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REVIEW ARTICLE

Minimizing the Risk of Bleeding with NOACs in the Elderly

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Abstract Novel oral anticoagulants (NOACs) such as dabigatran, rivaroxaban, apixaban and edoxaban have gained a lot of popularity as alternatives to warfarin for anticoagulation in various clinical settings. However, there is conflicting opinion regarding the absolute benefit of NOAC use in elderly patients. Low body mass, altered body composition of fat and muscle, renal impairment and concurrent presence of multiple comorbidities predispose elderly patients to many adverse effects with NOACs that are typically not seen in younger patients. There have been reports that NOAC use, in particular dabigatran, is associated with a higher risk of gastrointestinal bleeding in the elderly. Diagnosis and management of NOAC-associated bleeding in the elderly is difficult due to the absence of commonly available drug-specific antidotes that can rapidly reverse the anticoagulant effects. Moreover, in elderly patients, a number of factors such as the presence of other comorbid medical conditions, renal insufficiency, drug interactions from polypharmacy, risk of falls and dementia need to be considered before prescribing anticoagulation therapy. Elderly patients frequently have compromised renal function, and therefore dose adjustments according to creatinine clearance for NOACs need to be made. As each NOAC comes with its own unique advantages and safety profile, an individualized case by case approach should be adopted to decide on the appropriate anticoagulation regimen for elderly patients after weighing the overall risks and benefits of therapy.

Key Points

Novel oral anticoagulants (NOACs) have emerged as popular alternatives to warfarin for the purpose of anticoagulation in elderly patients given the advantages of convenient oral dosing, more predictable pharmacokinetic profiles, fewer drug and food interactions, avoidance of routine monitoring, equal or superior efficacy and encouraging safety profiles including significantly lower rates of intracranial hemorrhage.

A significantly increased risk of gastrointestinal bleeding in elderly patients is observed with dabigatran, and use of this drug should be avoided in patients who have a history of, or are at an increased risk for, gastrointestinal bleeding.

Low body mass, altered body composition of fat and muscle, presence of renal impairment, multiple comorbidities, dementia and risk of falls are some of the issues that predispose patients to adverse effects of NOACs, making anticoagulation therapy in elderly patients a challenging task. Assessment of the benefits versus risks of anticoagulation therapy should be performed on an individual basis.

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1 Introduction

With advancing age, there is a progressive increase in the incidence of both arterial and venous thromboembolic events [1–3]. In elderly patients (conventionally defined as those aged 75 years and above), not only is age by itself a strong risk factor for venous thromboembolism (VTE) [2, 4], other factors such as diabetes mellitus, hypertension, stroke, heart failure and myocardial infarction are also more prevalent [3, 5], making them a high-risk population for thromboembolic events. The incidence of a first episode of deep vein thrombosis (DVT) or pulmonary embolism (PE) is estimated to be below one per 1000 person-years in people less than 50 years of age, but rises steeply to six per 1000 person-years in patients aged above 80 years [6]. The incidence of atrial fibrillation (AF), the most commonly encountered arrhythmia in clinical practice, also increases with age [7]. Approximately a third of all patients who have AF are aged 80 years or older, and it is estimated that by 2050, half of all patients who have AF are likely to be in this age group [8]. It is not surprising that the age of the patient is one of the most important components of the popular $CHADS_2VASC$ scoring system for estimating the risk of developing stroke in patients with AF [9]. The risk of ischemic stroke increases 1.5-fold for every 10 years of age increase [10]. Data from the Framingham Heart Study showed that almost 24 % of strokes in individuals aged 80 years and above are due to AF [11].

Therefore, from a therapeutic standpoint, anticoagulant therapy in elderly patients plays a very crucial role in day to day clinical practice. The vitamin K antagonist (VKA) warfarin has conventionally been used for anticoagulation in these patients. Previous studies have shown that anticoagulation with warfarin is superior to antiplatelet treatment with aspirin for the prevention of stroke in patients with AF, even in the elderly [12, 13]. Warfarin use, however, has a number of limitations, such as risk of major bleeding, the need for regular international normalized ratio (INR) monitoring, a narrow therapeutic range and interactions with several drugs and foods [14]. Almost half a century after the approval of warfarin, novel oral anticoagulants (NOACs) such as the direct thrombin inhibitor dabigatran, and factor Xa inhibitors rivaroxaban, apixaban and edoxaban were developed as alternative anticoagulant agents. The NOACs have a more predictable pharmacokinetic profile than warfarin, fewer dietary and drug interactions and do not require routine monitoring [15]. However, there are conflicting opinions regarding the efficacy and safety of NOACs in the elderly population, particularly with respect to the risk of bleeding. Low body mass, altered body composition of fat and muscle, a high prevalence of renal impairment and concurrent presence of multiple comorbidities may predispose geriatric patients to adverse effects of these drugs, which are otherwise well tolerated in younger patients [16]. The purpose of this review is to briefly describe the risk of bleeding with use of NOACs in the elderly, with an emphasis on prevention and management strategies.

2 NOAC Use in the Elderly: Current State of Evidence

Most of the available evidence regarding the efficacy and safety of NOACs in elderly patients comes from subgroup analysis of large randomized controlled trials (RCTs). A brief overview of the available data for each NOAC is described below.

2.1 Rivaroxaban

Rivaroxaban is an oxazolidinone derivative that functions by inhibiting both free factor Xa and factor Xa bound in the prothrombinase complex [17]. This highly selective direct factor Xa inhibitor has high oral bioavailability, a relatively fast onset of action and a predictable pharmacokinetic profile across a wide spectrum of patients with respect to age, gender, weight and race [18].

The ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial compared rivaroxaban 20 mg daily with dose-adjusted warfarin for prevention of stroke or systemic embolism in patients with non-valvular AF [19]. Patients with renal insufficiency and a creatinine clearance of 30–49 ml/min were given a reduced dose of rivaroxaban (15 mg daily). In the intention-to-treat analysis, rivaroxaban was found to be similar to warfarin in preventing stroke or systemic embolism [hazard ratio (HR) 0.88, 95 % confidence interval (CI) 0.75–1.03] [19]. Thirty-eight percent of patients in the trial were aged ≥75 years. The event rates of both stroke/systemic embolism as well as anticoagulant-associated bleeding were higher in elderly patients aged 75 years and above. Similar to the analysis of the trial's primary outcome, subgroup analysis for elderly patients aged 75 years or over demonstrated that rivaroxaban was non-inferior to warfarin for prevention of stroke or systemic embolism (HR 0.80, 95 % CI 0.63–1.02). The rates of major bleeding were noted to be similar in both elderly and younger patients (≥75 years 4.86 % rivaroxaban vs. 4.40 % warfarin per 100 patient-years; HR 1.11, 95 % CI 0.92–1.34; <75 years 2.69 vs. 2.79 % per 100 patient-

years; HR 0.96, 95 % CI 0.78–1.19; interaction $P = 0.336$) [20]. The risk of intracranial hemorrhage (ICH) was lower with rivaroxaban (HR 0.67, 95 % CI 0.47–0.93), with no significant variations noted across different age groups. In summary, the efficacy and safety of rivaroxaban compared with warfarin did not differ with age, thereby supporting the use of rivaroxaban as an alternative anticoagulant in elderly patients.

The EINSTEIN DVT [21] (patients with acute symptomatic DVT but no PE) and the EINSTEIN PE [22] (patients with symptomatic PE, with or without concomitant DVT) studies showed that rivaroxaban was non-inferior to standard therapy with low-molecular-weight heparin (LMWH) followed by an adjusted-dose VKA for treatment of symptomatic DVT and PE. Pooled analysis from both studies showed that the efficacy of rivaroxaban was consistent among all age groups. Rates of major bleeding were similar, occurring in 1 % of patients in the rivaroxaban group and 1.7 % in the LMWH/VKA group (HR 0.54, 95 % CI 0.37–0.79) [23]. Increasing age and declining renal function was associated with a reduction in major bleeding in favor of rivaroxaban, being most pronounced in elderly patients with a creatinine clearance of <50 ml/min.

2.2 Apixaban

Apixaban is a direct competitive inhibitor of factor Xa that is approximately 25 % excreted by the kidney and has 50 % net bioavailability [24].

The AVERROES (Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients who have Failed or are Unsuitable for Vitamin K) trial demonstrated that apixaban 5 mg twice daily (BID) lowered the risk of stroke or systemic embolism when compared with 81–324 mg aspirin in patients with prior stroke/transient ischemic attack (TIA) (HR 0.29, 95 % CI 0.15–0.60) as well as in patients with no prior stroke/TIA (HR 0.29, 95 % CI 0.15–0.60) [25]. Major bleeding was more frequent in patients with a history of stroke or TIA than in patients without this history (HR 2.88, 95 % CI 1.77–4.55), but risks did not differ between treatment groups. Overall, apixaban was well tolerated and showed a profile of adverse events similar to that of aspirin. Subgroup analysis showed that in elderly patients aged 75 and above, there was a significantly reduced risk of stroke or embolism with apixaban when compared with aspirin (2 % per year vs. 6.1 % per year). However, the rate of major bleeding was similar between both apixaban and aspirin in this age group (2.2 % per year with apixaban vs. 2.6 % per year with aspirin) [25].

The ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial showed that apixaban 5 mg BID was superior to dose-adjusted warfarin for prevention of stroke or systemic embolism in patients with AF (HR 0.79, 95 % CI 0.66–0.95) [26]. A reduced dose of apixaban 2.5 mg BID was used for patients with two out of three of the following criteria: age ≥80 years, body weight ≤60 kg and creatinine ≥1.5 mg/dl. Thirty-one percent of patients enrolled in this trial were aged ≥75 years. Efficacy of apixaban was similar in patients aged 75 years or older with respect to the primary outcome (HR 0.71, 95 % CI 0.53–0.95). The rate of major bleeding was 2.13 % per year in the apixaban group, as compared with 3.09 % per year in the warfarin group (HR 0.69, 95 % CI 0.60–0.80). No significant variation in the rate of major bleeding was observed across different age groups [26].

The AMPLIFY trial showed that apixaban alone was non-inferior to conventional therapy with enoxaparin followed by warfarin for treatment of acute VTE [relative risk (RR) 0.84, 95 % CI 0.6–1.18] and was associated with significantly less major bleeding (RR 0.31, 95 % CI 0.17–0.55) [27]. The efficacy and safety of apixaban was consistent across all subgroups, including elderly patients aged 75 years and above.

2.3 Edoxaban

Edoxaban is a direct oral factor Xa inhibitor that was recently approved by the Food and Drug Administration (FDA) for the prevention of stroke and non–central-nervous-system (CNS) systemic embolism in patients with non-valvular AF. Pharmacokinetically, edoxaban achieves maximum concentrations within 1–2 h, is 50 % renally excreted and has approximately 62 % bioavailability [15].

The ENGAGE AF-TIMI 48 trial demonstrated that edoxaban (60 and 30 mg once daily) was non-inferior to dose-adjusted warfarin for reduction of stroke or systemic embolism (modified intent-to-treat population, $P = 0.001$ and $P = 0.005$ for non-inferiority, respectively; intent-to-treat population, $P = 0.08$ and $P = 0.10$ for superiority, respectively) [28]. The annual rate of major bleeding was 3.43 % with warfarin versus 2.75 % with high-dose edoxaban (HR 0.80, 95 % CI 0.71–0.91) and 1.61 % with low-dose edoxaban (HR 0.47, 95 % CI 0.41–0.55). Compared with warfarin, there were lower rates of major bleeding with both high-dose edoxaban (3.43 vs. 2.75 %) and low-dose edoxaban (3.43 vs. 1.61 %). No significant difference in the primary efficacy endpoint of stroke/systemic embolism, or the primary safety endpoint of major bleeding was noted in elderly patients ≥75 years, compared with those <75 years.

The HOKUSAI VTE Trial compared edoxaban 60 mg once daily with dose-adjusted warfarin following initial treatment with heparin for treatment of symptomatic VTE

[29]. Edoxaban was administered at a reduced dose of 30 mg once daily for patients with a creatinine clearance of 30–50 ml/min or those with a body weight below 60 kg. Results of the trial showed that edoxaban was non-inferior to warfarin for prevention of recurrent VTE (HR 0.89, 95 % CI 0.70–1.13). The safety outcome of major/clinically relevant non-major bleeding occurred in 8.5 % of patients in the edoxaban group and 10.3 % of patients in the warfarin group (HR 0.81, 95 % CI 0.71–0.94). No significant difference in safety profile was observed across different age groups.

2.4 Dabigatran

Dabigatran is a direct thrombin inhibitor that is FDA approved for treatment and reduction in risk of recurrence of DVT/PE as well as for prevention of stroke in non-valvular AF.

The RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial, which compared dabigatran 110 or 150 mg BID with dose-adjusted warfarin, showed that dabigatran 150 mg BID was superior to warfarin for reduction of the risk of stroke or systemic embolism (RR 0.66, 95 % CI 0.53–0.82), while dabigatran 110 mg BID was non-inferior to warfarin in reducing the risk of stroke or systemic embolism (RR 0.91, 95 % CI 0.74–1.11) [30]. However, dabigatran 110 mg BID was associated with a lower risk of major bleeding compared with warfarin (2.87 vs. 3.57 %; $P = 0.002$), while dabigatran 150 mg BID was associated with a similar risk of major bleeding (3.31 vs. 3.57 %; $P = 0.32$). Both doses of dabigatran demonstrated a reduction in ICH compared with warfarin [31]. Forty percent of patients in the RE-LY trial were aged ≥75 years. The event rates of both stroke/systemic embolism as well as anticoagulant-associated bleeding were higher in elderly patients aged 75 years and above. In elderly patients, the efficacy of both doses of dabigatran for stroke prevention was similar to that observed in patients aged <75 years (*P*-interaction 0.81). However, the risk of bleeding with dabigatran versus warfarin was significantly higher for both doses of dabigatran in elderly patients (HR 1.18, 95 % CI 0.98–1.42, for 150 mg BID and HR 1.01, 95 % CI 0.83–1.23, for 110 mg BID) compared with younger patients (HR 0.70, 95 % CI 0.57–0.86, for 150 mg BID and HR 0.62, 95 % CI 0.5–0.77, for 110 mg BID) [31]. This implied that the risk of bleeding with dabigatran increased significantly with advancing age, compared with the risk of bleeding with warfarin. A similar steep rise in the incidence of dabigatran-associated bleeding was observed in very elderly patients aged 80 years and above (HR 1.35, 95 % CI 1.03–1.77, for 150 mg BID and HR 1.13, 95 % CI 0.85–1.5, for 110 mg BID) [32]. Further analysis showed that in elderly patients aged 75 years and above, the risk of ICH was lower with both doses of dabigatran (110 mg BID/150 mg BID) in comparison with warfarin (0.37/0.42 % per year vs. 1 %), but the risk of extracranial bleeding was higher with dabigatran (4.1/4.7 % per year vs. 3.4 %) [31].

The RE-COVER I, RE-COVER II and RE-MEDY trials evaluated the efficacy and safety of dabigatran versus standard therapy with heparin or LMWH/VKA for treatment of VTE. Limited data are available on outcomes for elderly patients in these trials.

2.5 Evidence from Meta-Analyses

Two major meta-analyses of RCTs have investigated the efficacy and safety of NOACs in elderly patients aged 75 years and above.

1. Our first analysis (Sardar et al. [16]) included pooled data from ten RCTs involving the first three FDA approved NOACs: dabigatran, rivaroxaban and apixaban [16]. Analysis revealed that the risk of stroke and systemic embolism was significantly lower with NOACs than conventional therapy or pharmacologically active agents [3.3 vs. 4.7 %; odds ratio (OR) 0.65, 95 % CI 0.48–0.87; absolute risk reduction (ARR) 1.4 %, number needed to treat (NNT) 71]. NOAC use also resulted in a significantly lower risk of VTE or VTE-related death than conventional therapy (3.7 vs. 7.0 %; OR 0.45, 95 % CI 0.27–0.77; ARR 3.3 %, NNT 30) and pharmacologically active agents (3.9 vs. 6.6 %; OR 0.61, 95 % CI 0.45–0.81; ARR 2.6 %, NNT 38) [16]. For the safety analysis, we found that there was no significant difference in the risk of major or clinically relevant bleeding between NOACs and conventional therapy in individuals aged 75 years and older (6.4 % with NOAC vs. 6.3 % with conventional anticoagulants; OR 1.02, 95 % CI 0.73–1.43). On subgroup analysis according to type of conventional anticoagulant, we observed that there was no increased risk of bleeding with NOACs compared with both warfarin (6.5 vs. 7.1 %; OR 0.76, 95 % CI 0.51–1.12) and LMWH/LMWH followed by VKA (6.9 vs. 5.3 %; OR 1.27, 95 % CI 0.54–2.98). On subgroup analysis according to type of NOAC, we found that compared with conventional therapy, there was no increased risk of major or clinically relevant bleeding with rivaroxaban (OR 1.18, 95 % CI 0.64–2.19) or apixaban (OR 0.80, 95 % CI 0.43–1.51) in elderly patients. However, safety data on dabigatran was more limited (OR 1.07, 95 % CI 0.90–1.28) [16].
2. Another recent meta-analysis (Sharma et al. 2015) included pooled data from 11 RCTs involving all four NOACs in elderly patients aged 75 years and above

[33]. The results of this study showed that each NOAC was at minimum as effective as VKA in reducing the risk of stroke or systemic embolism in AF, as well as recurrent VTE in VTE. In patients with AF, a significant benefit in reducing the risk of stroke or systemic embolism in comparison with VKA was observed for dabigatran 150 mg (OR 0.66; 95 % CI 0.49–0.90) and apixaban (OR 0.70; 95 % CI 0.52–0.93). Overall efficacy of NOACs in the elderly was similar to that of the total trial population. A significant reduction in the risk of major bleeding in comparison with VKA was observed in elderly patients for apixaban (OR 0.63, 95 % CI 0.51–0.77), edoxaban 60 mg (OR 0.81, 95 % CI 0.67–0.98) and edoxaban 30 mg (OR 0.46, 95 % CI 0.38–0.57). Dabigatran 150 mg showed a non-significant, higher risk of major bleeding in comparison with VKA in elderly patients (OR 1.18, 95 % CI 0.97–1.44). However, risk of major bleeding was similar to VKA with the dabigatran 110-mg dose. Data on gastrointestinal bleeding in elderly patients were reported only for dabigatran. Analysis revealed that risk of gastrointestinal bleeding was significantly higher with dabigatran 150 mg (OR 1.78, 95 % CI 1.35–2.35) and 110 mg (OR 1.40, 95 % CI 1.04–1.90) in comparison with VKA. However, in the total population, increased risk of gastrointestinal bleeding was seen with dabigatran 150 mg, but not 110 mg. A similar increased risk was also observed with rivaroxaban and edoxaban 60 mg in the total population. In elderly patients, a significant reduction in the risk of ICH in comparison with VKA was observed for dabigatran 150 mg (OR 0.43, 95 % CI 0.26–0.72), dabigatran 110 mg (OR 0.36, 95 % CI 0.22–0.61) and apixaban (OR 0.38, 95 % CI 0.24–0.59). A non-significant reduction in ICH was also observed for rivaroxaban, whereas data were not available for edoxaban in the elderly. In comparison with VKA in elderly patients, there was a reduced risk of clinically relevant bleeding with apixaban (OR 0.64, 95 % CI 0.54–0.76), while there was a reduced risk of fatal bleeding observed with rivaroxaban (OR 0.53, 95 % CI 0.30–0.93). Rates of clinically relevant bleeding and fatal bleeding with other NOACs were not significantly different from VKA [33].

3 Discussion

The absolute incidence of both thrombotic and bleeding events increases with advancing age, making anticoagulation therapy in elderly patients a double-edged sword. It involves a delicate balancing act between maintaining the benefits of thromboembolism prevention while harboring the risks of increased bleeding in a population of patients already burdened with numerous comorbidities. However, current evidence suggests that the overall benefits of anticoagulation outweigh the risks, even in elderly patients who are at a higher risk of bleeding or falls [34]. While it is prudent to proceed with caution in elderly patients, age by itself should not be a reason to avoid antithrombotic therapy. Special considerations that need to be kept in mind when prescribing NOACs to elderly patients have been described below.

3.1 Bleeding Risks with NOACs in the Elderly

Results from RCTs and evidence from meta-analyses have shown that NOACs are more effective than warfarin for the purpose of anticoagulation in elderly patients (aged ≥75 years) with AF and VTE. However, despite their similar efficacy in elderly patients, the NOACs carry a safety profile that is characteristically different from warfarin. Dabigatran 150 mg was shown to carry a non-significant higher risk of major bleeding in the elderly population in comparison with warfarin, despite having a statistically significant lower risk of major bleeding in the total population with the 110-mg regimen. Apixaban and edoxaban have both been shown to have a lower risk of major bleeding than warfarin in elderly patients [33]. There is no evidence to suggest that NOAC use in elderly patients predisposes patients to a higher risk of fatal bleeding in comparison with warfarin. Current evidence suggests that gastrointestinal bleeding rates are higher with rivaroxaban, edoxaban 60 mg and dabigatran 150 mg in all age groups combined. However, in elderly patients aged 75 years and above, risk of gastrointestinal bleeding appears to be significantly higher for both doses of dabigatran (150 and 110 mg). Higher concentrations of the active form of dabigatran may be found locally in the gastrointestinal tract from metabolism of the pro-drug dabigatran etexilate by esterases in the gut flora. With advancing age, there is a higher incidence of gastrointestinal tract pathology such as diverticulosis and angiodysplasia in elderly patients [35]. There is an increased risk of bleeding from these diseased areas by direct exposure to dabigatran. Moreover, higher systemic drug concentrations of dabigatran from age-related decline in renal function and drug clearance could also account for the increased bleeding risk observed in elderly patients.

ICH is one of the most devastating complications of anticoagulation therapy and carries a high burden of morbidity and mortality. All four NOACs have been shown to carry a reduced risk of ICH in comparison with warfarin

[36]. Current evidence suggests that this benefit is preserved in the elderly population as well, despite their greater susceptibility to falls and head trauma.

3.2 Renal Insufficiency in Elderly Patients

There is progressive pathophysiologic decline in renal function seen with advancing age, which directly affects the pharmacokinetics of numerous drugs. This becomes extremely relevant in elderly patients on anticoagulation therapy with novel agents because all NOACs are eliminated by the kidneys to different extents. Moreover, elderly patients frequently develop acute changes in their kidney function due to decreased fluid intake and water loss, infections, use of multiple medications, etc. Accurate estimation of the patient's creatinine clearance using the Cockroft–Gault formula and close monitoring of the patient's renal function is recommended. Subsequent dose adjustment for NOACs according to changes in renal function needs to be made to avoid toxicity. The FDA recommendations for dose adjustments according to renal function for NOACs are shown in Table 1. Of note, severe renal impairment was a strict exclusion criterion in most of the clinical trials involving NOACs. For example, patients with a creatinine clearance of <30 ml/min were excluded from RE-LY, ROCKET AF and ENGAGE AF-TIMI 48 trials, while patients with a creatinine clearance of <25 ml/min were excluded from ARISTOTLE and AVERROES trials. Lower bleeding rates observed with NOACs in RCTs may be partly due to exclusion of patients with advanced kidney disease. In general, it is advised not to prescribe NOACs in elderly patients with severe renal impairment, as there is a paucity of data regarding the absolute safety of NOACs in this setting.

3.3 Drug Interactions

One major advantage of NOACs over warfarin is that NOACs have fewer drug–drug and drug–food interactions. This is particularly relevant in elderly patients who are frequently prescribed multiple medications, which increases the likelihood of adverse reactions. However, few relevant drug interactions with NOACs have been described in the medical literature.

The metabolism and excretion of rivaroxaban is modulated by the enzymes CYP3A4, CYP2J2, P-glycoprotein (P-gp) and breast cancer resistance protein ABCG2. Studies have shown that rivaroxaban should not be administered with combined CYP3A4, P-gp and ABCG2 inhibitors such as antimycotics and HIV protease inhibitors, which can predispose patients to rivaroxaban toxicity and major bleeding [37]. P-gp is a drug efflux pump involved in the metabolism of a number of xenobiotics and its activity is modulated by a variety of drug and food components [38]. All four NOACs are substrates for P-gp. Moreover, P-gp–modulating drugs are commonly given to elderly people with AF, which can directly affect the pharmacokinetic activity of NOACs in these patients and increase the risk of adverse effects.

3.4 Risk of Falls in the Elderly

One of the major concerns of avoiding anticoagulation in elderly patients is the risk of falls [39]. There is evidence that AF itself is an independent risk factor for non-accidental falls in elderly patients [40]. As a lot of elderly patients with AF are on chronic anticoagulation therapy, these patients are at a significantly higher risk of developing catastrophic events such as major bleeding and ICH following falls. Although this risk remains irrespective of whether the patients are anticoagulated with NOACs or warfarin, NOAC activity is difficult to monitor and treat, thereby making NOAC-associated falls challenging to manage. This should be kept in mind when deciding the appropriate anticoagulation regimen for the patient after carefully assessing risks and benefits of therapy.

3.5 Dementia in Elderly Patients

It is well known that elderly patients, especially those with dementia, have difficulty managing multiple medications taken at different times throughout the day. Unfortunately, polypharmacy is fairly common in the geriatric population. While rivaroxaban and edoxaban are once a day medications, apixaban and dabigatran have to be taken twice daily, making it likely that elderly patients will be less compliant with this dosing regimen. It is difficult to monitor the anticoagulant activity of NOACs with common laboratory tests. Moreover, NOACs have a short half-life, which implies that missing a dose significantly raises the risk of developing an embolic event. One major advantage of warfarin in this setting is that it is taken once daily and its activity can be readily measured by checking INR levels. Dose adjustments can be made accordingly to maintain a therapeutic INR without predisposing to embolic risks if a dose is missed.

3.6 Monitoring of NOAC Activity

While the anticoagulant activity of warfarin can easily be monitored by measuring the INR, it is not a useful test to gauge the anticoagulant effects of NOACs. This is because the INR test is calibrated for use with VKA only and INR levels do not provide a linear correlation with NOAC concentration and effects. As rivaroxaban, apixaban and edoxaban are direct inhibitors of factor Xa, the anti-factor Xa assay is the most sensitive method of monitoring their

Table 1 FDA-recommended dose adjustments for NOAC use in the setting of renal impairment

NOAC	CrCl (ml/min)	Dose adjustment
Rivaroxaban	15–50	Decrease dose to 15 mg PO daily
	<30	Contraindicated for DVT prophylaxis only
	<15	Contraindicated
Dabigatran	Mild to moderate renal impairment with CrCl >30	No dose adjustment required, continue 150 mg PO BID
	15–30	Decrease dose to 75 mg PO BID
	<15	No recommendations available
Apixaban	Any renal impairment	No recommended dose adjustments for patients with renal impairment alone, including those with end-stage renal disease maintained on hemodialysis. However, there is a recommended dose adjustment to 2.5 mg PO BID for those patients with any two or more of the following: age ≥80 years, body weight ≤60 kg or creatinine ≥1.5 mg/dl
Edoxaban	>95	Contraindicated in patients with non-valvular atrial fibrillation and CrCl >95 ml/min
	15–50	Decrease dose to 30 mg PO daily
	<15	Not recommended

BID twice daily, *CrCl* creatinine clearance, *DVT* deep vein thrombosis, *FDA* Food and Drug Administration, *NOAC* novel oral anticoagulant, *PO* oral

anticoagulant activity [41]. Tests that can be used to detect dabigatran activity include activated partial thromboplastin time (aPTT) and the more sensitive ecarin clotting time (ECT) [42].

3.7 Management of NOAC-Associated Bleeding

In contrast to warfarin, NOAC-associated bleeding can be difficult to manage because of the absence of commonly available drug-specific antidotes that can rapidly reverse the anticoagulant effects. General resuscitation measures including emergency management of an unstable patient with administration of fluids and blood products should always be the first step in management of NOAC-associated bleeding.

Prothrombin complex concentrates (PCC) had previously been suggested as potential agents to help in NOAC reversal, but specific data regarding their efficacy are lacking [43]. Recently, idarucizumab, a monoclonal antibody fragment that binds free and thrombin-bound dabigatran, therein neutralizing its activity, was developed to reverse the anticoagulant effects of dabigatran. The RE-VERSE AD (Reversal Effects of idarucizumab on Active Dabigatran) study showed that 5 g idarucizumab administered intravenously rapidly and completely reversed the anticoagulant effect of dabigatran in 88–98 % of the patients who had elevated clotting times at baseline [44]. This led to idarucizumab becoming the first FDA approved NOAC-specific reversal agent. Unfortunately, the drug is not commonly available yet in most medical centers throughout the country. There is also uncertainty regarding the clinical utility of idarucizumab, as the median time for hemostasis in the RE-VERSE AD study was 11.4 h in patients who had severe bleeding. Andexanet alfa (andexanet), a recombinant modified human factor Xa decoy protein, was developed as a specific reversal agent designed to neutralize the anticoagulant effects of both direct and indirect factor Xa inhibitors. Results of the ANNEXA-A (apixaban) and ANNEXA-R (rivaroxaban) trials were recently published and showed that andexanet reversed the anticoagulant activity of apixaban and rivaroxaban in older healthy participants within minutes after infusion, without evidence of clinical toxic effects [45]. These results are promising, and effective reversal agents for all NOACs may soon become commonly available, which will encourage more physicians to prescribe NOACs in elderly patients. However, in day to day clinical practice today, reversal of NOAC effect mostly relies on the short half-lives of these novel agents (5–17 h), which ensures rapid reductions in anticoagulant levels with time in patients who do not have concomitant renal or hepatic dysfunction. Because of its high renal clearance, dabigatran is the only NOAC that can be effectively removed from circulation with dialysis. After initial resuscitation, site-specific interventions such as gastrointestinal endoscopy, computerized tomography angiography and surgery may eventually be required to achieve hemostasis.

4 Recommendations for Clinical Practice

Current evidence supports anticoagulation with NOACs in elderly patients. Despite their proven benefits, NOACs in elderly patients should be initiated with caution due to the complex management of NOAC-associated bleeding. Every effort should be taken to minimize these risks in elderly patients. Dabigatran should be avoided in elderly

patients who have a history of and/or are at a greater risk for gastrointestinal bleeding, as recent data suggests that both doses of dabigatran are associated with a higher risk of gastrointestinal bleeding in the geriatric population [33]. However, data on the other NOACs with respect to gastrointestinal bleeding in elderly patients are lacking, and therefore no official recommendations have been made by the FDA in this clinical setting. In elderly patients with AF, objective criteria for calculating the risk of stroke (such as the popular $CHADS_2VASC$ system) as well as the risk of bleeding (e.g., the $HEMORR_2HAGES$ score and the HAS-BLED score) can be used to help in deciding anticoagulation therapy [9]. This can be done on a case by case basis, and an individualized antithrombotic regimen can be created for patients with different baseline characteristics and comorbid medical conditions. Individuals with a higher calculated stroke risk benefit the most from anticoagulation. Patients in whom the calculated risk of bleeding clearly outweighs the risk of stroke should be advised against anticoagulation therapy. However, individual preference is an important factor to take into consideration and an informed decision should be made together with the patient after explaining both the risks and benefits of therapy.

In collaboration with the patient's primary care physician and/or geriatrician, an extensive evaluation should be performed prior to initiation of NOAC therapy, investigating the patient's level of independence, cognitive function, mobility level, risk of falls and conceivable problems with drug compliance [46]. Input from the patient's caregivers is extremely important in this setting as they will play an active role in helping to manage the patient's anticoagulation regimen, while looking out for early side effects. Use of multiple medications in elderly patients should be avoided whenever possible, as these are often prescribed without proven clinical benefit but considerably increase the likelihood of adverse drug interactions and also contribute towards medication non-compliance. NOACs should not be co-administered with medications that dually inhibit CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, clarithromycin, etc.).

Many elderly patients on aspirin also take nonsteroidal anti-inflammatory drugs (NSAIDs) for chronic pain. If these patients require anticoagulation with a NOAC, it is recommended to stop taking NSAIDs and switch to another analgesic drug to minimize the risk of bleeding. Dose adjustments for specific NOACs should be made depending on the patient's age, body weight and renal function. For apixaban, the FDA recommends a lower dose (2.5 mg BID taken orally) in elderly adults with at least one comorbidity in addition to older age (i.e., those with two or more of the following: age $\geq$80 years, body weight $\leq$60 kg and serum creatinine $\geq$1.5 mg/dl) [3]. Renal function for elderly patients should be checked prior to initiating therapy with NOACs and then at least once every 8–12 months. More frequent monitoring of renal function is warranted in patients who have known kidney disease, when they are prescribed other nephrotoxic drugs and when they are suffering from acute illness. Strict adherence to dose adjustments for creatinine clearance (Table 1) is recommended for all NOACs.

5 Conclusions

NOACs have emerged as popular alternatives to warfarin for the purpose of anticoagulation in elderly patients, given the advantages of convenient oral dosing, more predictable pharmacokinetic profiles, fewer drug and food interactions, avoidance of routine monitoring, equal or superior efficacy and an encouraging safety profile including significantly lower rates of ICH. Gastrointestinal bleeding remains a concern, particularly with dabigatran use in elderly patients. Current evidence favors the use of NOACs in elderly patients. However, most of our evidence regarding the safety of NOACs comes from RCTs, and to what extent the data from these trials correlate with 'real world' patients in day to day clinical practice remains to be seen. Each NOAC has its own advantages, unique pharmacokinetics and distinct safety profile. Unfortunately, there is no uniform therapeutic algorithm for anticoagulation therapy with NOACs in elderly patients. The anticoagulation regimen should be customized for each patient on an individual basis after taking into consideration multiple factors such as the patient's risk of thromboembolic events, risk of bleeding, comorbid medical conditions, personal preference, financial liability and parameters such as age, body weight and renal function.

Compliance with Ethical Standards

Conflict of interest All authors declare they have no conflicts of interest that are relevant to the content of this review.

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References

1. Robert-Ebadi H, Le Gal G, Righini M. Use of anticoagulants in elderly patients: practical recommendations. Clin Interv Aging. 2009;4:165–77.
2. Spyropoulos AC, Merli G. Management of venous thromboembolism in the elderly. Drugs Aging. 2006;23:651–71.
3. Deedwania PC. New oral anticoagulants in elderly patients with atrial fibrillation. Am J Med. 2013;126:289–96.

4. Engbers MJ, van Hylckama Vlieg A, Rosendaal FR. Venous thrombosis in the elderly: incidence, risk factors and risk groups. J Thromb Haemost. 2010;8:2105–12.
5. Cowie CC, Rust KF, Ford ES, Eberhardt MS, Byrd-Holt DD, Li C, et al. Full accounting of diabetes and pre-diabetes in the US population in 1988–1994 and 2005–2006. Diabetes Care. 2009;32:287–94.
6. Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrøm J. Incidence and mortality of venous thrombosis: a population-based study. J Thromb Haemost. 2007;5:692–9.
7. Chugh SS, Havmoeller 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(8):837–47.
8. 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(18):2370–5.
9. Lane DA, Lip GY. Use of the CHA(2)DS(2)-VASc and HAS-BLED scores to aid decision making for thromboprophylaxis in nonvalvular atrial fibrillation. Circulation. 2012;126(7):860–5.
10. van Walraven C, Hart RG, Connolly S, Austin PC, Mant J, Hobbs FD, et al. Effect of age on stroke prevention therapy in patients with atrial fibrillation: the atrial fibrillation investigators. Stroke. 2009;40:1410–6.
11. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke. 1991;22:983–8.
12. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 2007;146:857–67.
13. Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, 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 randomized controlled trial. Lancet. 2007;370:493–503.
14. Sen P, Kundu A, Sardar P, Chatterjee S, Nairooz R, Amin H, et al. Outcomes after cardioversion in atrial fibrillation patients treated with non-vitamin K antagonist oral anticoagulants (NOACs): insights from a meta-analysis. Am J Cardiovasc Drugs. 2016;16(1):33–41.
15. Ogata K, Mendell-Harary J, Tachibana M, Masumoto H, Oguma T, Kojima M, et al. Clinical safety, tolerability, pharmacokinetics, and pharmacodynamics of the novel factor Xa inhibitor edoxaban in healthy volunteers. J Clin Pharmacol. 2010;50(7): 743–53.
16. Sardar P, Chatterjee S, Chaudhari S, Lip GY. New oral anticoagulants in elderly adults: evidence from a meta-analysis of randomized trials. J Am Geriatr Soc. 2014;62(5):857–64.
17. Roehrig S, Straub A, Pohlmann J, Lampe T, Pernerstorfer J, Schlemmer KH, et al. Discovery of the novel antithrombotic agent 5-chloro-*N*-({(5S)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl} methyl)thiophene-2-carboxamide (BAY 59-7939): an oral, direct factor Xa inhibitor. J Med Chem. 2005;48(19):5900–8.
18. Eriksson BI, Borris LC, Dahl OE, Haas S, Huisman MV, Kakkar AK, et al. A once-daily, oral, direct factor Xa inhibitor, rivaroxaban (BAY 59-7939), for thromboprophylaxis after total hip replacement. Circulation. 2006;114(22):2374–81.
19. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883–91.
20. 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(2):138–46.
21. EINSTEIN Investigators, Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010;363(26):2499–510.
22. EINSTEIN–PE Investigators, Büller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med. 2012;366(14):1287–97.
23. Prins MH, Lensing AW, Bauersachs R, van Bellen B, Bounameaux H, Brighton TA, et al. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN–DVT and PE randomized studies. Thromb J. 2013;11(1):21.
24. Eikelboom JW, Weitz JI. New anticoagulants. Circulation. 2010;121(13):1523–32.
25. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, et al. Apixaban in patients with atrial fibrillation. N Engl J Med. 2011;364(9):806–17.
26. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban vs warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981–92.
27. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med. 2013;369(9):799–808.
28. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369(22):2093–104.
29. Investigators Hokusai-VTE, Büller HR, Décousus H, Grosso MA, Mercuri M, Middeldorp S, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med. 2013;369(15):1406–15.
30. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A. Dabigatran vs warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361(12):1139–51.
31. Eikelboom JW, Wallentin L, Connolly SJ, Ezekowitz M, Healey JS, Oldgren J, 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;123:2363–72.
32. Coppens M, Eikelboom J, Ezekowitz M, Clemens A, Healy J, Wallentin L, et al. Dabigatran versus warfarin in very elderly patients with atrial fibrillation: results from the RE-LY trial. Circulation. 2012;126:A15l537.
33. 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(3):194–204.
34. Zarraga IG, Kron J. Oral anticoagulation in elderly adults with atrial fibrillation: integrating new options with old concepts. J Am Geriatr Soc. 2013;61(1):143–50.
35. Strate LL. Lower GI bleeding: epidemiology and diagnosis. Gastroenterol Clin North Am. 2005;34(4):643–64.
36. Kundu A, Sen P, Sardar P, Chatterjee S, Kapoor A, McManus DD. Intracranial hemorrhage with target specific oral anticoagulants in patients with atrial fibrillation: an updated meta-analysis of randomized controlled trials. Int J Cardiol. 2016;203:1000–2.
37. Mueck W, Kubitza D, Becka M. Co-administration of rivaroxaban with drugs that share its elimination pathways: pharmacokinetic effects in healthy subjects. Br J Clin Pharmacol. 2013;76:455–66.

38. Marchetti S, Mazzanti R, Beijnen JH, Schellens JH. Concise review: clinical relevance of drug–drug and herb–drug interactions mediated by the ABC transporter ABCB1 (MDR1, P-glycoprotein). Oncologist. 2007;12(8):927–41.
39. Rosenman MB, Baker L, Jing Y, Makenbaeva D, Meissner B, Simon TA, et al. Why is warfarin underused for stroke prevention in atrial fibrillation? A detailed review of electronic medical records. Curr Med Res Opin. 2012;28:1407–14.
40. Sanders NA, Ganguly JA, Jetter TL, Daccarett M, Wasmund SL, Brignole M, et al. Atrial fibrillation: an independent risk factor for nonaccidental falls in older patients. Pacing Clin Electrophysiol. 2012;35:973–9.
41. Mani H, Rohde G, Stratmann G, Hesse C, Herth N, Schwers S, et al. Accurate determination of rivaroxaban levels requires different calibrator sets but not addition of antithrombin. Thromb Haemost. 2012;108(1):191–8.
42. Hawes EM, Deal AM, Funk-Adcock D, Gosselin R, Jeanneret C, Cook AM, et al. Performance of coagulation tests in patients on therapeutic doses of dabigatran: a cross-sectional pharmacodynamic study based on peak and trough plasma levels. J Thromb Haemost. 2013;11(8):1493–502.
43. Levi M, Moore KT, Castillejos CF, Kubitza D, Berkowitz SD, Goldhaber SZ, et al. Comparison of three-factor and four-factor prothrombin complex concentrates regarding reversal of the anticoagulant effects of rivaroxaban in healthy volunteers. J Thromb Haemost. 2014;12(9):1428–36.
44. Pollack CV Jr, Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, et al. Idarucizumab for dabigatran reversal. N Engl J Med. 2015;373(6):511–20.
45. Siegal DM, Curnutte JT, Connolly SJ, Lu G, Conley PB, Wiens BL, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. N Engl J Med. 2015;373(25):2413–24.
46. Stöllberger C, Finsterer J. Concerns about the use of new oral anticoagulants for stroke prevention in elderly patients with atrial fibrillation. Drugs Aging. 2013;30(12):949–58.