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Review · **Open Access** ·

Efficacy and safety of novel anticoagulants in the elderly

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Abstract

Atrial fibrillation and venous thromboembolism (VTE) are common disorders associated with maleficent thrombotic events, particularly in the elderly patients. Polypharmacy, co-morbidities, and altered pharmacokinetics, often present in these patients, render the use of anticoagulants quite challenging. Novel oral anticoagulants (NOACs) have recently emerged as alternatives to Vitamin K Antagonists (VKAs) and are gradually increasing their popularity mainly because of their fewer drug and food interactions and ease of use. Their effectiveness and safety has been well-established in the general population but the balance between benefit and harm in the elderly is still unclear. Routine use in these patients is uncommon. Accumulating data have shown that the benefit of NOACs is consistent among all age groups, featuring equal or greater efficacy in preventing thrombotic events. Excess bleedings were lower with NOACs in comparison to VKAs, but bleeding patterns were disparate among them and head to head comparison is not available. The present review highlights on the efficacy and safety of novel anticoagulants in the elderly population.

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1 Introduction

Aging is regarded as a significant risk factor for atrial fibrillation (AF) and venous thromboembolism (VTE).[1,2] AF is the most common cardiac arrhythmia, its prevalence increases with age and has been proven to be a critical risk factor for stroke.[3] In the CHA_2DS_2-VASc score, a well-established stroke risk stratification scheme, patients of age 75 and older acquire two points to a maximum score of 9.[4] The remaining risk factors of this score such as heart failure, hypertension, prior stroke, and diabetes mellitus are often present in the elderly patient.[4] Likewise, VTE often emerges with the passing of time.[2,5] After the age of 40, the risk for developing VTE approximately doubles with every decade.[6,7] Thrombotic events associated with AF and VTE are common and the prognosis in the elderly can be severe, thus the urge for anticoagulant therapy is of utmost importance.[8–10]

Until 2009, the group of vitamin K antagonists (VKAs), mainly warfarin, was the single option for anticoagulant therapy. Even though VKAs' efficacy in preventing thrombotic events is well-established, their use in the elderly so far has been limited.[11–13] Drug and food interactions, increased risk of bleeding and the need for routine monitoring are the main reasons that VKAs are insufficiently used in the older patients.[14,15] Advanced age specifically is an accessional risk factor for major bleeding events when VKAs are used.[16] Nonetheless, even when VKAs are prescribed, their response to the elderly varies and target international normalized ratio is often difficult to achieve and maintain.[14,15]

Recently, four new oral anticoagulants (NOACs) have been released for prevention of thromboembolic complications in AF and VTE. These new anticoagulants dose-dependently inhibit either thrombin (Dabigatran) or factor Xa (Rivaroxaban, Apixaban and Edoxaban).[17] Their main advantages over VKAs are fewer drug and food interactions, rapid onset and offset of therapeutic action plus they don't require dose-level monitoring.[17] In the general population, each of them has been proven to be at least as effective and safe as warfarin for reducing the risk for stroke and systemic embolism (SE) in AF, as well as the risk for recurrence of VTE.[18–25]

2 Use of NOACs in elderly patients

Even though there are several studies in the general

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Table 1. Mean age and percentage of participants ≥ 75 years old in pivotal studies of NOACs.

	RE-LY[18] Dabigatran			ROCKET-AF[19] Rivaroxaban		ARISTOTLE[20] Apixaban		ENGAGE AF-TIMI 48[21] Edoxaban		
	D150 mg (*n* = 6076)	D110 mg (*n* = 6015)	W (*n* = 6022)	R (*n* = 7131)	W (*n* = 7133)	A (*n* = 9120)	W (*n* = 9081)	E60 mg (*n* = 7035)	E30 mg (*n* = 7034)	W (*n* = 7036)
Age (years)	71.5 ± 8.8	71.4 ± 8.6	71.6 ± 8.6	73 (65–78)	73 (65–78)	70 (63–76)	70 (63–76)	72 (64–68)	72 (64–78)	72 (64–78)
≥75 yrs	40%	38%	39%	43%	43%	31%	31%	41%	40%	40%

A: apixaban; D: dabigatran; E: edoxaban; NOACs: new oral anticoagulants; R: rivaroxaban; W: warfarin.

population regarding the efficacy and safety of NOACs, no randomized controlled trial that involves only elderly patients, has been conducted yet.[26] As shown in Table 1, the mean age and percentage of participants ≥ 75 years old varies in the pivotal studies of NOACs (RE-LY for dabigatran, ROCKET-AF for rivaroxaban, ARISTOTLE for apixaban and ENGAGE-AF TIMI 48 for edoxaban).[18–21,27]

Because of predisposing factors such as high frequency of renal failure, low body mass index, differed body composition of muscle and fatty issue in the elderly, there are several concerns about the use of NOACs in this subgroup of patients.[16,28,29] Comorbidities and polypharmacy, often present in the elderly, are additional factors that raise these concerns.[16,28,29] Moreover, occasional reports suggested that NOACs are related to a higher potential risk of bleeding in the elderly.[30,31]

So far, there have been 11 studies including data about the safety and efficacy of NOACs in the elderly (Tables 2 & 3).[18–25,32–42] Recent reviews and meta-analyses demonstrate at least equal efficacy compared to VKAs in reducing thromboembolic events associated with AF and VTE.[26, 27, 43]

Table 2. Major clinical trials with NOACs reporting data in patients ≥ 75 years old and atrial fibrillation.

Dabigatran	Rivaroxaban	Apixaban	Edoxaban
BIBR 1048[32]	ROCKET-AF[19]	ARISTOTLE[20]	Edox-P2[36]
PETRO[33]	J-ROCKET AF[34]	ARISTOTLE-J[35]	Edox-P2A[37]
RE-LY[18]			Edox-J[38]
			Engage-AF-TIMI 48[21]

NOACs: novel oral anticoagulants.

Table 3. Major clinical trials with NOACs reporting data in patients ≥ 75 years old and venous thromboembolism.

Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Recover I[22]	Einstein-DVT dose Study[40]	Botticelli-DVT[42]	Hokusai-VTE[25]
Recover II[39]	Einstein-DVT[23]	Amplify[24]	
	Einstein-PE[41]		

DVT: deep venous thrombosis; NOACs: novel oral anticoagulants; VTE: venous thromboembolism.

Their benefit is consistent across all the age-groups examined, including that of the elderly.[26,27,43,44] Likewise bleeding risks seem to be similar between NOACs and warfarin.[26,27,43,45] However, bleeding patterns that were noticed showed significant heterogeneity between dabigatran, rivaroxaban, apixaban and edoxaban. No head to head comparison is available so far on this issue.[26]

2.1 Dabigatran

As featured in the RE-LY and RECOVER trials, dabigatran has been at least as effective as VKAs in the prevention of stroke/SE in AF and recurrence of VTE respectively.[18,22,26,27,39,43,45] Its efficacy has been observed across all age groups.[26,27,43,45] Dabigatran in the dose of 150 mg twice daily has been related to a significant reduction in stroke or SE compared to warfarin.[18,26,45] The latter superiority was not observed in the dosage 110 mg (b.i.d.), where on the corresponding rate was similar to warfarin.[26,43,45]

Risk for major bleedings seems to be similar between dabigatran 110 mg (b.i.d.) and warfarin in the elderly, while data have shown that dabigatran 150 mg (b.i.d.) is associated with a non-significant higher risk of major bleeding in this age-group.[26,45] Dabigatran 150 mg (b.i.d.) has also been related to an increased number of gastrointestinal bleedings in comparison to VKAs.[26,27,45] On the other hand, the risk of intracranial bleeding was significantly lower when dabigatran was used regardless of dose and age.[26,27,45]

Considering renal insufficiency is common in older patients and dabigatran's almost 80% renal clearance, it is important that renal function must be monitored more frequently in these patients, when dabigatran is prescribed.[46] In any case, dabigatran is contraindicated in patients with creatinine clearance (CrCl) < 30 mL/min. The European medicines agency (EMA) suggests that 150 mg (b.i.d.) should not be administered to patients of age ≥ 80 years and should instead follow the 110 mg twice daily route. That limitation is not applicable by the US Food and drug Association (FDA).[46]

2.2 Rivaroxaban

ROCKET-AF trial has demonstrated that rivaroxaban is as effective and safe as warfarin for stroke prevention (ischemic or haemorrhagic), featuring no significant differences among the rates of ischemic strokes and major bleedings across all age groups.[19] Halperin, *et al*.,[47] in a later meta-analysis of ROCKET-AF trial, gathering data of participants ≥ 75 years old, found no significant interaction between age and the overall study outcomes. Studies including elderly patients indicate that rivaroxaban is non-inferior to warfarin in secondary prevention of VTE.[23,26,43]

Recent meta-analyses have shown that rivaroxaban is superior compared to conventional therapy in fatal and intracranial bleeding, although gastrointestinal bleedings seem to be more often with rivaroxaban in the elderly.[26,45] Rivaroxaban 20 mg is administered once daily, preferably with the evening meal. Dose adjustment is not required in older patients, but those with CrCl 15–49mL/min should receive 15 mg (o.d.).[48]

2.3 Apixaban

Data from studies with elderly participants have shown that apixaban is more effective than warfarin in reduction of stroke/SE and not-inferior in managing recurrence of VTE.[26,27,43,44] A sub-analysis of the ARISTOTLE trial has proven that the efficacy and safety of apixaban is consistent among various groups of patients, as categorized by the $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED scores.[49]

Apixaban has been related to a significant reduction in major and clinical relevant bleedings in the elderly, as well as in intracranial haemorrhages compared to VKAs.[26,43,45] The benefits of apixaban in bleedings reduction seem to apply similarly in older patients with renal impairment.[50] However, there are not sufficient data yet available concerning gastrointestinal bleedings when apixaban is used in elderly patients.[26]

Apixaban is administered 5 mg twice daily, unless two or more of the following characteristics are present: age ≥ 80 years, body weight ≤ 60 kg and serum Creatinine ≥ 1.5 mg/dL (133 μmol/L). In that case the recommended dosage according to EMA/FDA is 2.5 mg (b.i.d.).

2.4 Edoxaban

Edoxaban is the latest NOAC that has received FDA/EMA approval, thus data regarding its use in the elderly are restricted. ENGAGE AF-TIMI 48 trial has shown that edoxaban in both 60 and 30 mg (o.d.) is as effective as warfarin in prevention of stroke/SE.[21] Edoxaban 60 mg (o.d.) was superior in comparison to 30 mg (o.d.) in stroke/SE prevention.[21] On the other hand, the 30 mg edoxaban treatment was related to a reduced risk of gastrointestinal bleeding and all-cause mortality compared to warfarin.[21] Outcomes of the study were consistent among all age-groups including the elderly.[26,45] In the Hokusai-VTE trial, 1104 patients ≥ 75 years old were studied among a total of 8292 participants and edoxaban was proven to be non-inferior in the treatment of symptomatic VTE compared to warfarin.[25] The FDA does not suggest age-dose adjustment for edoxaban, though patients with impaired renal function (CrCl: 15–50 mL/min) should receive the 30 mg regimen.

3 NOACs in the elderly: challenges and practical considerations

Considering bleedings, major or minor, are common in the elderly, preventive measures must be examined.[14,45,51] Such measures should include limited use of alcohol and drugs that enhance bleeding, such as antiplatelets, steroids or NSAIDs.[45,51,52] Blood pressure control is important and renal function must be monitored more often, specifically when dabigatran is prescribed.[45,51,52] Older patients receiving antithrombotic therapy, conventional or contemporary should generally avoid surgery, unless the necessity is absolute.[45]

Quite recently, idarucizumab, an antibody fragment, was developed to reverse the anticoagulant effects of dabigatran.[53,54] Studies including patients with life-threatening bleeding or in need of invasive procedures or emergency surgery have shown that it completely and rapidly reverses the anticoagulant effects of dabigatran in most of the participants.[55–57] However, the studies that have been conducted included mainly healthy volunteers and the clinical experience in the elderly is limited.[54,56,57] Idarucizumab has been approved by the FDA/EMA and is now available in the United States and Europe. Until now, no reversal agent is available for the anticoagulant effects of Rivaroxaban, Apixaban and Edoxaban.

Considering the enhanced risk of bleeding and related comorbidities in the elderly patients, an individualized case-by-case approach should be chosen, instead of a generalized "one drug fits all" approach. Modern medicine focuses on individualized treatment, rather than disease-oriented care. Physicians should follow a more personalised strategy that matches the particular NOAC to the particular patient, taking into consideration each and specific patient/drug characteristic.

4 Conclusions

Increasing life-expectancy brings forward older patients that were mostly neglected and under treated in the past. Elderly patients with AF and VTE are at elevated risk of thromboembolic events and bleeding compared to younger patients. NOACs slowly but surely increase their popularity among all age groups due to fewer drug/food interactions, rapid onset/offset of action and ease of use, without routine monitoring necessary. Recent studies and meta-analyses have shown that their efficacy and safety are largely preserved in older patients. However, because of other comorbidities such as renal insufficiency, low body weight and polypharmacy, physicians should proceed cautiously. Individual potential risk, benefit and harness of treatment must be carefully examined before matching a NOAC to a particular patient. Further research is required, including prospective, randomized controlled trials of NOACs concentrating in older adults and head to head comparison.

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