OPEN

Non–Vitamin K Antagonist Oral Anticoagulants and Factors Influencing the Ischemic and Bleeding Risk in Elderly Patients With Atrial Fibrillation: A Review of Current Evidence

Giuseppe Patti, MD and Sylvia Haas, MD, PhD†*

Abstract: Non–vitamin K antagonist oral anticoagulants (NOACs) are a widely prescribed treatment to prevent stroke in patients with nonvalvular atrial fibrillation, and a therapy and preventative measure to prevent recurrences following venous thromboembolism. Optimal use of NOACs requires a thorough knowledge of the pharmacology of these drugs, as well as an understanding of patient factors affecting their use. The 4 NOACs—dabigatran, apixaban, edoxaban, and rivaroxaban are available in a range of doses suitable for differing indications and with a variety of dose reduction criteria. Identification of the correct dose is one of the key challenges in the individualization of treatment. Elderly patients with atrial fibrillation are at a greater risk of both ischemic and bleeding events than younger patients. Consequently, it is essential to achieve balance in anticoagulation strategies. Medication adherence to NOACs is important for safe and effective treatment, particularly in elderly populations. A growing body of evidence shows that once-daily dosing improves adherence and persistence to therapy, without having an impact on bleeding risk.

Key Words: non–vitamin K oral anticoagulants, nonvalvular atrial fibrillation, adherence, dosing regimen, elderly

(*J Cardiovasc Pharmacol*™ 2021;77:11–21)

INTRODUCTION

Non–vitamin K antagonist anticoagulants (NOACs) have become established as alternative options to vitamin K antagonists (VKA) to prevent stroke in individuals with nonvalvular atrial fibrillation (AF), and the therapy for and to prevent recurrences of venous thromboembolism (VTE). Unlike warfarin, these drugs have preset doses and routine monitoring of coagulation is not mandated. Four NOACs—dabigatran, apixaban, edoxaban, and rivaroxaban—are now licensed for use in AF after demonstrating good efficacy and safety profiles in Phase III clinical trials.[1–4] Although the NOACs have revolutionized management of anticoagulation because of their effectiveness and reduced toxicity, the reduced monitoring is partly a result of the lack of sensitive monitoring and testing that is available. The NOACs have differences in pharmacokinetics and more importantly they differ in dosing regimen, which may vary depending on the indication for the same drug. For example, rivaroxaban is given once daily as stroke prophylaxis, twice daily in the acute treatment of VTE, and then once daily to provide secondary prevention of VTE.[5] Dabigatran and apixaban are always given twice daily,[6–9] whereas edoxaban is always given once daily.[10,11]

The prevalence of AF is likely to rise substantially in future because of the age increase in the population, and physicians will face greater challenges in treating AF in elderly patients.[12] Elderly patients (defined as those aged ≥75 years, except where stated) with AF are at greater risk of ischemic and bleeding events than are younger patients. Therefore, safe anticoagulation is a more difficult balancing act in ageing patients than in younger individuals.[13] Even though NOACs have more acceptable safety profiles than warfarin, elderly patients frequently do not receive this treatment because of the possibility of bleeding event or lack of patient adherence.[14] This article aims to examine the evidence base for the use of NOACs, the issues related to adherence with NOACs and once- versus twice-daily dosing regimens in elderly populations, mainly with AF. A summary of the issues affecting the reduction of ischemic or thromboembolic event risk in elderly patients with AF that are discussed in this article is shown in Figure 1.

Pharmacokinetics and Dosage Regimens of Non-VKA Anticoagulants

The NOACs all have fairly short elimination half-lives of around 12 hours (Table 1).[7,10,15–17] The half-lives vary with age and renal functioning. Increased age and reduced renal function are associated with elevation in plasma concentrations, a prolonged half-life and increasing patient exposure to the anticoagulant effects of the drug. Dabigatran has a high proportion of renal elimination (80%) and therefore its

Received for publication July 15, 2020; accepted October 4, 2020.

From the *Department of Translational Medicine, University of Eastern Piedmont, Maggiore della Carità Hospital, Novara, Italy; and †Formerly Technical University of Munich, Munich, Germany.

This paper was funded by Daiichi-Sankyo.

G. Patti: speaker/consultant/advisory board for Bayer, Boehringer-Ingelheim, BMS-Pfizer, Daiichi Sankyo. The remaining author reports no conflicts of interest.

Reprints: Giuseppe Patti, MD, Department of Translational Medicine, University of Eastern Piedmont, Maggiore della Carità Hospital, Via Solaroli, 17, 28100 Novara, Italy (e-mail: giuseppe.patti@uniupo.it).

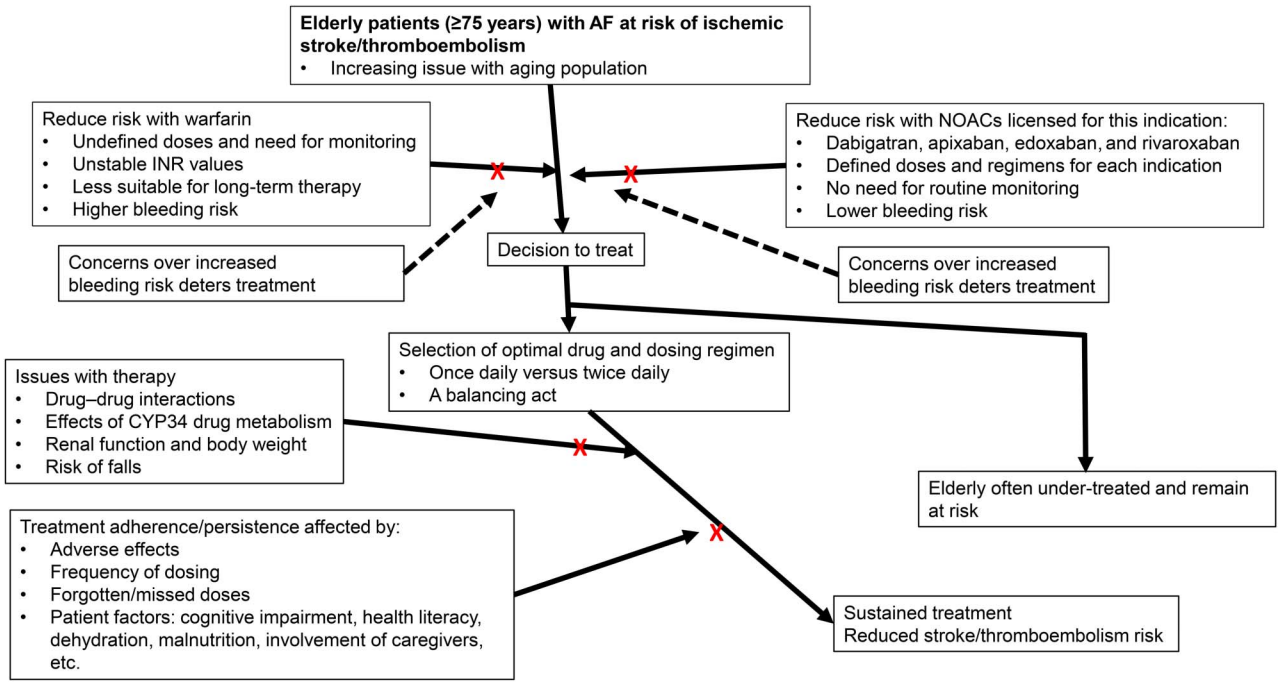

FIGURE 1. A summary of the issues affecting the reduction of ischemic or thromboembolic event risk in elderly patients with AF.

half-life is strongly affected by renal function; in fact, the half-life of dabigatran has been reported to lengthen from 12 to 17 hours in healthy subjects to 13–23 hours in patients with a moderate level of renal impairment (CrCl 30–50 mL/min) and even further, up to 22–35 hours, in subjects with a severe level of renal impairment (CrCl <30 mL/min).[18] Anti-Xa molecules have lower renal elimination and their half-life or area under the curve are less influenced by a decrease of renal function. Notably, the area under the curve in patients with CrCl 15–30 mL/min versus healthy subjects is increased by 530% with dabigatran, by 72% with edoxaban, 64% with rivaroxaban, and 44% with apixaban.[19]

For the NOACs, peak-to-trough ratios are for dabigatran: ~4.5,[20] rivaroxaban: ~10,[21] apixaban: ~10,[22] and edoxaban: ~10–30.[23] It has been suggested that peak-to-trough ratios should be maintained at the lowest achievable level to enable an optimal risk–benefit ratio in preventing thromboembolic and bleeding events over a 24-hour period.[24] However, recent evidence suggests that we need to change our view of the pathophysiology of bleeding in the setting of NOACs.[25] A Phase II study of edoxaban involving a correlation analysis of pharmacokinetic parameters associated with the incidence of bleeding found that bleeding rates correlated most closely with steady-state trough levels rather than peak levels.[26] It has also been hypothesized that bleeding rates may be related to the length of time when drug plasma levels are above a particular threshold, and these may not be sufficient duration for blood vessels to recover from micro-injuries. This time will be greater for a twice-daily dosing than for the same total dose administered once daily.[27] However, these remain hypotheses only and larger studies are needed to draw firm conclusions.

TABLE 1. Pharmacokinetic Characteristics of the Non-VKA Oral Anticoagulants Used to Treat Atrial Fibrillation and Standard Recommended Dosing Regimens

	Warfarin	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
Time to C_{max} inhibition	2–4 d	0.5–2 h	1–4 h	1–4 h	1–2 h
Elimination half-life in healthy individuals	40 h	12–17 h	12 h	5–9 h (young) 11–13 h (elderly)	10–14 h
Dosing*	Variable to maintain INR 2–3	150/110 mg twice daily	5 mg twice daily	20 mg once daily	60 mg once daily
Theoretical plasma peak → trough level*	—	2 h → 12 h	1–4 h →12 h	2–4 h → 24 h	1–2 h → 24 h

*For the prevention of AF-related thromboembolism, dabigatran is available as 75 mg (in the United States), 110 and 150 mg doses; apixaban is available as 2.5 and 5 mg doses; rivaroxaban is available as 15 and 20 mg doses; edoxaban is available as 30 and 60 mg doses. The lower doses allow for factors including renal impairment, low weight, older age, and limiting interactions with concomitant drugs.[6,7,10,15,16,29–32]

†This is theoretical and only true if dosing is precisely followed. Plasma concentrations have shown large variations between the 10th and 90th percentile at both peak and trough.

INR, international normalized ratio. Sources:[6,7,10,15,16,20–23]

The twice-daily dosing regimen with dabigatran was based on pharmacokinetic simulations showing that it minimized daily fluctuations in dabigatran plasma concentrations and maintained trough concentrations at levels that could prevent the emergence of thrombi, but also minimize the bleeding risk.[20] The dosage of apixaban for prevention of VTE was based on a dose-finding study conducted in patients undergoing major orthopedic surgery and receiving apixaban for VTE prevention.[9] Of importance, there were significant dose-related increases in the total adjudicated bleeding event incidence that were reported in patients receiving the once-daily ($P = 0.01$) and twice-daily ($P = 0.02$) apixaban, but no difference was observed between the 2 regimens. The twice-daily dose was selected because of a generally improved efficacy with this regimen. Similar rates of major bleeding were observed for twice- and once-daily apixaban arms at comparable total daily doses.[9] In the Phase II program for rivaroxaban, it was observed that the pharmacodynamic effects of rivaroxaban were of greater duration than would be expected from the elimination half-life. This led to the recommendation of once-daily dosing.[5] A Phase II study showed lower incidence of bleeding complications with edoxaban given once a day compared with the same daily dose given twice a day. This better safety profile of once-a-day edoxaban regimen has been correlated with lower minimum steady-state plasma concentrations (C_{min}) compared with the twice-a-day regimen.[26] It should be noted that unique NOAC dosages are selectively approved in some regions and additional NOAC doses to those given in Table 1 are approved in other countries. In particular, the dose for rivaroxaban in Japan is unique (ie, 15 mg once daily, rather than 20 mg), based on pharmacokinetic data,[28] whereas in South-East Asia, most physicians follow the dose recommendation for Japan, because of similar ethnic characteristics, such as low body weight. Moreover, the 75 mg dabigatran dosage is also licensed for use in the United States; this lower dose enables clinicians to address situations, including impaired renal function, low weight, frailty, or age >80 years.[7,10,15,16,29–32]

Antithrombotic Needs of Elderly Patients

The efficacy of any drug is affected by multiple factors, in particular patient criteria and pharmacokinetic and pharmacodynamic properties. Anticoagulant use is needed in elderly patients for both preventing stroke in AF and VTE treatment. The incidence of stroke increases with age and higher percentages of the causes of stroke are attributable to AF in elderly patients. In fact, age is one of the important factors for thromboembolism risk determination in the CHA_2DS_2-VASc score.[33] Patient age is also a substantial risk factor for both the development of VTE and the prevention of recurrent events.[34] The management of anticoagulant therapy is further complicated by older age being a risk factor for bleeding. Elderly patients are at risk of falls and often have a lower body mass index than younger individuals. In addition, they also have an altered muscle and fatty tissue composition. Furthermore, renal function declines with age and elderly people are more likely to have a range of comorbidities necessitating multiple concomitant medications incurring the risk of drug–drug interactions (DDIs).[14] Weight, fluctuations in renal function, and comorbidities may necessitate more individualized dosing strategies with NOACs in elderly patients (Table 2).[35]

Although the risks of NOAC use in the elderly should not be underestimated, the age-related increase of thromboembolic events in AF patients while not receiving oral anticoagulant therapy outweighs the bleeding risk related to oral anticoagulant therapy.[36] Thus, the overall benefit of oral anticoagulant therapy in AF increases with age and has been shown to be even greater in patients at age 90 years or older.[37] In the Birmingham Atrial Fibrillation Treatment of the Aged Study, which recruited at total of 973 patients with AF aged 75 years or older (mean age 81.5 years), warfarin showed twice the efficacy of aspirin in reducing the composite primary endpoint, which was derived from fatal or disabling stroke (ischemic or hemorrhagic), intracranial hemorrhage, or clinically significant arterial embolism; in particular, warfarin compared with aspirin reduced the risk of ischemic stroke, without concerns related to an increase in major bleeding.[38,39]

Anticoagulants are underused in elderly populations in routine clinical practice. The penetration of VKAs use in the elderly population with AF is low, because of the bleeding risk, comorbidities, and concerns about adherence, international normalized ratio control and DDIs of these agents.[14] Despite the generally more acceptable safety profiles of NOACs compared with warfarin, elderly patients continue to be insufficiently treated. In fact, in older populations, NOACs that remain under-prescribed, because of bleeding concerns,[14] are associated with inadequate adherence or are given at inappropriately reduced dosages.[40] Other factors to take note of when treating elderly patients receiving NOACs include cognitive impairment, health literacy, risk of falling, adverse effects, risks of gastrointestinal bleeding, low body weight, dehydration, renal function deterioration, malnutrition, hypoalbuminemia, involvement of caregivers, and patient–physician relationship.[14]

Evidence Supporting the Administration of Non-VKA Anticoagulants in Elderly Populations

There are substantial data from clinical trials supporting the treatment of elderly patients with NOACs. Among these, the Randomized Evaluation of Long-Term Anticoagulant Therapy trial showed that in patients with AF who were aged ≥75 years, a lower dabigatran dose (110 mg twice daily) was associated with major bleeding rates that were similar to warfarin. A higher dose (150 mg twice daily), however, resulted in a higher risk of major bleeding. This prompted the recommendation to use only lower dabigatran dose (110 mg twice daily) in patients older than 80 years.[41,42]

Further support of NOACs comes from the Apixaban for the Prevention of Stroke in Subjects with Atrial Fibrillation (ARISTOTLE) study. This included a patient population comprising 39% who were aged 65–74 years, 18% 75–79 years, and 13 ≥80 years. In this study, apixaban treatment resulted in decreased major bleeding, total bleeding, and intracranial hemorrhage than the comparator treatment, warfarin, regardless of age.[43]

TABLE 2. Recommended Dose Adjustments for Non-VKA Oral Anticoagulants According to Age, Renal Function, and Weight

Drug	Age	Renal Function	Weight
Dabigatran	<75 yrs: 150 mg 75–80 yrs: 150 mg (110 mg should be considered when the risk of stroke is low and the bleeding risk is high). >80 yrs: 110 mg	CrCl 30–50 mL/min: recommended dose is 150 mg (110 mg for patients with high risk of bleeding). CrCl <30 mL/min: Contraindicated.	No dose adjustment necessary. However, close clinical follow-up is required for patients with body weight <50 kg.
Rivaroxaban	No dose adjustment necessary	CrCl 15–49 mL/min: 15 mg CrCl <15 mL/min: not recommended.	No dose adjustment necessary
Apixaban	Recommended dose: 5 mg 2.5 mg twice daily in case of at least 2 of the following characteristics: age ≥80 yrs, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL No dose adjustment is required based on age, unless criteria for dose reduction are met.	Recommended dose: 5 mg twice daily No dose adjustment is necessary in patients with mild or moderate renal impairment, unless criteria for dose reduction are met. CrCl 15–29 mL/min: 2.5 mg CrCl <15 mL/min or dialysis: not recommended.	No dose adjustment unless criteria for dose reduction are met.
Edoxaban*	No dose adjustment	CrCl 15–49 mL/min: 30 mg CrCl <15 mL/min: not recommended	Body weight >60 kg: 60 mg Body weight ≤60 kg: 30 mg

*In patients concomitantly taking edoxaban and the following P-gp inhibitors: ciclosporin, dronedarone, erythromycin, or ketoconazole, the recommended dose is 30 mg once daily. CrCl, creatine clearance. Sources:[7,10,15,16]

The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) study included a prespecified analysis comparing different age groups. This showed that elderly patients had greater stroke and major bleeding rates than younger patients, but there was no age difference between age groups in the efficacy and safety of rivaroxaban relative to warfarin.[44] In the rivaroxaban group, patients who were older had higher rates of major or clinically relevant nonmajor bleeding (the combined end point, $P = 0.009$). This difference was entirely because of extracranial bleeding, predominantly GI bleeding. A further analysis of net clinical benefit derived from avoidance of ischemic stroke, severe (life-threatening) bleeding, including intracranial hemorrhage, and all-cause mortality revealed a larger benefit from rivaroxaban versus warfarin in elderly than in younger recipients.

The Effective aNticoaGulation with factor Xa next GEneration in Atrial Fibrillation-Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF-TIMI 48) trial also included a planned analysis that supported NOAC use in the elderly. This showed that age has a greater influence on major bleeding than thromboembolic risk in patients with AF. Edoxaban produced consistently lower major bleeding, intracranial hemorrhage, and fatal bleeding events regardless of age and also conferred a greater absolute reduction in net clinical outcomes (death, stroke, and major bleeding) compared with warfarin.[45]

Pooled analyses of clinical studies have also added to the data in support of NOAC use in elderly patients. A meta-analysis of efficacy and safety findings using NOACs in elderly patients with AF, included data from 10 randomized clinical trials with a total of 25,031 participants.[46] This found that in elderly participants of clinical trials, NOAC administration did not result in excess bleeding and produced equal or higher efficacy than conventional therapy. Another analysis of studies involving elderly patients with both VTE and AF, showed that in patients with AF, treatment with NOACs significantly reduced the risk of stroke and embolism, and decreased the number of recurrent VTE events or VTE-related deaths in participants with VTE.[47] More recently, a systematic review and meta-analysis of studies of patients with AF concluded that NOACs significantly reduce the risk of stroke and systemic embolism in elderly patients without increasing major bleeding events. The extent of stroke risk reduction was significantly greater in the elderly than in younger adults.[48]

Clinical trial data, however, have limitations. It should be noted that only 20% of patients aged over 75 years were recruited to the populations in randomized controlled trials of NOACs in AF, because of their high risk of falling and of bleeding, particularly intracranial hemorrhage.[49] In addition, elderly patients who participate in clinical trials are mostly quite healthy and are more likely to adhere to medication regimens. By contrast, discontinuation of and nonadherence to NOACs in older populations are more commonly seen in studies of routine clinical practice. This is despite adherence to NOACs being higher than to VKAs, and nonadherence to oral anticoagulant therapy is associated with worse outcomes, including a higher risk of stroke and bleeding.[50,51] Hence, the real-world data with NOACs in elderly populations are clinically relevant.

Fewer real-world studies have focused on older patients, but findings to date support the use of NOACs (Table 3). In a retrospective investigation, Avgil-Tsadoc et al concluded that dabigatran resulted in decreased rates of intracranial hemorrhage but increased rates of gastrointestinal

TABLE 3. Overview of Key Studies Investigating the Efficacy and Safety of Non-VKA Oral Anticoagulants in Elderly Patients

Reference	Study Type	Clinical Setting	Age	Intervention	Major Findings
Avgli-Tsadok et al[45]	Retrospective study, n = 15,918	AF	67.3% of patients were aged ≥75 yrs	Dabigatran vs. warfarin	Dabigatran was associated with lower rates of ICH (HR 0.60) and higher rates of gastrointestinal bleeding (HR 1.30) compared with warfarin.
Bando et al, 2018[46]	Retrospective registry study, n = 453	AF	≥80 yrs	Rivaroxaban	TE incidence 0.94%/person year; ICH 0.89%/person year
Chao et al, 2019[31]	Retrospective, database study, n = 25,722	AF	≥90 yrs	NOACs vs. warfarin	Compared with warfarin, NOACs had a lower risk of ICH (0.42%/year vs. 1.63%/year; HR 0.32, $P = 0.044$), with no difference in risk of ischemic stroke.
Fazio et al, 2018[47]	Retrospective study, n = 46	AF	84.6 ± 6.1 yrs, with concomitant severe renal impairment	Edoxaban	At an average follow-up of 9.13 ± 3.0 months, there were no major bleeding, stroke, systemic embolism, or CV death: 1 non-CV death and 5 nonmajor bleeding events.
Monelli et al, 2019[49]	Prospective, observational study, n = 221	AF	81.6 ± 6.1 yrs	All NOACs	Major bleeding incidence 4.4%, nonmajor bleeding 5.7%; cerebral ischemic events incidence 0.88%)
Kim et al, 2019[48]	Retrospective study, n = 687	AF	83.4 ± 3.2 yrs	NOACs (dabigatran, rivaroxaban or apixaban) vs. warfarin	Patients with NOAC showed a lower risk of TE (1.84 vs. 2.71 per 100 person-years, HR 0.13, $P = 0.002$), major bleeding (1.48 vs. 2.72 per 100 person-years, HR 0.11, $P = 0.001$), and all-cause death (2.57 vs. 3.50 per 100 person-years, HR 0.30, $P = 0.020$).
Patti et al, 2019[30]	Retrospective analysis on data from prospective registries, n = 3825	AF	≥75 yrs	NOACs vs. VKAs	Rate of the net composite endpoint, including major bleeding and ischaemic CV events, was 6.6%/year with NOACs vs. 9.1%/year with VKAs (OR 0.71, $P = 0.042$)

CV, cardiovascular; ICH, intracranial bleeding; TE, thromboembolic events.

bleeding in elderly patients versus warfarin. In this study, almost all elderly patients used the lower dose (80.1%), but younger patients mostly received the higher dose (80.0%).[52] In another retrospective study, Bando et al[53] showed that rivaroxaban has good efficacy and safety profiles when used in more elderly (aged ≥80 years) patients. Fazio et al[54] have also demonstrated the benefits of edoxaban in routine clinical practice in elderly patients with severe renal impairment. The real-world performance of edoxaban was assessed in a study of 130 elderly patients with AF.[55] Compared with VKA therapy, patients treated with edoxaban were found to have a numerically lower incidence of thromboembolism (2.3% vs. 1.5%, respectively), major bleeding events (3.1% vs. 1.5%), and therapy discontinuation (4.6% vs. 2.3%), with a trend toward improved adherence (78% vs. 81%).

Real-world, prospective data from comparisons of NOACs with VKAs in elderly patients with AF have also been recently published: data from a population of 3825 elderly patients included in the PREFER in AF and PREFER in AF PROLONGATION registries were pooled for analysis.[36] The incidence of the composite endpoint that was derived from major bleeding and ischemic cardiovascular events, was 6.6%/year with NOACs versus 9.1%/year with VKAs [OR 0.71, 95% confidence interval (CI) (0.51–0.99), $P = 0.042$]. Two other recent studies have concluded that NOAC use is safe and effective in elderly populations; in both studies the mean age of participants was older than 80 years.[56,57]

The outcome with NOACs versus VKAs in AF was compared in a database of octogenarians (279 with NOACs, 774 with VKAs).[58] Overall, the study found no difference in

thromboembolic and major bleeding events, but a significantly lower all-cause mortality and a net clinical benefit were observed in the NOACs group. Furthermore, NOACs were compared with VKAs in an observational investigation of 71 octogenarians with low body weight (≤60 kg), where all-cause death was 14.91/100 versus 37.94/100 person/years, respectively (P = 0.003), without significant difference in major bleeding events.[59] These findings support the safety of NOACs versus VKAs in octogenarians, but further evidence is welcome.

A substantial advantage of NOACs is their rapid offset; however, there has been concern among physicians regarding the use of these drugs in older patients because of the potential for fatal outcomes after low-level falls and the lack of reversal agents (in the case of anti-Xa agents). However, recent studies found that patients taking NOACS who experienced traumatic brain injury after low-level falls did not have increased morbidity or mortality compared with those treated with warfarin or who were not treated with anticoagulants.[60] One study on head trauma in elderly patients (>65 years of age, n = 1365) found a lower incidence of intracranial hemorrhage with NOACs than warfarin.[61] The risk of falls may be reduced by appropriate strategies, in particular with a multidisciplinary assessment of the risk, the treatment of remediable pathologies and the prescription of preventive interventions such as exercise programs; home environmental assessment, etc. A Markov decision analytic model showed that a patient receiving VKAs would need to fall 295 times for the risk of a subdural hematoma to exceed the benefits derived from anticoagulation.[62] Because of the reduced bleeding risk, the number of falls would be even higher during treatment with NOACs compared with VKAs. Therefore, propensity to fall should not be a discriminatory factor in the decision of optimal antithrombotic strategy in elderly patients with AF.

The incidence of DDIs is a possible drawback of NOAC use in older populations because most elderly people are taking multiple medications. The assumption is that concomitant drugs may modify NOACs plasmatic concentrations through the inhibition or induction of the P-glycoprotein (P-gp) pathway or the CYP3A4 metabolism. P-gp is responsible for the gastrointestinal re-secretion of all NOACs, and CYP3A4 is significantly involved in the metabolism of apixaban and rivaroxaban. NOACs should not be used or should be used with caution in combination with drugs that strongly influence P-gp and/or CYP3A4.[17] A recent literature review concluded that there is a scarcity of clinical data on this topic. Most DDIs have been reported for dabigatran, but this may reflect the fact that dabigatran has been in use for longer than the other NOACs.[63] Possible DDIs, in combination with other clinical risk factors that are likely to affect NOAC plasma levels, are important aspects in the choice of a particular NOAC for each individual patient.[64]

Use of Non-VKA Anticoagulants in Elderly Patients With Atrial Fibrillation Undergoing Invasive Cardiac Procedures or With Special Conditions

The NOACs have shown benefits for elderly AF populations undergoing invasive cardiac procedures or with various specific conditions, which are factors affecting ischemic and bleeding risks. One example is in patients receiving percutaneous coronary intervention (PCI). In one study, PCI patients (n = 289) aged ≥75 years and on triple therapy (TT, oral anticoagulation plus dual antiplatelet therapy: aspirin plus clopidogrel) had a lower rate of thromboembolism than those receiving dual antiplatelet therapy (DAPT; 0.6% vs. 6.9%, HR = 0.08, P = 0.004).[65] Overall mortality was also lower with TT than DAPT (HR = 0.33, P = 0.02). A further investigation of elderly PCI patients with AF (n = 2725) found that the risk of bleeding was reduced in patients who received dual therapy with dabigatran and a $P2Y_{12}$ inhibitor (15.4%) than in those treated with TT with warfarin, a $P2Y_{12}$ inhibitor and aspirin (26.9%, $P < 0.001$).[66] The incidence of thromboembolism and serious adverse events was similar in both treatments. Another large study (n = 2124) demonstrated that in patients with AF undergoing PCI with stent placement, a treatment with low-dose (15 mg) rivaroxaban in combination with a $P2Y_{12}$ inhibitor or very-low-dose (2.5 mg BID) rivaroxaban plus DAPT was associated with less bleeding than a standard therapy with warfarin and DAPT for up to 12 months; this was consistent in the subgroup of elderly patients.[67]

For patients receiving catheter ablation of AF or implantation of cardiac electronic devices, the Chest Guideline and Expert Panel Report suggests performing the procedure during continued VKA or NOAC treatment, although the evidence supporting this is, as yet, weak.[68]

A high proportion of elderly patients can be described as frail—a geriatric syndrome that is caused by subclinical impairments in multiple organ systems leading to loss of homeostatic reserve and resiliency.[69,70] A registry study found that among elderly patients with AF, those who were frail were less likely to receive NOAC treatment than those who were not frail (3.5% vs. 6.0%).[71] It is likely that this was because of a perceived higher bleeding risk among frail patients, but the use of NOACs in this setting needs further investigation and more robust data.[69]

A further common issue in the elderly is an impaired renal function. This is a concern, because some NOACs are cleared via the renal route (approximately 80% in the case of dabigatran).[72] The Randomized Evaluation of Long-Term Anticoagulant Therapy study, discussed above, showed that the rates of stroke or systemic embolism increased with decreasing renal function.[73] However, the efficacy of 2 different dose levels of dabigatran, was unaffected by renal function. This and other evidence indicate that NOACs may be beneficial in older patients with some degree of renal impairment; it is especially true with the use of anti-Xa inhibitors, having a lower percentage of renal elimination, but they require a dose-adjustment according to renal function. In addition, there is mounting evidence that NOACs can also be effectively and safely used in combination with different antiplatelet drugs and even with thrombolytic agents.[74,75]

Inappropriate Drug Reduction, Adherence, and Persistence to Dosing Regimen

Inappropriate dosing is common in elderly patients taking NOACs and clinical follow-up often falls short of

recommended standards.[76–78] In a retrospective study of 1234 AF patients aged ≥65 years, inappropriate dosing was reported in 11.8% of cases. In addition, concomitant use of contraindicated drugs was reported in 19.1% of patients.[78] An inappropriate dosing reduction is associated with suboptimal prevention from stroke and other thromboembolic events. In a recent Korean study, over a third of patients who were prescribed NOACs actually received an off-label decreased dose. Compared with those receiving an on-label standard regimen, these patients were likely to be older (≥75 years), women with lower body weights (≤60 kg), to have renal dysfunction (creatinine clearance ≤50 mL/min), previous stroke, previous bleeding, hypertension, concomitant dronedarone use, and antiplatelet use.[79] Apixaban is the NOAC that is most frequently prescribed at inappropriate reduced dosages, probably because of bleeding concerns when one criterion for dose reduction is present.

Adherence, which is preferred over the older term compliance, and persistence are critical factors in the long-term efficacy of NOAC treatment.[80] Adherence is defined as active and voluntary involvement of the patient, in collaboration with a health care provider, in a course of behavior (taking medication, following a diet, and/or executing lifestyle changes) to produce a therapeutic result.[81,82] Persistence refers to duration of time from initiation to discontinuation of a therapy.[81] Optimal adherence and persistence are needed for patients to derive the maximal benefit from effective evidence-based therapies.[81,82]

Poor adherence to warfarin has been reported, and this has a significant effect on anticoagulation control.[83] Suboptimal adherence would also severely diminish the treatment benefits of NOACs.[84] Adequate adherence to NOAC therapy is associated with beneficial effects on stroke severity at admission and functional outcome at discharge in patients with AF.[85] In elderly patients with AF, there are likely to be multiple other ongoing conditions that impair compliance and adherence to anticoagulant treatment. In a US registry study (n = 24,596), however, persistence with apixaban and dabigatran (the only NOACs for which data were available) was better than for warfarin in elderly populations. Persistence was significantly better for patients given rivaroxaban compared with patients given warfarin, at 180 days (66.0 vs. 58.1%; $P < 0.001$) and at 360 days (53.1 vs. 25.5%; $P < 0.001$) after treatment was started. Dabigatran resulted in greater persistence than VKA at 180 days (60.3% vs. 58.1%) but this difference was not significant. After 360 days, however, the difference was significant ($P < 0.001$).[50] Prior bleeding and risk of fall have been associated with lower adherence to NOACs,[50] and polytherapy, cognitive impairment, and low socio-economic status. Patients receiving NOACs should always be informed of the importance of adhering to the planned dosing regimen.[19]

A recent investigation compared the risk of treatment discontinuation of individual NOACs versus phenprocoumon in Germany. In the confounder-adjusted analysis, the risk of treatment discontinuation was higher for phenprocoumon compared with rivaroxaban [HR 1.04, 95% CI (1.02–1.07)], similar for apixaban [HR 1.00, 95% CI (0.96–1.03)] and lower for edoxaban [HR 0.81, 95% CI (0.76–0.86)]. In patients with renal disease, the risk was lower for rivaroxaban [HR 0.82, 95% CI (0.78–0.87)], apixaban [HR 0.77, 95% CI (0.73–0.82)], and edoxaban [HR 0.61, 95% CI (0.53–0.70)]. In frail, elderly, and diabetes patients, strong risk reductions for discontinuation of NOACs were also observed relative to phenprocoumon.[86] It must be emphasized, however, that when interpreting these data, the variability in patient groups, risk level, methods for adherence assessment, and indicators of medication use should be considered.

The dosing frequency of medications is an important determinant of adherence. The percentage of doses taken is generally higher with less frequent dosing regimens and simple dosing schedules are generally advantageous, and because long-term outcomes may be affected by adherence, once-daily dosing theoretically could improve stroke prevention rates in patients with AF.[84] A Canadian survey investigated patient (n = 266) and physician (n = 178) preferences and values related to the use of OACs in stroke prevention (no edoxaban data as the latter had not been approved in Canada at the time), in patients who were prescribed once-daily medications (rivaroxaban or warfarin). This showed better compliance with their once-daily OAC therapy and patients were less likely to consider discontinuing OAC therapy. Notably, 6% and 14% of the patients receiving rivaroxaban or warfarin, took their OAC as twice-daily doses instead of once daily. In addition, 27% and 30% of patients who received dabigatran and apixaban, respectively, took their OAC once daily instead of the recommended twice-daily regimen ($P < 0.001$).[87] In this study, a marked difference was shown in patient preference between patient and physician; patients rated once-daily dosing as significantly more important than did physicians ($P < 0.001$).[87] Another study conducted in France, Germany, and the United Kingdom, examined AF patient preference for different characteristic NOACs.[88] This concluded that the characteristic patients mainly preferred was a once-daily regimen followed by a shorter distance to travel to their treating physician, a small-sized tablet and intake that was independent of food. Furthermore, in a multicenter study of 2214 patients with AF (median age 71 years), once-daily NOAC dosing resulted in greater adherence to treatment, which was not associated with bleeding events. The authors suggested that other risk factors may independently affect nonadherence, and the combined action of these factors is necessary for the development of bleeding complications.[89]

To date, the only specific study of adherence to NOACs in elderly patients with nonvalvular AF (here defined as aged 65 or older), involved 103 patients. Of these, 76 showed adequate adherence to anticoagulant therapy, whereas in the remaining 27, the adherence was inadequate. Twice-daily administration was almost 3 times as likely to be associated with inappropriate adherence [OR 2.88; $P = 0.048$, 95% CI (1.003–8.286)].[90] In a study that recruited patients with VTE, those receiving once-daily dosing regimens (n = 4867) were 39%–61% more likely to adhere to treatment than patients receiving twice-daily dosing (n = 1069).[91]

However, data from therapeutic approaches with protease inhibitors in HIV-infected patients hypothesized that a twice-daily dosing warrants more stable drug plasma levels

compared with once-daily dosing for agents with half-life of 12 hours; this can be associated with a greater degree of continuity of drug effect and better therapeutic coverage, despite higher rates of prescribed doses being taken with the once-daily regimen.[92] However, whether these pharmacokinetic observations derived from different settings of patients, different drugs with different modalities of action can be extrapolated to the use of NOACs in patients with AF is unknown and here a more specific evidence is needed. Notably, regarding NOACs with once-daily regimen, there is evidence that an older age per se does not have an impact on the drug levels, but these levels are essentially affected only by impairment of renal function for rivaroxaban and by concomitant drugs, low body weight, or impairment of renal function for edoxaban.

Impact of a Missed Dose Between Once- and Twice-Daily Non-VKA Antagonist Anticoagulants

The effects of fluctuating doses of NOACs are currently unknown and, until this aspect is better understood, it is important that patients take drugs in accordance with prescribed regimens. The recommendations for dealing with dosing errors may also potentially lead to overdosing. According to the 2018 European Heart Rhythm Association Practical Guide, a forgotten dose can be taken until 50% of the dosing interval has passed.[17] This means that for NOACs with a twice-daily dosing regimen, a forgotten dose can be taken up to 6 hours after the scheduled intake. For patients with a high stroke risk and low bleeding risk, this can be extended up until the time of the next scheduled dose.

For NOACs with a once-daily dosing regimen, a forgotten dose can be taken up until 12 hours after the scheduled intake. After this, the dose should be skipped and the next scheduled dose should be taken. Again, the 12-hour interval may be extended in patients with a high stroke risk.[17] A recent study compared the pharmacokinetics and anticoagulation effects of apixaban and rivaroxaban. Although overall exposure to the 2 drugs was similar, rivaroxaban 20 mg once daily produced inhibition of thrombin generation that was greater and longer sustained than apixaban 5 mg twice daily.[93]

Missed doses of NOACs are concerning because patients may have a greater risk of stroke if one or more doses are not received.[20] The impact of missing a dose has a differing effect on NOAC blood concentration depending on once- or twice-daily administration.[19,94] Modelling data hypothesized that there is a potentially larger decrease in anticoagulant effect when one pill was omitted from a once-daily dosing regimen than when one or even 2 pills were omitted from a twice-daily regimen. This suggests that a missed dose in a once-daily regimen may be more serious, in lower effectiveness, than in a twice-daily regimen.[92,95] However, this hypothesis was based purely on pharmacodynamic considerations. In an observational study, twice-daily dosing was not found to be more forgiving than once daily when doses were missed.[96] Furthermore, because decreasing daily dosage may increase the adherence to the treatment, patients receiving a once-daily drug can have better adherence and are less likely to miss a dose compared with twice-daily dosing.[87]

Anticoagulation in Palliative Care

There are no guidelines designed specifically for the use of NOACs in palliative care or elderly care home settings. However, the ease of use of NOACs facilitates the ambulatory care.[97] VTE is the second most frequent cause of death in people with cancer, and it is recommended that all cancer patients admitted to hospital should be evaluated to receive anticoagulant therapy.[98] Patients with advanced cancer in hospice care are at high risk of VTE, usually because of older age, advanced or metastatic disease, and decreased mobility. The use of NOACs is beneficial in this setting, where the goal is promoting quality of life rather than lengthening survival, because treatment may reduce unpleasant symptoms of thromboembolism, such as pain, edema, and dyspnea.[99] However, there are challenges to using anticoagulants in palliative care, including the risk of discontinuing anticoagulation, the risk of bleeding, which is further increased in patients with renal failure and malnutrition, and potential DDIs.[100] When considering the use of NOACs in end-of-life care, it is essential to make decisions based on each individual case and consider the patient's wishes and those of care givers and family as appropriate.[97]

CONCLUSIONS

The dosing regimen of NOACs varies according to indication and treatment phase and it is not possible to determine whether once-daily or twice-daily dosing is safer or more efficacious. However, suboptimal treatment adherence is a major concern and often falls to below 50% within a year of starting a new medication.[101] This is a particular concern for elderly patients with AF, who are at a greater risk of both ischemic and bleeding events than younger patients.[102–105] Elderly people are suboptimally treated with VKAs, but to a smaller extent, also with NOACs. Studies to date indicate that elderly patients, even the very elderly, benefit from anticoagulation, because the risk of thromboembolism outweighs that from potentially serious bleeding in most cases. Patients prescribed once-daily NOACs have shown better adherence and persistence than those prescribed twice daily, with fewer missed doses. Most patients, especially elderly patients, prefer a once-daily rather than a twice-daily oral anticoagulation medication regimen. Because a good compliance is associated with better outcomes, once-daily NOACs may be an appropriate choice for elderly patients, although the treating physician should also be aware of other criteria, such as the patient risk profile, comorbidities, and concomitant medications. All these factors must be carefully considered on individual basis for appropriately matching an NOAC to a particular patient.

ACKNOWLEDGMENTS

The authors are grateful to the technical editing support provided by Katrina Mountfort, James Gilbart and Bettina Vine of Medical Media Communications (Scientific) Ltd

REFERENCES

1. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009;361:1139–1151.
2. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2013;369:2093–2104.
3. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011;365:981–992.
4. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med.* 2011;365:883–891.
5. Kubitza D, Berkowitz SD, Misselwitz F. Evidence-based development and rationale for once-daily rivaroxaban dosing regimens across multiple indications. *Clin Appl Thromb Hemost.* 2016;22:412–422.
6. Ingleheim B. *Pradaxa (dabigatran etexilate). Summary of Product Characteristics*. 2020. Available at: https://www.ema.europa.eu/en/documents/product-information/pradaxa-epar-product-information_en.pdf. Accessed August 14, 2020.
7. *Eliquis 5 mg Film-Coated Tablets. Summary of Product Characteristics*. Available at: https://www.ema.europa.eu/en/documents/product-information/eliquis-epar-product-information_en.pdf. Accessed May 30, 2020.
8. Ezekowitz MD, Reilly PA, Nehmiz G, et al. Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO Study). *Am J Cardiol.* 2007;100:1419–1426.
9. Lassen MR, Davidson BL, Gallus A, et al. The efficacy and safety of apixaban, an oral, direct factor Xa inhibitor, as thromboprophylaxis in patients following total knee replacement. *J Thromb Haemost.* 2007;5:2368–2375.
10. *Lixiana 15 Mg Film-Covered Tablets. Summary of Product Characteristics*. Available at: http://ec.europa.eu/health/documents/community-register/2015/20150619132091/anx_132091_en.pdf. Accessed May 30, 2020.
11. Fuji T, Fujita S, Tachibana S, et al. A dose-ranging study evaluating the oral factor Xa inhibitor edoxaban for the prevention of venous thromboembolism in patients undergoing total knee arthroplasty. *J Thromb Haemost.* 2010;8:2458–2468.
12. Morillo CA, Banerjee A, Perel P, et al. Atrial fibrillation: the current epidemic. *J Geriatr Cardiol.* 2017;14:195–203.
13. Lip GY, Clementy N, Pericart L, et al. 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.
14. Benedetti G, Neccia M, Agati L. Direct oral anticoagulants use in elderly patients with non valvular atrial fibrillation: state of evidence. *Minerva Cardioangiol.* 2018;66:301–313.
15. *Xarelto 2.5 Mg Film-Coated Tablets. Summary of Product Characteristics*. Available at: https://www.ema.europa.eu/en/documents/product-information/xarelto-epar-product-information_en.pdf. Accessed May 30, 2020.
16. *Pradaxa 75mg Hard Capsules. Summary of Product Characteristics*. Available at: https://www.ema.europa.eu/en/documents/product-information/pradaxa-epar-product-information_en.pdf. Accessed May 30, 2020.
17. Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: executive summary. *Europace.* 2018;20:1231–1242.
18. van Ryn J, Stangier J, Haertter S, et al. Dabigatran etexilate–a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haemost.* 2010;103:1116–1127.
19. Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. *Europace.* 2015;17:1467–1507.
20. Clemens A, Haertter S, Friedman J, et al. Twice daily dosing of dabigatran for stroke prevention in atrial fibrillation: a pharmacokinetic justification. *Curr Med Res Opin.* 2012;28:195–201.
21. Mueck W, Stampfuss J, Kubitza D, et al. Clinical pharmacokinetic and pharmacodynamic profile of rivaroxaban. *Clin Pharmacokinet.* 2014;53:1–16.
22. Frost C, Wang J, Nepal S, et al. Apixaban, an oral, direct factor Xa inhibitor: single dose safety, pharmacokinetics, pharmacodynamics and food effect in healthy subjects. *Br J Clin Pharmacol.* 2013;75:476–487.
23. Ogata K, Mendell-Harary J, Tachibana M, et al. Clinical safety, tolerability, pharmacokinetics, and pharmacodynamics of the novel factor Xa inhibitor edoxaban in healthy volunteers. *J Clin Pharmacol.* 2010;50:743–753.
24. Clemens A, Noack H, Brueckmann M, et al. Twice- or once-daily dosing of novel oral anticoagulants for stroke prevention: a fixed-effects meta-analysis with predefined heterogeneity quality criteria. *PLoS One.* 2014;9:e99276.
25. Renda G, De Caterina R. The new oral anticoagulants in atrial fibrillation: once daily or twice daily?. *Vascul Pharmacol.* 2013;59:53–62.
26. Weitz JI, Connolly SJ, Patel I, et al. Randomised, parallel-group, multicentre, multinational phase 2 study comparing edoxaban, an oral factor Xa inhibitor, with warfarin for stroke prevention in patients with atrial fibrillation. *Thromb Haemost.* 2010;104:633–641.
27. Salazar DE, Mendell J, Kastrissios H, et al. Modelling and simulation of edoxaban exposure and response relationships in patients with atrial fibrillation. *Thromb Haemost.* 2012;107:925–936.
28. Tanigawa T, Kaneko M, Hashizume K, et al. Model-based dose selection for phase III rivaroxaban study in Japanese patients with nonvalvular atrial fibrillation. *Drug Metab Pharmacokinet.* 2013;28:59–70.
29. Physicians' Desk Reference (PDR). *Dabigatran Etexilate Mesylate—Drug Summary*. 2020. Available at: https://www.pdr.net/drug-summary/Pradaxa-dabigatran-etexilate-mesylate-100.4423. Accessed August 16, 2020.
30. Physicians' Desk Reference (PDR). *Apixaban—Drug Summary*. 2020. Available at: https://www.pdr.net/drug-summary/Eliquis-apixaban-3039. Accessed August 16, 2020.
31. Physician's Desk Reference (PDR). *Rivaroxaban—Drug Summary*. 2020. Available at: https://www.pdr.net/drug-summary/Xarelto-rivaroxaban-278. Accessed August 16, 2020.
32. Physisican's Desk Reference (PDR). *Edoxaban—Drug Summary*. 2020. Available at: https://www.pdr.net/drug-summary/Savaysa-edoxaban-3667. Accessed August 16, 2020.
33. Lip GY, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation. *Chest.* 2010;137:263–272.
34. Montagnana M, Favaloro EJ, Franchini M, et al. The role of ethnicity, age and gender in venous thromboembolism. *J Thromb Thrombolysis.* 2010;29:489–496.
35. Fava JP, Starr KM, Ratz D, et al. Dosing challenges with direct oral anticoagulants in the elderly: a retrospective analysis. *Ther Adv Drug Saf.* 2018;9:405–414.
36. Patti G, Lucerna M, Pecen L, et al. Thromboembolic risk, bleeding outcomes and effect of different antithrombotic strategies in very elderly patients with atrial fibrillation: a sub-analysis from the PREFER in AF (PREvention oF Thromboembolic Events-European Registry in Atrial Fibrillation). *J Am Heart Assoc.* 2017;6:e005657.
37. Chao TF, Liu CJ, Lin YJ, et al. Oral anticoagulation in very elderly patients with atrial fibrillation: a nationwide cohort study. *Circulation.* 2018;138:37–47.
38. Mant J, Hobbs FD, Fletcher K, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham atrial fibrillation treatment of the aged study, BAFTA): a randomised controlled trial. *Lancet.* 2007;370:493–503.
39. Russo V, Carbone A, Rago A, et al. Direct oral anticoagulants in octogenarians with atrial fibrillation: it is never too late. *J Cardiovasc Pharmacol.* 2019;73:207–214.
40. Patti G, Pecen L, Lucerna M, et al. Net clinical benefit of non-vitamin k antagonist vs vitamin K antagonist anticoagulants in elderly patients with atrial fibrillation. *Am J Med.* 2019;132:749–757.e5.
41. Eikelboom JW, Wallentin L, Connolly SJ, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. *Circulation.* 2011;123:2363–2372.
42. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J.* 2016;37:2893–2962.

43. Halvorsen S, Atar D, Yang H, et al. Efficacy and safety of apixaban compared with warfarin according to age for stroke prevention in atrial fibrillation: observations from the ARISTOTLE trial. *Eur Heart J.* 2014;35:1864–1872.
44. Halperin JL, Hankey GJ, Wojdyla DM, 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.
45. Kato ET, Giugliano RP, Ruff CT, et al. Efficacy and safety of edoxaban in elderly patients with atrial fibrillation in the ENGAGE AF-TIMI 48 Trial. *J Am Heart Assoc.* 2016;5:e003432.
46. Sardar P, Chatterjee S, Chaudhari S, et al. New oral anticoagulants in elderly adults: evidence from a meta-analysis of randomized trials. *J Am Geriatr Soc.* 2014;62:857–864.
47. Sadlon AH, Tsakiris DA. Direct oral anticoagulants in the elderly: systematic review and meta-analysis of evidence, current and future directions. *Swiss Med Wkly.* 2016;146:w14356.
48. Caldeira D, Nunes-Ferreira A, Rodrigues R, et al. Non-vitamin K antagonist oral anticoagulants in elderly patients with atrial fibrillation: a systematic review with meta-analysis and trial sequential analysis. *Arch Gerontol Geriatr.* 2019;81:209–214.
49. Suarez Fernandez C, Formiga F, Camafort M, et al. Antithrombotic treatment in elderly patients with atrial fibrillation: a practical approach. *BMC Cardiovasc Disord.* 2015;15:143.
50. Garkina SV, Vavilova TV, Lebedev DS, et al. Compliance and adherence to oral anticoagulation therapy in elderly patients with atrial fibrillation in the era of direct oral anticoagulants. *J Geriatr Cardiol.* 2016;13:807–810.
51. Kachroo S, Hamilton M, Liu X, et al. Oral anticoagulant discontinuation in patients with nonvalvular atrial fibrillation. *Am J Manag Care.* 2016;22:e1–8.
52. Avgil-Tsadok M, Jackevicius CA, Essebag V, et al. Dabigatran use in elderly patients with atrial fibrillation. *Thromb Haemost.* 2016;115:152–160.
53. Bando S, Nishikado A, Hiura N, et al. Efficacy and safety of rivaroxaban in extreme elderly patients with atrial fibrillation: analysis of the Shikoku Rivaroxaban Registry Trial (SRRT). *J Cardiol.* 2018;71:197–201.
54. Fazio G, Dentamaro I, Gambacurta R, et al. Safety of edoxaban 30 mg in elderly patients with severe renal impairment. *Clin Drug Investig.* 2018;38:1023–1030.
55. Russo V, Attena E, Mazzone C, et al. Real-life performance of edoxaban in elderly patients with atrial fibrillation: a multicenter propensity score-matched cohort study. *Clin Ther.* 2019;41:1598–1604.
56. Kim HM, Choi EK, Park CS, et al. Effectiveness and safety of non-vitamin K antagonist oral anticoagulants in octogenarian patients with non-valvular atrial fibrillation. *PLoS One.* 2019;14:e0211766.
57. Monelli M, Molteni M, Cassetti G, et al. Non-vitamin K oral anticoagulant use in the elderly: a prospective real-world study—data from the REGIstry of patients on Non-vitamin K oral Anticoagulants (REGINA). *Vasc Health Risk Manag.* 2019;15:19–25.
58. Russo V, Attena E, Di Maio M, et al. Clinical profile of direct oral anticoagulants versus vitamin K anticoagulants in octogenarians with atrial fibrillation: a multicentre propensity score matched real-world cohort study. *J Thromb Thrombolysis.* 2020;49:42–53.
59. Russo V, Attena E, Di Maio M, et al. Non-vitamin K vs vitamin K oral anticoagulants in patients aged > 80 year with atrial fibrillation and low body weight. *Eur J Clin Invest.* 2020;e13335. doi: 10.1111/eci.13335. Online ahead of press.
60. Batey M, Hecht J, Callahan C, et al. Direct oral anticoagulants do not worsen traumatic brain injury after low-level falls in the elderly. *Surgery.* 2018;164:814–819.
61. Scotti P, Séguin C, Lo BWY, et al. Antithrombotic agents and traumatic brain injury in the elderly population: hemorrhage patterns and outcomes. *J Neurosurg.* 2019;133:486–495.
62. Man-Son-Hing M, Nichol G, Lau A, et al. Choosing antithrombotic therapy for elderly patients with atrial fibrillation who are at risk for falls. *Arch Intern Med.* 1999;159:677–685.
63. Stollberger C. Drug interactions with new oral anticoagulants in elderly patients. *Expert Rev Clin Pharmacol.* 2017;10:1191–1202.
64. Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J.* 2018;39:1330–1393.
65. Sambola A, Mutuberria M, Garcia Del Blanco B, et al. Impact of triple therapy in elderly patients with atrial fibrillation undergoing percutaneous coronary intervention. *PLoS One.* 2016;11:e0147245.
66. Cannon CP, Bhatt DL, Oldgren J, et al. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. *N Engl J Med.* 2017;377:1513–1524.
67. Gibson CM, Mehran R, Bode C, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N Engl J Med.* 2016;375:2423–2434.
68. Lip GYH, Banerjee A, Boriani G, et al. Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report. *Chest.* 2018;154:1121–1201.
69. Bibas L, Levi M, Touchette J, et al. Implications of frailty in elderly patients with electrophysiological conditions. *JACC Clin Electrophysiol.* 2016;2:288–294.
70. Diez-Villanueva P, Alfonso F. Atrial fibrillation in the elderly. *J Geriatr Cardiol.* 2019;16:49–53.
71. Steinberg BA, Holmes DN, Piccini JP, et al. Early adoption of dabigatran and its dosing in US patients with atrial fibrillation: results from the outcomes registry for better informed treatment of atrial fibrillation. *J Am Heart Assoc.* 2013;2:e000535.
72. Huisman MV, Lip GY, Diener HC, et al. Dabigatran etexilate for stroke prevention in patients with atrial fibrillation: resolving uncertainties in routine practice. *Thromb Haemost.* 2012;107:838–847.
73. Hijazi Z, Hohnloser SH, Oldgren J, et al. Efficacy and safety of dabigatran compared with warfarin in relation to baseline renal function in patients with atrial fibrillation: a RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) trial analysis. *Circulation.* 2014;129:961–970.
74. Andreotti F, Navarese EP, Crea F. The NOACs in special situations: the elderly, renal impairment, combination with antiplatelet agents and thrombolytics. In: Camm JA, Luscher T, Maurer G, et al, eds. *ESC CardioMed*. 3rd ed. Oxford, United Kingdom: Oxford University Press; 2018.
75. Andreotti F, Rocca B, Husted S, et al. Antithrombotic therapy in the elderly: expert position paper of the European society of cardiology working group on thrombosis. *Eur Heart J.* 2015;36:3238–3249.
76. Camm AJ, Amarenco P, Haas S, et al. XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. *Eur Heart J.* 2016;37:1145–1153.
77. Grant SJ, Kothari S, Gimotty PA, et al. Quality of direct oral anticoagulant prescribing in elderly patients with non-valvular atrial fibrillation: results from a large urban health system. *J Thromb Thrombolysis.* 2018;46:1–6.
78. Han S, Jeong HS, Kim H, et al. The treatment pattern and adherence to direct oral anticoagulants in patients with atrial fibrillation aged over 65. *PLoS One.* 2019;14:e0214666.
79. Lee SR, Lee YS, Park JS, et al. Label adherence for non-vitamin K antagonist oral anticoagulants in a prospective cohort of Asian patients with atrial fibrillation. *Yonsei Med J.* 2019;60:277–284.
80. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med.* 2005;353:487–497.
81. Cramer JA, Roy A, Burrell A, et al. Medication compliance and persistence: terminology and definitions. *Value Health.* 2008;11:44–47.
82. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. *Circulation.* 2009;119:3028–3035.
83. Kimmel SE, Chen Z, Price M, et al. The influence of patient adherence on anticoagulation control with warfarin: results from the International Normalized Ratio Adherence and Genetics (IN-RANGE) Study. *Arch Intern Med.* 2007;167:229–235.
84. Amara W, Antoniou S. Benefits of once-daily dosing with non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J Suppl.* 2016;18(suppl D):D1–D6.
85. Yamashiro K, Kurita N, Tanaka R, et al. Adequate adherence to direct oral anticoagulant is associated with reduced ischemic stroke severity in patients with atrial fibrillation. *J Stroke Cerebrovasc Dis.* 2019;28:1773–1780.

86. Schmedt N, Kreutz R, Kloss S, et al. Comparative persistence of non-vitamin-K oral anticoagulants and phenprocoumon in patients with non-valvular atrial fibrillation—results from the Reloaded study. *Pharmacoepidemiol Drug Saf.* 2019;28(suppl 2):454.
87. Andrade JG, Krahn AD, Skanes AC, et al. Values and preferences of physicians and patients with nonvalvular atrial fibrillation who receive oral anticoagulation therapy for stroke prevention. *Can J Cardiol.* 2016; 32:747–753.
88. Wilke T, Meinecke AK, Schaefer B, et al. Patient preferences for nonvitamin K antagonist oral anticoagulants in stroke prevention: a multicountry discrete choice experiment. *Cardiol Res Pract.* 2019; 2019:5719624.
89. Emren SV, Zoghi M, Berilgen R, et al. Safety of once- or twice-daily dosing of non-vitamin K antagonist oral anticoagulants (NOACs) in patients with nonvalvular atrial fibrillation: a NOAC-TR study. *Bosn J Basic Med Sci.* 2018;18:185–190.
90. Rossi AP, Facchinetti R, Ferrari E, et al. Predictors of self-reported adherence to direct oral anticoagulation in a population of elderly men and women with non-valvular atrial fibrillation. *J Thromb Thrombolysis.* 2018;46:139–144.
91. Laliberte F, Nelson WW, Lefebvre P, et al. Impact of daily dosing frequency on adherence to chronic medications among nonvalvular atrial fibrillation patients. *Adv Ther.* 2012;29:675–690.
92. Comte L, Vrijens B, Tousset E, et al. Estimation of the comparative therapeutic superiority of QD and BID dosing regimens, based on integrated analysis of dosing history data and pharmacokinetics. *J Pharmacokinet Pharmacodyn.* 2007;34:549–558.
93. Kreutz R, Persson PB, Kubitza D, et al. Dissociation between the pharmacokinetics and pharmacodynamics of once-daily rivaroxaban and twice-daily apixaban: a randomized crossover study. *J Thromb Haemost.* 2017;15:2017–2028.
94. Ageno W, Beyer-Westendorf J, Rubboli A. Once- versus twice-daily direct oral anticoagulants in non-valvular atrial fibrillation. *Expert Opin Pharmacother.* 2017;18:1325–1332.
95. 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.
96. Alberts MJ, Peacock WF, Fields LE, et al. Association between once- and twice-daily direct oral anticoagulant adherence in nonvalvular atrial fibrillation patients and rates of ischemic stroke. *Int J Cardiol.* 2016; 215:11–13.
97. Maclean R. *Anticoagulation at the End of Life*. Available at: https://www.sth.nhs.uk/clientfiles/File/Anticoagulation%20at%20the%20end%20of%20life%20Nov%202014.pdf. Accessed May 30, 2020.
98. Hogg K, Carrier M. Prevention and treatment of venous thromboembolism in patients with cancer. *Ther Adv Hematol.* 2012;3:45–58.
99. Tassinari D, Santelmo C, Scarpi E, et al. Controversial issues in thromboprophylaxis with low-molecular weight heparins in palliative care. *J Pain Symptom Manage.* 2008;36:e3–4.
100. Holmes HM, Bain KT, Zalpour A, et al. Predictors of anticoagulation in hospice patients with lung cancer. *Cancer.* 2010;116:4817–4824.
101. Brown MT, Bussell JK. Medication adherence: WHO cares? *Mayo Clin Proc.* 2011;86:304–314.
102. *Phase 2 Healthy Volunteer Study to Evaluate the Ability of PRT064445 to Reverse the Effects of Several Blood Thinner Drugs on Laboratory Tests*. Available at: https://clinicaltrials.gov/ct2/show/NCT01758432. Accessed August 16, 2020.
103. Cavallari I, Patti G. Efficacy and safety of oral anticoagulation in elderly patients with atrial fibrillation. *Anatol J Cardiol.* 2018;19: 67–71.
104. Patti G, Cavallari I, Hanon O, et al. The safety and efficacy of non-vitamin K antagonist oral anticoagulants in atrial fibrillation in the elderly. *Int J Cardiol.* 2018;265:118–124.
105. Rohla M, Weiss TW, Pecen L, et al. Risk factors for thromboembolic and bleeding events in anticoagulated patients with atrial fibrillation: the prospective, multicentre observational PREvention oF thromboembolic events—European Registry in Atrial Fibrillation (PREFER in AF). *BMJ Open.* 2019;9:e022478.