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Non-vitamin K antagonist oral anticoagulants in older and frail patients with atrial fibrillation

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Elderly and frail patients with atrial fibrillation (AF) are at increased risk of thrombotic events, bleeding, and death compared to their counterparts, making their management challenging. With the introduction of non-vitamin K antagonist (VKA) oral anticoagulants (NOACs) in the past decade, the risk:benefit balance in such high-risk patients with AF has tipped in favor of treating these patients with anticoagulation, and in most cases with a NOAC instead of a VKA. In patients ≥75 years of age with AF, each of the 4 approved NOACs reduced stroke or systemic embolism and vs warfarin in their landmark clinical trial and lowered mortality. However, only apixaban and edoxaban significantly reduced major bleeding vs warfarin. A similar pattern was seen in even older cohorts (≥80 and ≥85 years). Among patients age ≥80 who are not candidates for oral anticoagulants at the approved dose, edoxaban 15 mg may be a reasonable alternative. In elderly or frail individuals who are on multiple comedications (particularly if ≥1 moderate or strong cytochrome P-450 inhibitor), only edoxaban consistently reduced major bleeding compared to warfarin. Regardless of the specific OAC selected, appropriate dosing in the elderly (who frequently qualify for dose reduction per the prescribing label) is critical. In elderly and frail patients with AF, factors that may modify the efficacy-safety profile of specific oral OACs should be carefully considered to permit the optimal selection and dosing in these vulnerable patients.

Introduction

In older patients, the incidence of atrial fibrillation (AF), the risk of stroke or systemic embolic events (SEE) among those with AF, and the rates of bleeding in patients treated with antithrombotic therapy to prevent stroke/SEE are each increased with advancing age. In addition to chronologic age, the presence of frailty also increases the risks of thromboembolic events and bleeding. Thus, elderly and frail patients with AF represent a particularly challenging group to manage given the simultaneous risks of increased stroke/SEE and bleeding. In this article, the data from high-quality studies with non-vitamin K antagonist oral anticoagulants (NOACs) in elderly and frail patients with AF are reviewed. The data underlying this article are available in the article, its online supplementary material, and from the referenced manuscripts.

Relationship of age and atrial fibrillation

The prevalence and incidence of AF, as well as deaths attributed to AF rise with increasing age, peaking in the 8th–9th decades of life (*Figure 1*).[1] Among patients with AF who are not anticoagulated, the frequency and severity of stroke increases strongly with age.[2] However, older age is an independent risk factor for bleeding as well as thromboembolism,[3] and advanced age are integral elements of both stroke and bleeding risk scores.

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Among patients anticoagulated with warfarin, age is closely correlated with both stroke/SEE and major bleeding (*Figure 2*).[4] Furthermore, use of VKAs in the elderly are associated with increased rate of intracranial haemorrhage (ICH), which carries a high fatality rate.[5] These concerns have led to a widespread underuse of VKAs in elderly patients with AF,[6] and in some cases, substitution of antiplatelet therapy, which is no longer supported by AF Guidelines.[7] Therefore, the mandate for a safer and effective anticoagulant to prevent stroke in elderly patients with AF is clear.

Trials with non-vitamin K oral antagonists

In the absence of head-to-head randomized controlled trials (RCTs) between NOACs, the highest quality data in elderly patient with AF are derived from four large, international, RCTs of NOACs vs. warfarin,[4,8-10] one RCT comparing NOAC vs. aspirin,[11] and one RCT comparing very low-dose NOAC vs. placebo.[12] The designs of these trials differed in several important ways, including the populations studied, enrolling countries, treatment and control arms, risk factors, and duration of follow-up (*Table 1*). A

Figure 1 Age-specific counts and rates of prevalent cases (*A*), incident cases (*B*), and deaths (*C*) of atrial fibrillation by sex, 2017. Error bars and shading represent 95% uncertainty intervals. *Source*: Dai *et al*.[1] (with permission).

trial-level meta-analysis of the four RCTs comparing NOACs with warfarin regardless of age demonstrated significant reductions favouring NOACs in the prevention of stroke/SEE [hazard ratio (HR) 0.81, 95% confidence interval (CI) 0.73-0.91], ICH (HR 0.48, 95% CI 0.39-0.59), and all-cause mortality (HR 0.90, 95% 0.85-0.95), with no significant between trial heterogeneity.[13]

Outcomes in the elderly with non-vitamin K oral antagonist vs. warfarin

Trial-level meta-analyses of the same four trials have also compared treatments outcomes in patients of differing age groups.[14] Most relevant to the elderly, an analysis in patients age $\geq$75 showed similar efficacy of the four NOACs in preventing stroke/SEE as compared to warfarin, with an overall highly significant reduction in relative risk (RR) of 0.70 (95% CI 0.61-0.80) favouring NOACs, and risk with no significant heterogeneity between trials (*P*-heterogeneity = 0.83) (*Figure 3A*). There was a more modest risk reduction in stroke/SEE with NOACs vs. warfarin in patients <75 years of age (RR 0.87, 95% CI 0.77-0.99), with statistical evidence of an increased efficacy in elderly compared to younger patients (*P* = 0.02 for age subgroup differences).[15]

In a similar analysis of major bleeding (*Figure 3B*) in the elderly, the pooled results of the four trials showed no reduction in major bleeding.[14] However, due to high degree of heterogeneity between trials (I^2 = 86%, *P* < 0.0001), the results should be analysed by individual trial rather than combined. In the ARISTOTLE and ENGAGE AF-TIMI 48 trials, elderly patients experienced significantly fewer major bleeding events with apixaban 5/2.5 mg twice daily (RR 0.67, 95% CI 0.55-0.82) and edoxaban 60/30 mg once daily (RR 0.82, 95% CI 0.69-0.97), respectively, compared to warfarin. In contrast, neither dabigatran (RR 1.10, 95% CI 0.94-1.29) nor rivaroxaban (RR 1.14, 95% 0.97-1.37) reduced bleeding in the elderly compared to warfarin. Although ICH is one of the most feared complications of anticoagulant therapy, data from each of the four trials showed lower ICH rates with NOACs vs. warfarin in patients age $\geq$75 years (by $\geq$50% with dabigatran,[10] apixaban,[9] edoxaban,[4] and by 20% with rivaroxban[8]).

Although <20% of patients were age $\geq$80 and <5% were age $\geq$85 years in these four trials comparing NOAC vs. warfarin, the results in these very elderly patients are consistent with those age $\geq$75 years (*Table 3*).

A more recent patient-level meta-analysis of the four RCTs comparing NOACs with warfarin explored the relationship between age as a continuous variable and outcomes of stroke/SEE, major bleeding, and death.[16] Patients randomized to dabigatran 110 mg or to the lower-dose edoxaban regimen (30/15 mg) were excluded. Across the age range of 50-100 years, there was no significant treatment interaction for the outcomes of stroke/SEE or death; however, the HRs for NOACs vs. warfarin were close to 1.0 in the youngest patients and tended to favour NOACs (lower HRs) as age increased. In contrast, for the endpoint of major bleeding, the HR of NOAC vs. warfarin increased by 10.2% (95% CI 1.3-19.9%) per 10-year increase in age, with a reduction in bleeding with the NOACs vs. warfarin present
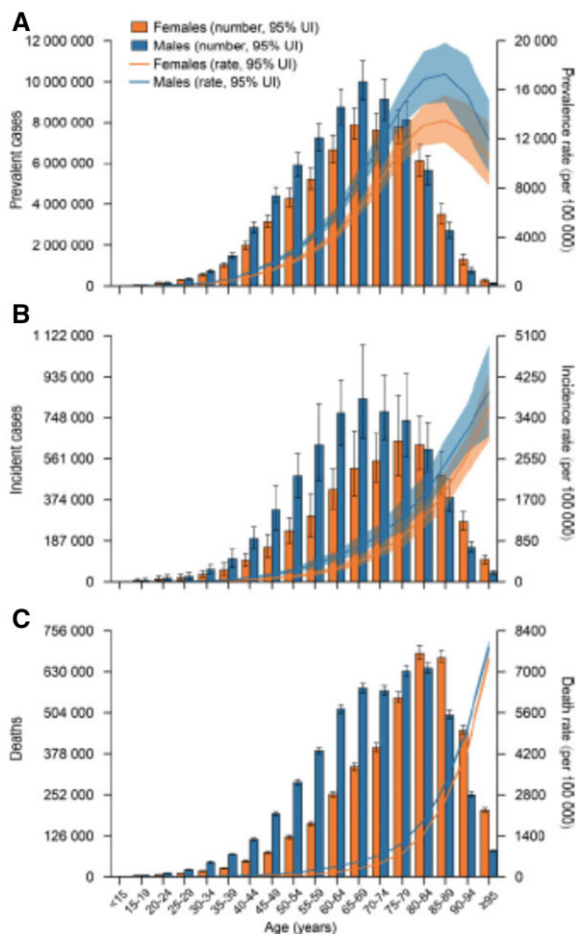
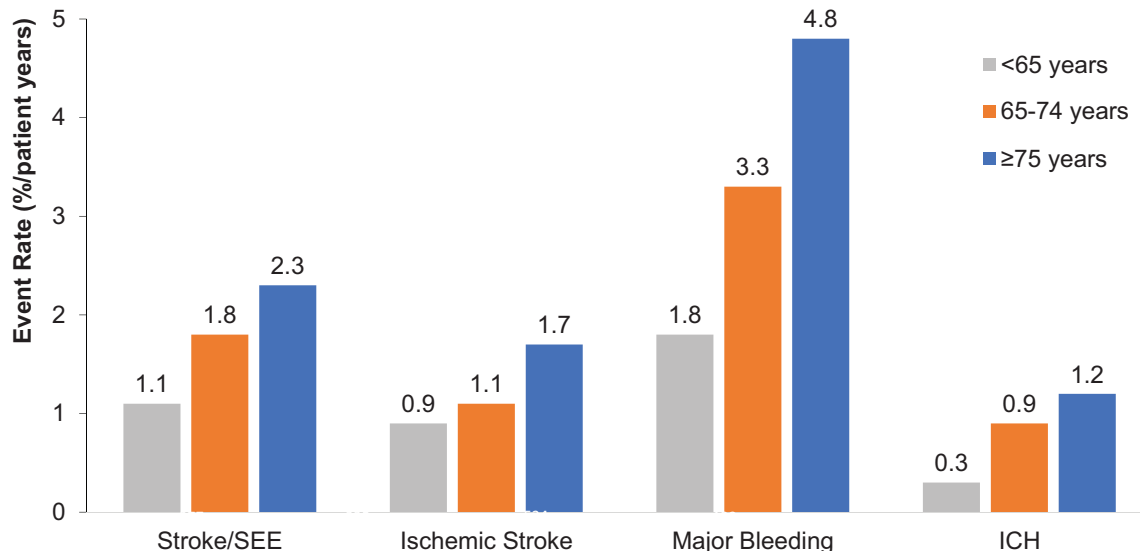| Adjusted HR (95% CI)				
65-74 vs <65 years	1.45 (1.04-2.00)	1.13 (0.77-1.67)	1.83 (1.40-2.39)	3.30 (1.72-6.31)
≥75 vs <65 years	1.83 (1.32-2.54)	1.81 (1.24-2.63)	2.68 (2.04-3.52)	3.77 (1.94-7.30)

Figure 2 Influence of age on outcomes (warfarin group only) from the ENGAGE AF-TIMI 48 trial. Multivariable model included all baseline characteristics with univariate $P < 0.05$ (body mass index, sex, creatinine, hypertension, dyslipidaemia, diabetes, smoking, prior stroke or transient ischaemic attack, heart failure, type of atrial fibrillation, race, region, increased risk of falling, risk of neuropsychiatric disease, coronary artery disease, history of hepatic disease, history of non-intracranial haemorrhage, alcohol intake, and medication predisposing to bleeding). CI, confidence interval; HR, hazard ratio. *Source*: Kato *et al*.[4] (with permission).

only in younger patients (*P*-interaction 0.02). However, since the relationship between age and major bleeding varies significantly between trials comparing the different NOACs to warfarin (*Figure 3B*), pooling results across trials may obscure the actual true relationships between age, bleeding, and specific NOACs.

Non-vitamin K oral antagonists in elderly patients not candidates for standard anticoagulants

Two large, double-blind, RCTs compared NOACs vs. non-anticoagulant therapy in patients who were not considered candidates for the standard anticoagulants at the time. In the AVERROES trial, apixaban 5/2.5 mg twice daily was compared to aspirin in patients with AF and one additional stroke risk factor.[17] Of the 5599 patients enrolled, 1898 (34%) were age ≥75 years and 366 (6.5%) were age ≥85 years. Compared to aspirin, in patients age ≥75, apixaban reduced stroke/SEE by 67% (HR 0.33, 95% CI 0.19-0.54) with no significant increase in major bleeding (HR 1.21, 95% CI 0.69-2.12).[11] Similarly, in patients age ≥85 years, apixaban reduced stroke/SEE by 86% (HR 0.14, 95% CI 0.02-0.48) with similar annualized rates of major bleeding (4.7% vs. 4.9%).

In the ELDERCARE AF trial, edoxaban 15 mg once daily (1/4th of the standard dose) was compared with placebo in 984 Japanese patients age ≥80 years with AF who were not considered appropriate candidates for oral anticoagulation.[12] Edoxaban 15 mg daily significantly reduced the risk of stroke/SEE by 66% (HR 0.34, 95% CI 0.19-0.61), which is very similar to the 64% reduction in stroke

reported in a meta-analysis of six trials comparing warfarin with placebo/control performed three decades ago.[18] The rates of major bleeding with edoxaban 15 mg daily compared to placebo were 3.3% vs. 1.8% (HR 1.87, 95% CI 0.89-3.89). In the prespecified subgroup of 537 patients (55%) who were age ≥86 years, edoxaban 15 mg daily reduced stroke/SEE by 64% (HR 0.36, 95% CI 0.17-0.73) compared to placebo without increasing the risk of major bleeding (HR 1.49, 95% CI 0.67-3.29).

Frail patients with atrial fibrillation

While older age is arguably the most important single factor in the assessment of thromboembolic and bleeding risks in patients with AF, patients who are considered 'frail' are also at increased risk. Of the aforementioned six RCTs, only the ELDERCARE trial in elderly Japanese patients prespecified an analysis of frail patients. All patients in ELDERCARE were categorized at randomization as robust, prefrail, or frail using a standardized frailty assessment tool[19,20] that included recent weight loss, self-reported exhaustion, activity level, grip strength, and comfortable walking speed in a weighted score. In the 402 patients (41%) who were considered frail, edoxaban 15 mg daily reduced stroke/SEE by 65% (HR 0.35, 95% CI 0.14-0.87), without increasing major bleeding (HR 1.67, 95% CI 0.58-4.75).

In lieu of a formal prespecified standard assessment of frailty, the four RCTs of NOAC vs. warfarin explored other subgroups of patients who may be considered 'frail'. These approaches included identifying patients who were at increased risk of falling, had multiple comorbidities,

Table 1 Randomized trial data in the elderly (Age ≥ 75 years) with atrial fibrillation

	RE-LY[10]	ROCKET-AF[8]	ARISTOTLE[9]	ENGAGE AF-TIMI 48[4]	AVERROES[11]	ELDERCARE[12]
NOAC Dose(s)	Dabigatran 150 mg, 110 mg	Rivaroxaban 20/15 mg	Apixaban 5/2.5 mg	Edoxaban 60/30 mg, 30/15 mg	5/2.5 mg	15 mg
≥75 years, N (%)	7258 (40)	6229 (44)	5678 (31)	8474 (40)	1898 (34)	984 (100[a])
NOAC dose reduced	NA	~40%[b]	14%	41%	18%	NA
Comparator	Warfarin	Warfarin	Warfarin	Warfarin	Aspirin	Placebo
Median TTR	—	57%	67%	70%	NA	NA
Design	PROBE	Double-blind	Double-blind	Double-blind	Double-blind	Double-blind
Median follow-up, years	2.0	1.9	1.8	2.8	1.1	1.3
Age (mean), years	79.4	79 (median)	79.6	79 (median)	80.4	86.6
Weight (mean), kg	77	BMI 27 (median)	77	76 (median)	73	50.6
Female	42%	46%	42%	45%	48%	57%
CHA_2DS_2-VASc (mean)	4.3	—	4.4	5.0	—	4.9
$CHADS_2$ (mean)	2.6	3.7	2.7	3.2	2.7	3.1
Heart failure	25%	59%	24%	45%	37%	54%
Hypertension	75% (on Rx)	92%	83%	93%	80% (on Rx)	82%
Diabetes	20%	34%	21%	28%	19%	23%
Prior stroke or TIA	19%	42%	22%	25%	17%	24%
Paroxysmal AF	32%	17%	13%	26%	24%	47%
Renal function	eGFR 58 (mean)	CrCl 55 (median)	CrCl 58 (mean)	CrCl 56 (median)	eGFR 60 (mean)	CrCl 36 (mean)
HAS-BLED, mean	—	—	2.2	2.8	—	2.3
Prior VKA experienced	61% (OAC at randomization)	66%	60%	61%	43%	43%
Antiplatelet	39% (aspirin)	35% (aspirin)	30% (aspirin)	29% (aspirin) 2% (thienopyridine)	—	30% (aspirin) 24% (other)
Prior MI	17%	18%	15%	12%	12%	—

AF, atrial fibrillation; BMI, body mass index in kg/m^2; $CHADS_2$, 1 point each for Congestive heart failure, Hypertension, Age >65 years, Diabetes mellitus, and 2 points for prior Stroke or TIA; CHA_2DS_2-VASc, 1 point for Congestive heart failure, 1 point for Hypertension, 2 points for Age ≥75 years, 1 point for Diabetes mellitus, 2 points for prior Stroke or TIA, and 1 point each for prior Vascular disease, Age >65 years, or female Sex; CrCl, creatinine clearance estimated using the Cockgroft-Gault equation in mL/min; eGFR, estimated glomerular filtration rate in mL/min/1.73 m^2; HAS-BLED, Score 0-9 based on 1 point each for Hypertension, Abnormal renal and liver function (1 point each), Stroke, Bleeding tendency or predisposition, Labile INRs, Elderly (age ≥ 65 years) Drugs (concomitant aspirin or NSAIDs) or excess alcohol use (1 point each); MI, myocardial infarction; NA, not applicable; NOAC, non-vitamin K antagonist anticoagulant; OAC, oral anticoagulant; PROBE, prospective, randomized, open-label, blinded endpoint assessment; Rx, treatment; TIA, transient ischaemic attack.
— indicated data were not available.
[a]All patients enrolled in ELDERCARE AF were age ≥80 years by design.
[b]Estimated from the median and interquartile range of the reported creatinine clearance.

or were treated with multiple comedications (i.e. 'poly-pharmacy'). While an increased risk of falls is a well-known and frequently inappropriate reason to withhold oral anti-coagulation in patients with AF,[21] recent registry data demonstrated that multimorbidity and polypharmacy are also common reasons cited for the non-use of oral anti-coagulants (OACs).[22]

In ENGAGE AF-TIMI 48, 900 patients (4.3%) were considered at increased risk of falling based on the presence of at least one of eight criteria from the literature (prior history of falls, lower extremity weakness, poor balance cognitive impairment, orthostatic hypotension, use of psychotropic drugs, severe arthritis, or dizziness).[23] No treatment interactions were present in the analyses of the relative efficacy and safety of edoxaban vs. warfarin. However, because patients who were at an increased risk of falling had higher rates of severe bleeding and death, the absolute reductions in these events with edoxaban were greater. In the ARISTOTLE trial, 753 patients (4.1%) had a fall within 1 year prior to randomization.[24] No differential effects of apixaban compared with warfarin were observed for any of the efficacy or safety outcomes, regardless of history of falling. Importantly, in patients with a recent fall, subdural bleeding occurred in 0% vs. 1.3% of patients treated with apixaban vs. warfarin.
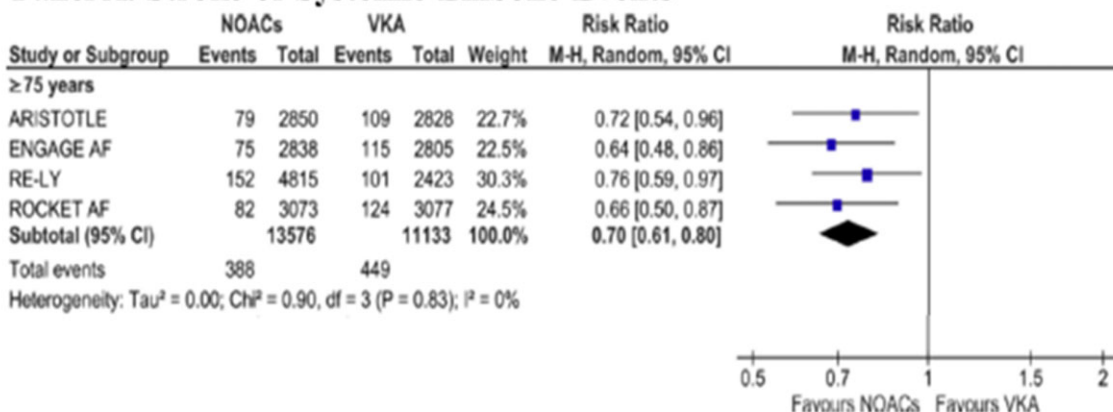
Both the ARISTOTLE and ENGAGE AF-TIMI 48 trials analysed the subgroup of patients with multimorbidity. In ARISTOTLE, 10 713 (64%) had three or more comorbid conditions (from a list 17 that were collected at baseline). Compared to patients with 0-2 comorbidities, patients with multi-morbidity had higher rates of stroke/SEE, death, and major bleeding; however, the efficacy and safety profile of apixaban vs. warfarin was similar regardless of the presence or absence of multi-morbidity. In

Table 2 Outcomes in the very elderly

Trial	RE-LY[10]		ARISTOTLE[9]	ENGAGE AF-TIMI 48[4]	
NOAC	Dabigatran 150 mg	Dabigatran 110 mg	Apixaban 5/2.5[a] mg	Edoxaban 60/30[a] mg	Edoxaban 30/15[a] mg
Patients age 80–84 years (RE-LY), age >80 (ARISTOTLE, ENGAGE AF-TIMI 48)					
Patients, N (%)	2305 (12.7%)		2436 (13.4%)	3591 (17.0%)	
Stroke/SEE	0.67 (0.41–1.10)	0.75 (0.46–1.23)	0.81 (0.51–1.29)	0.88 (0.64–1.20)	1.01 (0.75–1.36)
Major bleeding	1.41 (1.02–1.94)	1.18 (0.84–1.65)	0.66 (0.48–0.90)	0.75 (0.58–0.98)	0.42 (0.31–0.56)
ICH	0.55 (0.25–1.21)	0.30 (0.11–0.82)	0.36 (0.17–0.77)	0.41 (0.22–0.77)	0.29 (0.15–1.57)
Patients age ≥ 85 years (data only available for RE-LY and ENGAGE AF-TIMI 48)					
Patients, N (%)	722 (4.0%)		—	899 (4.3%)	
Stroke/SEE	0.70 (0.31–1.57)	0.52 (0.21–1.29)	—	0.73 (0.40–1.33)	1.01 (0.58–1.76)
Major bleeding	1.22 (0.74–2.02)	1.01 (0.59–1.73)	—	0.58 (0.35–0.94)	0.36 (0.20–0.64)
ICH	0.61 (0.20–1.87)	0.13 (0.02–1.04)	—	0.61 (0.20–1.88)	0.51 (0.15–1.70)

Data are not available from ROCKET-AF in patients ≥age 80 years and from ARISTOTLE in patients age ≥85 years.
Results shown are hazard ratios with 95% confidence intervals for non-vitamin K antagonist oral anticoagulant (NOAC) vs. warfarin.
ICH, intracranial haemorrhage; N, number of patients in the specified age group; SEE, systemic embolic event.
[a]Reduced dose administered in selected patient per protocol criteria.
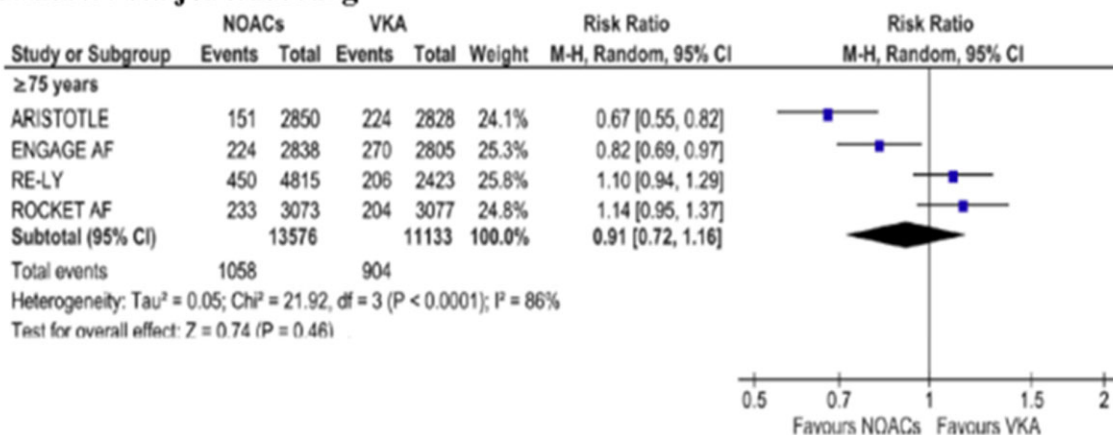

Figure 3 Forest plot of a trial-level meta-analysis of NOACs vs. warfarin in patients age ≥75 years from the RE-LY, ROCKET-AF, ARISTOTLE, and ENGAGE AF-TIMI 48 trials. Panel *A* shows results for stroke or systemic embolic events and panel *B* for major bleeding. *Source*: Caldeira *et al.*[14,15] (with permission).
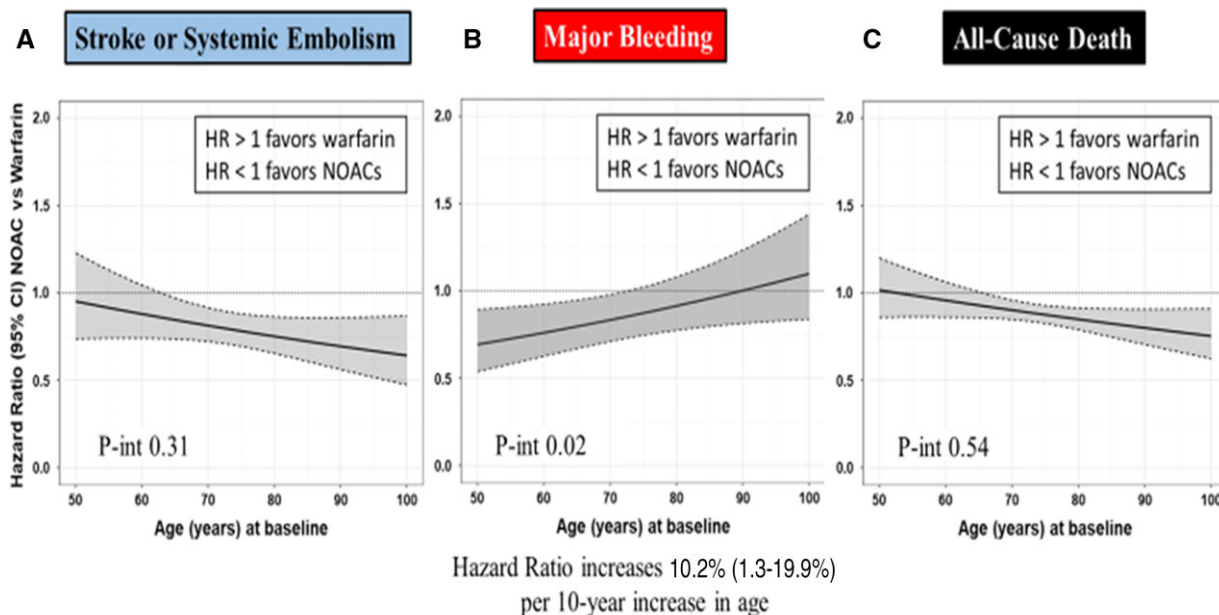
Figure 4 Patient-level meta-analysis of standard-dose NOAC regimens vs. warfarin from the RE-LY, ROCKET-AF, ARISTOTLE, and ENGAGE AF-TIMI 48 trials across the age range 50-100 years for the outcomes of stroke or systemic embolism (*A*), major bleeding (*B*), and death (*C*). Data exclude results with dabigatran 110 mg and edoxaban 30/15 mg. *Source*: Carnicelli *et al*.[16] (with permission).

Table 3 NOAC vs. warfarin stratified by degree of polypharmacy

Trial	# Comedications (% patients)	Stroke/SEE NOAC vs. warfarin	Death NOAC vs. warfarin	Major bleeding with NOAC vs. warfarin	Ref #
ROCKET-AF	0-4 (36%)	0.87 (0.66-1.16)	0.93 (0.74-1.17)	0.71 (0.52-0.95)	[27]
	5-9 (51%)	0.88 (0.70-1.10)	0.92 (0.79-1.08)	1.23 (1.01-1.49)	
	>10 (13%)	0.88 (0.54-1.42)	0.86 (0.65-1.13)	1.17 (0.87-1.56)	
		P_{int} 0.99	P_{int} 0.94	**P_{int} 0.0074**	
ARISTOTLE	0-5 (38%)	0.86 (0.83-1.17)	0.86 (0.70-1.05)	0.50 (0.38-0.66)	[28]
	6-8 (36%)	0.76 (0.57-1.03)	0.89 (0.74-1.06)	0.72 (0.56-0.91)	
	>9 (26%)	0.76 (0.45-1.07)	0.94 (0.77-1.14)	0.84 (0.67-1.06)	
		P_{int} 0.82	P_{int} 0.81	**P_{int} 0.017**	
ENGAGE AF-TIMI 48	0-3[a] (37%)	0.91 (0.70-1.18)	0.82 (0.69-0.98)	0.83 (0.66-0.98)	[29]
	4[a] (25%)	1.03 (0.75-1.41)	1.10 (0.91-1.34)	0.85 (0.65-1.34)	
	5[a] (38%)	0.74 (0.58-0.96)	0.91 (0.778-1.06)	0.77 (0.64-1.06)	
		P_{int} 0.27	P_{int} 0.09	P_{int} 0.83	

ARISTOTLE: adjusted hazard ratios are shown.
ENGAGE AF-TIMI 48: unadjusted hazard ratios are shown.
ROCKET-AF: unadjusted odds ratios are shown for stroke or systemic embolic events (SEE), and for death; unadjusted hazard ratios for major bleeding.
[a]In ENGAGE AF-TIMI 48, instead of number of individual comedication, the number of classes of medications (e.g. antiarrhythmics, diuretics, neuro-psychiatric, hormone) were analysed, and patients could have been on more than 1 medication within the 17 prespecified classes.

ENGAGE AF-TIMI 48, the updated Charlson Comorbidity Index (CCI)[25] was used to assess comorbidity. The annualized rate of the primary net outcome of stroke/SEE, major bleeding, or death ranged from 5.9% (CCI = 0) to 13.6% (CCI ≥ 4), *P*-trend <0.001. The relative efficacy and safety profile of edoxaban vs. warfarin was preserved regardless of the number of comorbidities.

The influence of polypharmacy on the relative efficacy and safety outcomes were assessed in three of the four NOAC vs. warfarin RCTs (*Table 3*), albeit using different criteria given the lack of consensus on how polypharmacy should be defined.[26] In the ROCKET-AF trial, 64% of patients were on ≥5 concomitant medications at baseline, which was associated with a higher risk of bleeding, but not stroke.[27] The number of comedications did not modify the relative efficacy of rivaroxaban vs. warfarin. In contrast, there was effect modification for major bleeding, such that in patients on 0-4 comedications, rivaroxaban

significantly reduced major bleeding relative to warfarin, while in patients taking more comedications, the risk of major bleeding with rivaroxaban was greater than with warfarin (P-interaction 0.0074).

In ARISTOTLE, polypharmacy (≥6 comedications) was present in 77% of patients and was associated with significant increased risks of stroke/SEE, major bleeding, and mortality.[28] While the reduction in stroke/SEE and mortality with apixaban vs. warfarin were consistent across groups stratified by the number of comedications at baseline, there was significant treatment effect modification by the number of comedications on major bleeding. The reduction in major bleeding with apixaban was significantly attenuated as the number of comedications increased and was no longer significant in the group on ≥9 comedications (P-interaction 0.017).

In ENGAGE AF-TIMI 48, 63% of patients were taking ≥4 medication classes, and polypharmacy was associated with increased rates of bleeding and death, but not stroke/SEE.[29] No significant treatment interactions were seen between edoxaban and warfarin for efficacy and safety outcomes when stratified by the number of comedication classes. Potential explanations for the consistent reduction in bleeding with edoxaban compared to warfarin regardless of the number of comedication classes (which was not seen with rivaroxaban and apixaban) include: (i) lack of significant metabolism of edoxaban by the cytochrome P-450 system (unlike apixaban and rivaroxaban), (ii) protocol mandated 50% reduction in edoxaban dose in patients who were taking strong P-glycoprotein inhibiting cardiac medications that was unique to ENGAGE AF-TIMI 48, and (iii) dynamic dose adjustment of edoxaban post-randomization in patients whose criteria for dose adjustment changed, which was not performed in the other trials.

A retrospective cohort study from the Taiwan National Health Insurance database in 91 330 patients with AF who received either dabigatran, rivaroxaban, or apixaban showed that concurrent use of amiodarone, fluconazole, rifampin, and phenytoin were associated with increased risk of major bleeding.[30] These findings may be mediated via the known drug-drug interactions with P-glycoprotein inhibitors (affecting all NOACs) and/or cytochrome P-450 inhibitors (relevant for rivaroxaban and apixaban). A detailed description of drug-drug interactions of NOACs including recommendations on when to administer, dose-reduce, or avoid specific NOACs is provided in the 2021 European Heart Rhythm Association (EHRA) Practical Guide on the Use of NOACs in Patients with AF.[31]

Guideline recommendations in elderly and frail patients

In elderly patients, NOACs provide large reductions in stroke/SEE without increasing bleeding when compared with aspirin or no therapy. Furthermore, NOACs reduce stroke/SEE, death, and intracranial bleeding in elderly patients compared with warfarin. Thus, NOACs are the preferred antithrombotic therapy in elderly patients.[7,32]

Use of off-label reduced doses of NOACs in patients who are eligible for the standard dose anticoagulants is discouraged, since this increased the risk of ischaemic stroke in a randomized trial[31,33] and propensity-matched analyses of observational data.[34,35] However, in elderly patients in whom standard dose anticoagulation is considered contraindicated, edoxaban 15 mg daily may have a role.[32] Elderly patients are at increased risk of cerebral amyloid angiopathy, and in these patients, a patient-centred decision is recommended to determine whether a NOAC, left-atrial appendage exclusion, or neither is preferred.[32] However, cerebral microbleeds seen on brain magnetic resonance imaging, when present in isolation of other pathology, are not considered a contraindication to NOAC therapy, despite an increase risk of symptomatic ICH.[32]

Most frail patients, either formally assessed or based on an increased risk of falling, multimorbidity, or polypharmacy, should receive OAC since the benefits outweigh the absolute risk of bleeding.[7] However, patients who are severely frail (completely dependent for personal care) or approaching end of life may have limited benefit from OAC, thus an individualized patient-centred approach is recommended.[32]

General approach to selection of oral anticoagulant in the elderly and frail patients

Patients who are eligible for standard dose OAC should be considered for a NOAC instead of VKA, unless there is an absolute contraindication to a NOAC (e.g. mechanical heart valve) (*Graphical Abstract*). Among the NOACs, apixaban 5/2.5 mg twice daily or edoxaban 60/30 mg once daily is preferred since these two NOACs significantly reduced major bleeding in elderly patients in ARISTOTLE and ENGAGE AF-TIMI 48, respectively. However, in elderly patients at low risk of bleeding, dabigatran 110 mg twice daily or rivaroxaban 20/15 mg once daily may be reasonable alternatives. In elderly patients who are ineligible for standard dose OAC, edoxaban 15 mg once daily is promising regimen based on the ELDERCARE trial—this regimen was approved in Japan in August 2021 and is currently undergoing regulatory review in other countries.

The above recommendations generally also apply to frail patients, although the data are less robust. In patients treated with multiple comedications, attention to drug-drug interactions, in particular coadministration of strong P-glycoprotein interfering drugs (which interact with all NOACs) and strong cytochrome P-450 inhibitors (which affect the metabolism of rivaroxaban and apixaban) is mandatory since such interactions can increase the risk of bleeding. Edoxaban may be the preferred NOAC in patients on strong P-glycoprotein inhibiting cardiac medications or strong cytochrome P-450 inhibitors, given the data with 30 mg daily edoxaban with the former and lack of significant interaction with the latter.
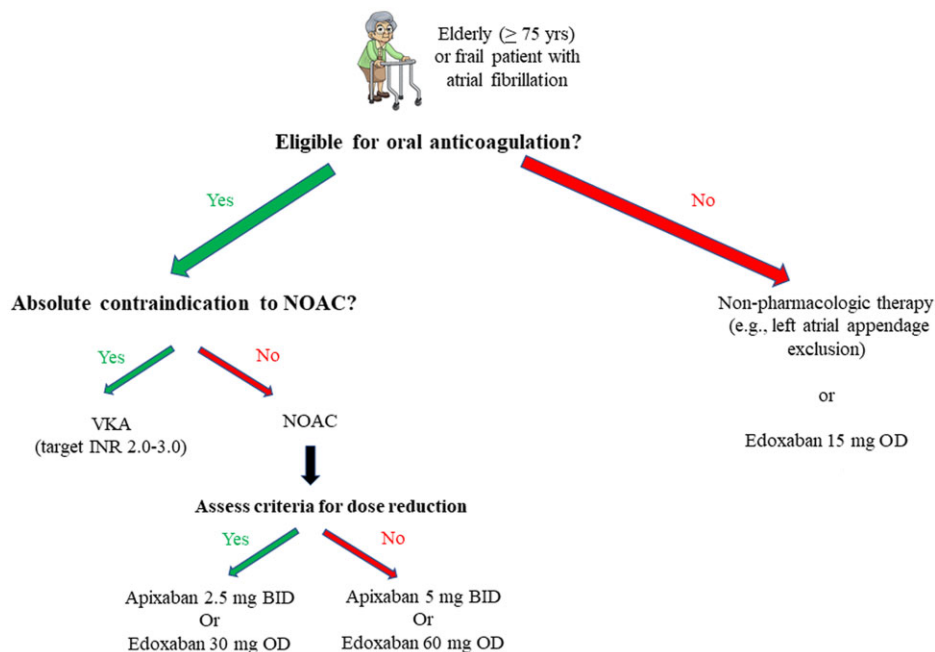
Graphical Abstract   In patients with atrial fibrillation who are elderly (age ≥ 75 years) and/or frail, first assess whether the patient is eligible for oral anticoagulation. If the patient is eligible for anticoagulation, non-vitamin K oral antagonists (NOACs) are preferred, unless there are absolute contraindications (e.g. mechanical heart valve), in which case a vitamin K antagonist should be used targeted an international normalized ratio of 2.0-3.0. In patients eligible for NOACs, apixaban or edoxaban are recommended given their consistent reduction in stroke or systemic embolism events, major bleeding, and mortality, regardless of age. In patients at low risk of bleeding, dabigatran 110 mg twice daily or rivaroxaban may be considered as alternatives to apixaban and edoxaban. When using a factor Xa inhibitors, it is critical to assess the criteria for dose reduction that are specific to each agent, and select the appropriate dose. In patients who are ineligible for standard oral anticoagulant regimens, either a non-pharmacologic therapy (e.g. left atrial appendage exclusion) or edoxaban 15 mg once daily may considered. *Alternatives if low bleeding risk*: Dabigatran 110 mg b.i.d. or rivaroxaban 20/15[a] mg o.d. [a]Reduced dose of factor Xa based on dose reduction criteria as described in the prescribing label. BID, twice daily; OD, once daily

Knowledge gaps

A major gap in the data with NOACs in patients with AF is the lack of a large RCT comparing NOACs head-to-head. While numerous registry and observational studies have been published, the lack of randomization and blinding to anticoagulant renders treatment comparisons unreliable despite advanced statistical techniques to adjust for measured confounders. In addition, observational studies are not conducted with the same rigour regarding data collection and endpoint assessment; hence they are more prone to bias. Thus, the best available data are from subgroup analyses of the large NOAC RCTs (which enrolled a limited number of elderly or frail patients) and the considerably smaller ELDERCARE trial in 984 elderly Japanese patients.

Additional studies (preferably randomized) in patients who were under-represented or excluded from the large RCTs (e.g. age ≥ 90 years, severe renal dysfunction, high bleeding risk, residence in an assisted living facility), larger prospective trials using established frailty criteria (such as the ongoing FRAIL-AF trial[36]) and evaluation of key outcomes that are particularly important in older patients (quality of life, physical function, and maintenance of independence) are needed.[37] In very high-risk patients, comparisons of standard vs. lower-dose NOAC regimens, as well as trials that include non-anticoagulant therapies (e.g. left atrial appendage exclusion, AF ablation with intensive rhythm control) would be of interest.

Conclusions

Elderly and frail patients with AF are at increased risk of stroke, bleeding, and death. In the absence of an absolute contraindication, an OAC should be administered to elderly and frail patients to reduce the risk of stroke/SEE and death rather than an antiplatelet agent. Among the anticoagulant options: (i) NOACs should be the first-line therapy as they are more effective than warfarin to reduce stroke/SEE and death, and (ii) data from large RCTs comparing NOACs individually to warfarin support the preferential use of apixaban or edoxaban since they reduce the risk of major bleeding (although head-to-head randomized trials between NOACs are lacking). Since elderly patients frequently are treated with multiple comedications, careful attention to potential drug-drug interactions is advised. In patients who are not eligible for standard dose OAC, a very low-dose NOAC (e.g. edoxaban 15 mg once daily) appears promising.

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