min) was an exclusion criterion in the pivotal clinical trials of DOACs.

Analyzing pharmacokinetic properties, it is important to point out that 80% of dabigatran is eliminated by the kidneys, while in the case of rivaroxaban, apixaban, and edoxaban, the renal clearance is 35, 25, and 50, respectively. Based on this, dabigatran is contraindicated in patients with CrCl<30 ml/min and all "anti-factor X" when the CrCl is less than 15 ml/min [15].

In patients with severe renal failure (CrCl <15 ml/min), including dialysis patients, clinical guidelines suggest not to anticoagulate [15].

4.2 Elderly patient with liver failure

Metabolism through cytochrome P450 (CYP3A4) is null or insignificant in dabigatran and edoxaban, about 25% in apixaban and 30% in rivaroxaban.

In mild hepatic insufficiency with no alteration of coagulation, the use of DOACs is safe, although it is recommended to avoid concomitant use with other drugs that are metabolized by CYP or glycoprotein P [58]. Moderate to severe hepatic failure (Child-Pugh B or C) is a contraindication for anticoagulation with both VKA and DOACs.

4.3 Elderly patient with malnutrition or dysphagia

Unlike VKA, DOACs do not interact with elements of the diet. Data available for elderly people with low weight and corporal mass index are poor. Current recommendations subscribe not to modify the doses of rivaroxaban or dabigatran in patients with low weight. In patients with <60 kg, the dose of edoxaban should be set (30 mg/24 h) and is one of the two criteria necessary to recommend the dose reduction of apixaban (2.5 mg/12 h) [48].

The DOAC binding-protein coefficient is variable: 35% dabigatran, 50% edoxaban, 90% apixaban, and > 90% rivaroxaban [58]. There are no specific recommendations in this regard, and the published data do not indicate to modify the doses [15].

4.4 Elderly patient with a history of bleeding

In elderly patients with an episode of major bleeding, whether intracranial or digestive, in treatment with anticoagulants, it is recommended to individualize the decision of restarting anticoagulation, based on several conditions such as age, control of blood pressure, the origin of bleeding, suitable anticoagulation at the time of the bleeding, the need for antiplatelet therapy, the risk of ischemic stroke, and, in the case of intracranial origin, the location and severity of it. Anticoagulation should be initiated after treatment of the cause, with anticoagulants with a low risk of bleeding, waiting 4–8 weeks if the origin was intracranial [49].

4.5 Elderly patient with cancer or terminal organ disease

There is no available evidence to establish recommendations on anticoagulant therapy in elderly patients with atrial fibrillation and cancer or terminal organ disease. In cancer patients with atrial fibrillation, the low efficacy and safety of VKA have been documented given the interactions with cancer treatment [55]. In this scenario, DOACs could provide great advantages due to their predictable action at fixed doses. Possible limitations would come from the hemorrhagic risk, especially in gastrointestinal and central nervous system tumors, and the potential interactions with antineoplastic treatment, especially if metabolized via CYP or glycoprotein P. In the case of terminal organ disease, the prescription of drugs that prolong life or prevent disability should be avoided or interrupted, especially if the time necessary to obtain the benefit exceeds life expectancy. With regard to anti-coagulants, it is recommended to suspend whenever the life expectancy is less than 6 months and is not a case of high thromboembolic risk [2, 59, 60].

4.6 Elderly patient during the perioperative period and surgery

DOACs, unlike VKA, can be maintained perioperatively, without the need for bridging therapy with heparin, given that their half-life is short, and the anti-coagulant effect decreases rapidly after stopping the drug. Taking into account renal function and the risk of bleeding from surgery, a safety time period prior to the intervention can be established without the need for biological control [61].

In invasive procedures with low or moderate risk of bleeding, the anti-factor Xa must be suspended 24 hours before the intervention and 36 hours, in the event of severe renal insufficiency (CrCl <30 ml/min). In the case of dabigatran, the withdrawal should be 24–48 hours before, depending on the glomerular filtration rate. In high-risk bleeding procedures, anti-factor Xa must be discontinued 48 hours before the intervention and dabigatran 48–96 hours according to the glomerular filtration rate.

If urgent intervention is required, the procedure should be delayed at least the half-life of the drug (approximately 12 hours average) provided there is an end of effect parallel to the half-life (dabigatran, apixaban, and edoxaban) and considering the degree of renal elimination (25% apixaban, 50% edoxaban, and 80% dabigatran).

If this is not possible, there is an increased risk of bleeding that must be assessed against the urgency of the intervention. Prothrombin complex concentrates or recombinant factor VIIa should be used only in the event of significant hemorrhage, and not for prophylactic reversal [62]. In 2015, the European Medicine Agency approved the use of idarucizumab, a humanized monoclonal antibody, to reverse the effects of dabigatran in life-threatening bleeding episodes. Although not yet commercialized in Europe [63], the use of andexanet alfa has been tested for the reversal of the effects of the factor Xa inhibitors with favorable and promising results in elderly patients, still awaiting approval [64].

The resumption of treatment will depend on the postoperative hemorrhagic risk. In the case of major or urological abdominal surgery, we should wait for the absence of active hemorrhage visualized by the drainages. In procedures with good hemostasis, it can be restarted 6 hours after the intervention, but normally the indications are to restart anticoagulation 24 hours after the intervention; unless there is a high risk of bleeding, then it is suitable to wait 48/72 hours [65].

In dental extractions and other dental procedures, there is currently no knowledge enough to establish recommendations with a high level of evidence. In the bibliography, being a low-risk procedure, it recommends limiting the extractions

to a maximum of two or three pieces and not stopping the anticoagulant treatment. It is recommended to perform the intervention about 12 hours after the last dose and not to take the next dose of DOAC until a good hemostasis is achieved, around 6 hours later [66].

4.7 Nonagenarian and centennial patients

There are no data available on the efficacy and safety of DOACs in nonagenarian and centennial patients [67]. As age increases, the risk of atrial fibrillation and embolism increases but also of bleeding [68]. Apixaban is the DOAC that has less renal elimination, and, compared to the VKA, apixaban and edoxaban at low doses (30 mg) are those that had lower rates of major hemorrhages in this age group, although the latter was less effective in the prevention of ischemic stroke. A subanalysis of the ARISTOTLE study concludes that patients with atrial fibrillation and a single associated factor (advanced age, low body weight, or renal dysfunction) have an increased risk of stroke or systemic embolism and major bleeding but show consistent benefits with the dose of 5 mg twice daily of apixaban vs. warfarin compared to patients without these characteristics. The dose of apixaban 5 mg twice daily is safe, effective, and appropriate for patients with only one dose-reduction criterion [69]. There is a study that indicates that there is an increased risk of ischemic stroke or systemic embolic event, in patients with a dose of apixaban 2.5 versus warfarin [70].

4.8 Elderly patient with poor therapeutic compliance or social isolation

The lack of adherence to chronic treatment with oral anticoagulants increases the risk of thromboembolic and hemorrhagic complications [71]. Multiple reasons have been described associated with the lack of adherence to anticoagulant treatment in the elderly, such as neuropsychiatric pathology, social situation, or lack of understanding of the disease [72]. DOACs present the advantages of the fixed dosage and do not need monitoring, which could improve the adherence and persistence of the treatment [71, 73, 74].

However, the transition from VKA to DOAC has not always been shown to ensure therapeutic compliance, which is even more important since this pharmacological group has a shorter half-life than VKA [22]. Therefore, an analysis of the reasons for nonadherence should always be performed before taking the anticoagulation decision and choosing the type of anticoagulant [1–31, 33–39, 43–69, 75–77] as well as, if indicated, carrying out strategies to ensure compliance with long-term treatment, regardless of the type of anticoagulant [78].

It is known that therapeutic regimens of a single dose per day can improve adherence [79], although this aspect is questioned given the variability of drug concentration and the risk of events when a dose is forgotten [80].

5. Comprehensive geriatric assessment before making a decision about OAC

As a result of what was previously exposed, it has been proposed to carry out a complete comprehensive geriatric assessment before to initiate anticoagulation treatment in people over 75 years with NVAF. The first step would be to assess a Barthel Index and Reisberg's GDS scale as represented in **Figure 2** [75]. Apart from the presence of Barthel Index ≥85 or GDS scale ≤5, it is also recommended to assess the short physical performance battery (SPPB) to identify frailty [35]. If frailty condition
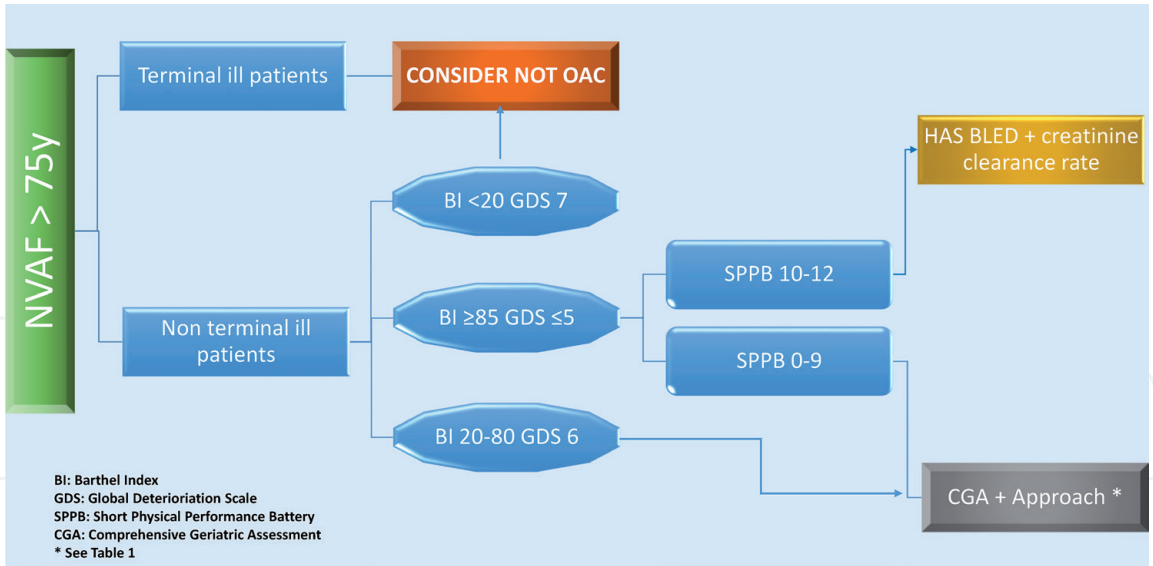
Figure 2.
Algorithm deciding oral anticoagulation in older patients. Modified from Petidier et al. [75].

CGA	Approach
CIRS-G	Prioritization
MNA-SF	Nutritional supplementation
Falls	Falling risk factor assessment Multicomponent exercise
Polypharmacy	STOPP/START

Table 1.
Comprehensive geriatric assessment and possible approaches before OAC.

was detected, Barthel Index is between 25 and 80, or if GDS scale is 6, it is necessary to include a comprehensive geriatric assessment with a Mini Nutritional Assessment Short Form (MNA-SF®) [43] for nutritional status, CIRS-G scale [76] to evaluate comorbidity], and STOPP/START criteria [77] to assess falling risk and polypharmacy and to identify potentially inappropriate medicines. Personalized anticoagulation use is the most important approach (**Table 1**).

6. Summary box

- The selection of the anticoagulant drug and its dose should be carried out individually and carefully, taking into account clinical, geriatric criteria, and the preferences of the patient.

- It seems reasonable that patients who do not receive such treatment should be limited to those with an obvious contraindication and those who are considered in short value because they are in the last days of their lives with very high competitive risks.

- In patients >75 years old, DOACs as a class were superior to warfarin with respect to both efficacy and safety, showing similar efficacy in the prevention of stroke and systemic embolization between them but with lowest risk of major bleeding for apixaban and lower rates of intracranial hemorrhage for apixaban, edoxaban, and dabigatran (than rivaroxaban or warfarin).

Conflict of interest

Alba María Costa Grille and Irene Criado Martín declare no conflict of interest. Roberto Petidier Torregrossa is a consultant for Bristol-Myers Squibb Company/ Pfizer Inc. and Daiichi Sankyo.

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References

[1] Chugh SS, Haymoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, et al. Worldwide epidemiology of atrial fibrillation: A global burden of disease 2010 study. Circulation. 2014;**129**:837-847

[2] Granziera S, Cohen AT, Nante G, Manzato E, Sergi G. Thromboembolic prevention in frail elderly patients with atrial fibrillation: A practical algorithm. Journal of the American Medical Directors Association. 2015;**16**:358-364

[3] Guindo Soldevila J, Martínez Ruíz MD, Duran Robert I, Tornos P, Martínez-Rubio A. Evaluación de riesgo tromboembólico y hemorrágico de los pacientes con fibrilación auricular. Revista Española de Cardiología Suplementos. 2013;**13**:9-13

[4] Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, et al. Prevalence of diagnosed atrial fibrillation in adults national implications for rhythm management and stroke prevention: The anticoagulation and risk factors In atrial fibrillation (ATRIA) study. JAMA. 2001;**285**:2370-2375

[5] Lefebvre MC, St-Onge M, Glazer-Cavanagh M, Bell L, Kha Nguyen JN, Viet-Quoc Nguyen P, et al. The effect of bleeding risk and frailty status on anticoagulation patterns in octogenarians with atrial fibrillation: The FRAIL-AF study. The Canadian Journal of Cardiology. 2016;**32**:169-176

[6] Barón Esquivias G, Escolar Albadalejo G, Zamorano JL, Betegón Nicolás L, Canal Fontcuberta C, Salas-Cansado M, et al. Análisis coste-efectividad de apixabán frente a acenocumarol en la prevención del ictus en pacientes con fibrilación auricular no valvular en España. Revista Española de Cardiología. 2015;**68**:680-690

[7] Annoni G, Mazzola P. Real-world characteristics of hospitalized frail elderly patients with atrial fibrillation: Can we improve the current prescription of anticoagulants? Journal of Geriatric Cardiology. 2016;**13**:226-232

[8] Suárez Fernández C, Formiga F, Camafort M, Cepeda Rodrigo M, Díez-Manglano J, Pose Reino A, et al. Antithrombotic treatment in elderly patients with atrial fibrillation: A practical approach. BMC Cardiovascular Disorders. 2015;**15**:143

[9] Edholm K, Ragle N, Rondina MT. Antihrombotic management of atrial fibrillation in the elderly. The Medical Clinics of North America. 2015;**99**:417-430

[10] Maes F, Dalleur O, Henrard S, Wouters D, Scavée C, Spinewine A, et al. Risk scores and geriatric profile: Can they really help us in anticoagulation decision making among older patients suffering from atrial fibrillation? Clinical Interventions in Aging. 2014;**9**:1091-1099

[11] De Caterina R, Husted S, Wallentin L, Andreotti F, Arnesen H, Bachmann F, et al. New oral anticoagulants in atrial fibrillation and acute coronary syndromes. Journal of the American College of Cardiology. 2012;**59**:1413-1425

[12] Halvorsen S, Atar D, Yang H, De Caterina R, Erol C, Garcia D, et al. Efficacy and safety of apixaban compared with warfarin according to age for stroke prevention in atrial fibrillation: Observations from the ARISTOTLE trial. European Heart Journal. 2014;**35**:1864-1872

[13] Halperin JL, Hankey GJ, Wojdyla DM, Piccini JP, Lokhnygina Y, Patel MR, et al. Efficacy and safety of rivaroxaban compared with

warfarin among elderly patients with nonvalvular atrial fibrillation in 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). Circulation. 2014;**130**:138-146

[14] Kato ET, Giugliano RP, Ruff CT, Koretsune Y, Yamashita T, Kiss RG, et al. Efficacy and safety of edoxaban in elderly patients with atrial fibrillation in the ENGAGE AF-TIMI 48 trial. Journal of the American Heart Association. 2016;**5**:e003432. DOI: 10.1161/ JAHA.116.003432

[15] Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei M, et al. ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. The task force for the management of atrial fibrillation of the European Society of Cardiology (ESC). European Heart Journal. 2016;**37**:2893-2962

[16] Heidenreich PA, Solis P, Estes NAM 3rd, Fonarow GC, Jurgens CY, Marine JE, et al. 2016 ACC/AHA clinical performance and quality measures for adults with atrial fibrillation or atrial flutter: A report of the American College of Cardiology/American Heart Association task force on performance measures. Journal of the American College of Cardiology. 2016;**68**:525-568

[17] Senoo K, Lau YC, Lip GY. Updated Nice guideline. Management of Atrial fibrillation. Expert Review of Cardiovascular Therapy. 2014;**12**:1037-1040

[18] Rich MW, Chyun DA, Skolnick AH, Alexander KP, Forman DE, Kitzman DW, et al. Knowledge gaps in cardiovascular care of the older adult population: A scientific statement from the American Heart Association, American College of Cardiology, and American Geriatrics Society. Journal

of the American College of Cardiology. 2016;**67**:2419-2440

[19] Sardar P, Chatterjee S, Chaudhari S, Lip GY. New oral anticoagulants in elderly adults: Evidence from a meta-analysis of randomized trials. Journal of the American Geriatrics Society. 2014;**62**:857-864

[20] Bai Y, Guo S-D, Deng H, Shantsila A, Fauchier L. Effectiveness and safety of oral anticoagulants in older patients with atrial fibrillation: A systematic review and meta-regression analysis. Age and Ageing. 2017:1-9

[21] Sennesael AL, Dogné JM, Spinewine A. Optimizing the safe use of direct oral anticoagulants in older patients: A teachable moment. JAMA Internal Medicine. 2015;**175**:1608-1609

[22] Wuthzler A, Ulmenstein S, Attanasio P, Huemer M, Shoker A, Hendrik L, et al. Treatment of nonagenarians with atrial fibrillation: Insights from the Berlin atrial Fibrillation (BAF) registry. Journal of the American Medical Directors Association. 2015;**16**:969-972

[23] Denoël P, Vanderstraeten J, Mols P, Pepersack T. Could some geriatric characteristics hinder the prescription of anticoagulants in atrial fibrillation in the elderly? Journal of Aging Research. 2014;**2014**:693740. DOI: 10.1155/2014/603740 Epub 2014 Sep 10

[24] Veiga F, Malfeito MR, Barros SM, Magariños MM. La anticoagulación oral en el anciano con fibrilación auricular no valvular. Revista Española de Geriatría y Gerontología. 2015;**50**:134-142

[25] Gil P. Reflexiones en torno a la anticoagulación en el anciano. Medicina Clínica (Barcelona). 2016;**147**:151-153

[26] Thomas IC, Sorrentino MJ. Bleeding risk prediction models in atrial

fibrillation. Current Cardiology Reports. 2014;**16**:432

[27] Hijazi Z, Oldgren J, Lindbäck J, Alexander JH, Connolly SJ, Eikelboom JW, et al. The novel biomarker-based ABC (age, biomarkers, clinical history)-bleeding risk score for patients with atrial fibrillation: A derivation and validation study. Lancet. 2016;**387**:2302-2311

[28] Tavassoli N, Perrin A, Bérard E, Gillette S, Vellas B, Rolland Y, et al. Factors associated with undertreatment of atrial fibrillation in geriatric outpatients with Alzheimer disease. American Journal of Cardiovascular Drugs. 2013;**13**:425-433

[29] O'Brien EC, Simon DN, Thomas LE, Hylek EM, Gersh B, Ansell JE, et al. The ORBIT bleeding score: A simple bedside score to assess bleeding risk in atrial fibrillation. European Heart Journal. 2015;**36**:3258-3264

[30] Anguita Sánchez M, Beromeu Fernandez V, Cequier Fillat A. Quality of vitamin K antagonist anticoagulation in Spain: Prevalence of poor control and associated factors. Revista Española de Cardiología. 2015;**68**:761-768

[31] Rosendaal FR, Cannegieter SC, van der Meer FJ, Briet E. A method to determine the optimal intensity of oral anticoagulant therapy. Thrombosis and Haemostasis. 1993;**69**:236-239

[32] Rodriguez-Mañas L, Fried LP. Frailty in the clinical scenario. Lancet. 2015;**385**(9968):e7-e9

[33] Formiga F, Robles J, Fort I. Dementia, a progressive disease: Severe dementia. Identification of end-stage dementia. Revista Española de Geriatría y Gerontología. 2009;**44**:2-8

[34] Stineman MG, Xie D, Pan Q, Kurichi JE, Zhang Z, Saliba D, et al. All-cause 1-, 5-, and 10-year mortality in elderly people according to activities of daily living stage. Journal of the American Geriatrics Society. 2012;**60**:485-492

[35] Freiberger E, de Vreede P, Schoene D, Rydwik E, Mueller V, Frändin K, et al. Performance-based physical function in older community-dwelling persons. A systematic review of instruments. Age and Ageing. 2012;**41**:712-721

[36] Pugh D, Pugh J, Mead GE. Attitudes of physicians regarding anticoagulation for atrial fibrillation: A systematic review. Age and Ageing. 2011;**40**:675-683

[37] Donzé J, Clair C, Hug B, Rodondi N, Waeber G, Cornuz J, et al. Risk of falls and major bleeds in patients on oral anticoagulation therapy. The American Journal of Medicine. 2012;**125**:773-778

[38] Gage BF, Birman-Deych E, Kerzner R, Radford MJ, Nilasena DS, Rich MW. Incidence of intracranial hemorrhage in patients with atrial fibrillation who are prone to fall. The American Journal of Medicine. 2005;**118**:612-617

[39] Man-Son-Hing M, Nichol G, Lau A, Lauoacis A. Choosing antithrombotic therapy for elderly patients with atrial fibrillation who are at risk for falls. Archives of Internal Medicine. 1999;**159**:677-685

[40] Steffel J, Giugluano RP, Braunwald E, Murphy SA, Mercuri M, Choi Y, et al. Edoxaban versus warfarin in atrial fibrillation patients at risk of falling. ENGAGE AF–TIMI 48 analysis. Journal of the American College of Cardiology. 2016;**68**:1169-1178

[41] Verheugt FW, Granger CB. Oral anticoagulants for stroke prevention in atrial fibrillation: Current status, special situations, and unmet needs. Lancet. 2015;**386**:303-310

[42] Correia MI, Hegazi RA, Higashiguchi T, Michel JP, Reddy BR, Tappenden KA, et al. Evidence-based recommendations for addressing malnutrition in health care: An updated strategy from the feed M.E. global study group. Journal of the American Medical Directors Association. 2014;**15**:544-550

[43] Kaiser MJ, Bauer JM, Ramsch C, Uter W, Guigoz Y, Cederholm T, et al. Validation of the mini nutritional assessment short-form (MNA®-SF): A practical tool for identification of nutritional status. The Journal of Nutrition, Health & Aging. 2009;**13**:782-788

[44] Studenski S, Perera S, Patel K, Rosano C, Faulkner K, Inzitari M, et al. Gait speed and survival in older adults. JAMA. 2011;**305**:50-81

[45] Sharma M, Cornelius VR, Patel JP, Davies JG, Molokhia M. Efficacy and harms of direct oral anticoagulants in the elderly for stroke prevention in atrial fibrillation and secondary prevention of venous thromboembolism: Systematic review and meta-analysis. Circulation. 2015;**132**:194-204

[46] Malik AH, Yandrapalli S, Aronow WS, Panza JA, Cooper HA. Meta-analysis of direct-acting ora anticoagulants compared with warfarin in patients >75 years of age. The American Journal of Cardiology. 2019;**123**:2051-2057

[47] Capranzano P, Miccichè E, D'Urso L, Privitera F, Tamburino C. Personalizing oral anticoagulant treatment in patients with atrial fibrillation. Expert Review of Cardiovascular Therapy. 2013;**11**:959-973

[48] Turagam MK, Velagapudi P, Flaker GC. Stroke prevention in the elderly atrial fibrillation patient with comorbid conditions: Focus on non-vitamin K antagonist oral anticoagulants. Clinical Interventions in Aging. 2015;**10**:1431-1444

[49] Diener HC, Aisenberg J, Ansell J, Atar D, Breithardt G, Eikelboom J, et al. Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: Part 2. European Heart Journal. 2017;**38**:860-868

[50] Wehling M, Collins R, Gil VM, Hanon O, Hardt R, Hoffmeister M, et al. Appropriateness of oral anticoagulants for the long-term treatment of atrial fibrillation in older people: Results of an evidence-based review and international consensus validation process (OAC-FORTA 2016). Drugs & Aging. 2017;**34**:499-507

[51] Yao X, Abraham NS, Sangaralingham LR, Bellolio F, McBane RD, Shah ND, et al. Effectiveness and safety of dabigatran, rivaroxaban and apixaban versus warfarin in nonvalvular atrial fibrillation. Journal of the American Heart Association. 2016;**5**:e003725. DOI: 10.1161/JAHA.116.003725

[52] Noseworthy PA, Yao X, Abraham NS, Sangaralingham LR, McBane RD, Shah ND. Direct comparison of dabigatran, rivaroxaban and apixaban for effectiveness and safety in nonvalvular atrial fibrillation. Chest. 2016;**150**:1302-1312

[53] Vinogradova Y, Coupland C, Hill T, Hippisley-Cox J. Risks and benefits of dierct oral anticoagulants versus warfarin in a real world setting: Cohort study in primary care. BMJ. 2018;**362**:k2505

[54] Olesen JB, Lip GY, Kamper AL, Hommel K, Kober L, Lane DA, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. The New England Journal of Medicine. 2012;**367**:625-635

[55] Friberg L, Benson L, Lip GY. Balancing stroke and bleeding risks in patients with atrial fibrillation and renal

failure: The Swedish atrial fibrillation cohort study. European Heart Journal. 2015;**36**:297-306

[56] Del-Carpio Munoz F, Gharacholou SM, Munger TM, Friedman PA, Asirvatham SJ, Packer DL, et al. Meta-analysis of renal function on the safety and efficacy of novel oral anticoagulants for atrial fibrillation. The American Journal of Cardiology. 2016;**117**:69-75

[57] Harel Z, Sholzberg M, Shah PS, Pavenski K, Harel S, Wald R, et al. Comparisons between novel oral anticoagulants and vitamin K antagonists in patients with CKD. JASN. 2014;**25**:431-442

[58] Rosanio S, Keylani AM, D'Agostino DC, DeLaughter CM, Vitarelli A. Pharmacology, benefits, unaddressed questions, and pragmatic issues of the newer oral anticoagulants for stroke prophylaxis in non-valvular atrial fibrillation and proposal of a management algorithm. International Journal of Cardiology. 2014;**174**:471-483

[59] O'Mahony D, O'Connor MN. Pharmacotherapy at the end-of-life. Age and Ageing. 2011;**40**:419-422

[60] Cruz-Jentoft AJ, Boland B, Rexach L. Drug therapy optimization at the end of life. Drugs & Aging. 2012;**29**:511-521

[61] Heidbuchel H, Verhamme P, Alings M, Antz M, Hacke W, Oldgren J, et al. European heart rhythm association practical guide on the use of new oral anticoagulants in patients with nonvalvular atrial fibrillation. EHRA Practical Guide. Europace. 2015;**17**:1467-1507. DOI: 10.1093/europace/euv309

[62] Niessner A, Tamargo J, Morais J, Koller L, Wassmann S, Husted SE, et al. Reversal strategies for non-vitamin K antagonist oral anticoagulants: A critical appraisal of available evidence and recommendations for clinical management—a joint position paper of the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy and European Society of Cardiology Working Group on Thrombosis. European Heart Journal. 2017;**38**:1710-1716

[63] Finks SW, Rogers KC. Idarucizumab (Praxbind®): The first reversal agent for a direct oral anticoagulant. The American Journal of Medicine. 2016. DOI: 10.1016/j.amjmed.2016.11.029. [Epub ahead of print]

[64] Connolly SJ, Milling TJ Jr, Eikelboom JW, Gibson CM, Curnutte JT, Gold A, et al. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. The New England Journal of Medicine. 2016;**375**:1131-1141

[65] Vivas D, Roldán I, Ferrandis R, Marín F, Roldán V, Tello-Montoliu A, et al. Manejoperioperatorioyperiprocedimiento del tratamiento antitrombótico: documento de consenso de SEC, SEDAR, SEACV, SECTCV, AEC, SECPRE, SEPD, SEGO, SEHH, SETH, SEMERGEN, SEMFYC, SEMG, SEMICYUC, SEMI, SEMES, SEPAR, SENEC, SEO, SEPA, SERVEI, SECOT y AEU. Revista Española de Cardiología. 2018;**71**:553-564. DOI: 10.1016/j.recesp.2018.01.001

[66] Altirriba J, Aparicio P. Anticoagulación oral en Atención Primaria. Revista Española de Sanidad Penitenciaria. 2017;**19**:28-44

[67] Stöllberger C, Brooks R, Finsterer J, Pachofszky T. Use of direct-acting oral anticoagulants in nonagenarians: A call for more data. Drugs & Aging. 2016;**33**:315-320

[68] Lip GY, Clementy N, Pericart L, Banerjee A, Fauchier L. Stroke and major bleeding risk in elderly patients aged ≥75 years with atrial fibrillation:

The Loire Valley atrial fibrillation project. Stroke. 2015;**46**:143-150

[69] Alexander JH et al. Apixaban 5 mg twice daily and clinical outcomes in patients with atrial fibrillation and advanced age, low body weight, or high creatinine a secondary analysis of a randomized clinical trial. JAMA Cardiology. 2016;**1**:673-681. DOI: 10.1001/jamacardio.2016.1829

[70] Nielsen PB, Skjøth F, Søgaard M, Kjældgaard JN, Lip GY, Larsen TB. Effectiveness and safety of reduced dose non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: Propensity weighted nationwide cohort study. British Medical Journal. 2017;**356**:j510

[71] Potpara TS, Lane DA, Lip GY. Optimizing stroke prevention in atrial fibrillation: Better adherence and compliance from patients and physicians leads to better outcomes. Europace. 2015;**17**:507-508

[72] Kneeland PP, Fang MC. Current issues in patient adherence and persistence: Focus on anticoagulants for the treatment and prevention of thromboembolism. Patient Preference and Adherence. 2010;**4**:51-60

[73] Zalesak M, Siu K, Francis K, Yu C, Alvrtsyan H, Rao Y, et al. Higher persistence in newly diagnosed nonvalvular atrial fibrillation patients treated with dabigatran versus warfarin. Circulation. Cardiovascular Quality and Outcomes. 2013;**6**:567-574

[74] Laliberte F, Cloutier M, Nelson WW, Coleman CI, Pilon D, Olson WH, et al. Real-world comparative effectiveness and safety of rivaroxaban and warfarin in nonvalvular atrial fibrillation patients. Current Medical Research and Opinion. 2014;**30**:1317-1325

[75] Petidier R, Abiazanda P, Nogueron A, Gonzalo M, Gutierrez J, Gil P, et al. Revista Española de Geriatría y Gerontología. 2018;**53**:344-355

[76] Miller MD, Paradis CF, Houck PR, Mazumdar S, Stack JA, et al. Rating chronic medical illness burden in geropsychiatric practice and research: Application of the Cumulative illness rating scale. Psychiatry Research. 1992;**41**:237-248

[77] O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: Version 2. Age and Ageing. 2015;**44**:213-218

[78] Rodriguez RA, Carrier M, Wells PS. Non-adherence to new oral anticoagulants: A reason for concern during long-term anticoagulation? Journal of Thrombosis and Haemostasis. 2013;**11**:390-394

[79] Srivastava K, Arora A, Kataria A, Cappelleri JC, Sadosky A, Peterson AM. Impact of reducing dosing frequency on adherence to oral therapies: A literature review and meta-analysis. Patient Preference and Adherence. 2013;**7**:419-434

[80] Vrijens B, Heidbuchel H. Non-vitamin K antagonist oral anticoagulants: Considerations on once- vs. twice-daily regimens and their potential impact on medication adherence. Europace. 2015;**17**:514-523