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REVIEW

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Managing older people with atrial fibrillation and preventing stroke: a review of anticoagulation approaches

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ABSTRACT

Introduction: Oral anticoagulants (OACs) are the cornerstone of stroke prevention in atrial fibrillation (AF), but prescribing decisions in older people are complicated. Clinicians must assess the net clinical benefit of OAC in the context of multiple chronic conditions, polypharmacy, frailty and life expectancy. The under-representation of high-risk, older adult sub-populations in clinical trials presents the challenge of choosing the right OAC, where a 'one-size-fits-all' approach cannot be taken.

Areas covered: This review discusses OAC approaches for stroke prevention in older people with AF and presents a prescribing aid to support clinicians' decision-making. High-risk older adults with multiple chronic conditions, specifically chronic kidney disease, dementia/cognitive impairment, previous stroke/transient ischemic attack or intracranial hemorrhage, polypharmacy, frailty, low body weight, high falls risk, and those aged ≥75 years are considered.

Expert opinion: Non-vitamin K antagonist OACs are the preferred first-line OAC in older adults with AF, including high-risk subpopulations, after individual assessment of stroke and bleeding risk, except those with mechanical heart valves and moderate-to-severe mitral stenosis. Head-to-head comparisons of NOACs are not available, therefore the choice of drug (and dose) should be based on an individual's risk (stroke and bleeding) and incorporate their treatment preferences. Treatment decisions must be person-centered and principles of shared decision-making applied.

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1. Introduction

Atrial fibrillation (AF) is the most common abnormal heart rhythm that increases the risk of stroke five-fold [1]. By 2060, it is estimated there will be 14.3 million people with AF in the European Union [2]. Advancing age is an independent risk factor for both AF and stroke [3–6], highlighting older people as a high-risk group. Multiple chronic conditions are another determinant of AF development [7], reported to affect between 55 to 98% of older people [7–9]. The number of chronic conditions a person has is dynamic and changes with age and incident health events, with implications for AF and stroke risk [10,11]. This reiterates the criticality of AF diagnosis and optimized management in older people, with appropriate expedition of strategies for stroke prevention in the context of multiple chronic conditions.

The cornerstone stroke prevention strategy is prescription of oral anticoagulants (OAC) such as vitamin K antagonists (VKAs; e.g. warfarin, acenocoumarol), or non-VKA oral anticoagulants (NOACs; e.g. apixaban, edoxaban, rivaroxaban, dabigatran). However, a 'one size fits all' approach cannot be taken. Older people are a heterogenous group and treatment decisions must be person-centered, apply principles of shared-decision making and be individualized to take account of emotional and functional status, chronic condition burden and predicted life expectancy rather than focussed solely on chronological age [12]. Currently, European and United Kingdom (UK) guidelines advocate stroke risk assessment in people with AF using the CHA_2DS_2-VASc score, recommending OAC consideration in males with a score of 1 and OAC initiation in men and women with a score of ≥ 2 [13,14]. Assessment of bleeding risk with stratification tools such as ORBIT [14] and HAS-BLED [13] is also recommended to inform decision making and help identify modifiable risk factors. Despite age being a key component of the CHA_2DS_2-VASc, HAS-BLED and ORBIT scores, their usefulness in supporting therapeutic decision making in older adults is limited because they fail to differentiate between sub-populations of older adults. Age is a continuous variable, and the link between frailty, cognitive status, falls risk and AF-related stroke or bleeding associated with OAC therapy is not well established, making it difficult to define arbitrary cutoffs for inclusion in risk stratification models.

Characteristics of an older (≥75 years) UK adult population ($n = 165,596$) identified as barriers to OAC prescription were age ≥90 years vs. 75–84 years (risk difference [RD] −0.40, 95% confidence interval [CI] −0.41 to − 0.39), dementia (RD − 0.34,

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Article highlights

- Non-vitamin K antagonist oral anticoagulants (NOACs) are first line for stroke prevention in eligible older people with atrial fibrillation (AF)
- Older people with chronic kidney disease, dementia/cognitive impairment, prior history of stroke/transient ischemic attack or intracranial hemorrhage, polypharmacy, frailty, low body weight and high falls risk should also be considered for NOAC therapy
- The choice of NOAC should be guided by the individual risk assessment, incorporating personal preference and the process of shared decision making should be followed
- In people without capacity, discussions regarding OAC for stroke prevention should be held with a person's next of kin or Power of Attorney for Health

95% CI – 0.35 to – 0.33) and history of falls and major bleeding (RD – 0.17, 95% CI – 0.18 to – 0.16 and RD – 0.17, 95% CI – 0.19 to – 0.15, respectively) [15]. In another study of 14,493 older care home residents in Wales (median age 87.0, interquartile range [IQR 82.6–91.2] years), increasing age was associated with a reduced odds of OAC prescription (adjusted odds ratio [aOR] 0.96 per 1-year age increase, 95% CI 0.95 to 0.96), as well as prescription of antiplatelet therapy (aOR 0.91, 95% CI 0.84 to 0.98) [16]. These findings also parallel a systematic narrative review of 34 studies ($n = 16$ pre-NOAC era) exploring physician perceptions and attitudes toward OAC prescription for AF. Thematic analysis revealed that physicians considered older age, complex multiple chronic conditions, and uncertainty and anxiety about causing bleeding, particularly in people with a tendency for falls, as potential barriers to OAC optimization [17]. Inappropriate prescription or non-prescription of OAC for stroke prevention in AF can have catastrophic consequences. In older people, a multifactorial management approach is required that advances beyond use of stroke and bleeding risk stratification tools that account for chronological age alone.

The measure of number needed to treat for net effect (NNT_{net}) (combined benefit and harm) and net clinical benefit (NCB) of OAC is prudent to inform decision-making. From 3,511 people included in real-word ($n = 1,306$, median age 76 [IQR 70–81] years, median CHA_2DS_2-VASc score 4 [IQR 3–5], median HAS-BLED score 2 [IQR 2–3]) and clinical trial ($n = 2,205$, median age 71 [IQR 65–77] years, median CHA_2DS_2-VASc score 3 [IQR 2–4], median HAS-BLED score 2 [IQR 1–2]) cohorts, the NNT_{net} at one year was 33 and 46, respectively [18]. The NNT_{net} was highest for people with a greater baseline risk of stroke [18]. The NCB of OAC therapy was investigated using prospective, real-world registry data on 6,412 people ($n = 5,907$ aged <85 years and $n = 505$ aged ≥85 years) with AF [19]. The incidence of thromboembolic events was lower in people aged ≥85 years treated with OAC (OAC 4.3% per year vs. no OAC 6.3% per year, 2% absolute reduction), and the risk of major bleeding was similar in people aged ≥85 years on OAC compared to antiplatelet therapy or no antithrombotic treatment (OAC 4.0% per year vs. antiplatelet or no antithrombotic 4.2% per year, $p = 0.77$) [19]. The NCB of OAC therapy was highest for people aged ≥ 85 (−2.78%, 95% CI – 9.13–3.58) compared to people <85 years (−1.92%, 95% CI – 4.09–0.24) [19]. This was attributed to the increased risk of stroke in older age outweighing any increased risk of bleeding [19]. In another study, the NCB of OAC in quality-adjusted life years (QALYs) was examined and found to decrease with age beyond 75 years [20]. The NCB of warfarin and apixaban decreased below the threshold of 0.1 lifetime QALYs (defined as a minimum clinically significant gain) after age 87 and 92 years, respectively [20]. Physicians are encouraged to consider the risk of mortality from other causes when deciding whether to initiate OAC therapy [20].

This review covers anticoagulant approaches for stroke prevention in older people with AF, with a focus on high-risk older adult sub-populations with multiple chronic conditions, including chronic kidney disease (CKD), dementia/cognitive impairment, prior history of stroke/transient ischemic attack (TIA) and intracranial hemorrhage, polypharmacy, frailty, low body weight, high falls risk and advanced age (≥75 years).

2. Anticoagulant approaches in older people: NOAC vs. VKA

Treatment approaches for stroke prevention in AF have changed substantially over the last 12–13 years [21]. The availability of NOACs in Europe from 2011 has improved accessibility to OAC therapy and likely explains the upwards trajectory in worldwide prescription of OAC for stroke prevention in AF, from 42% in 2010 to 78% in 2018 [22]. Both European and UK guidelines recommend NOACs as the first-line stroke prevention strategy in eligible people [13]. Pooled efficacy and safety data from randomized controlled trials (RCTs) [23–26] demonstrated a higher reduction in relative risk of stroke/systemic embolism (0.81, 95% CI 0.73–0.91, $p < 0.0001$), all-cause mortality (0.90, 95% CI 0.85–0.95, $p = 0.0003$) and intracranial hemorrhage (0.48, 95% CI 0.39–0.59, $p < 0.0001$) with NOACs vs. VKAs [27]. However, the risk of gastrointestinal bleeding was higher with NOAC therapy (1.25, 95% CI 1.01–1.55, $p = 0.04$) [27].

Ensuring adherence to licensed doses when prescribing in older people is critical as older age (apixaban ≥80 years if body weight ≤60 kg and/or creatinine ≥ 133 micromol/liter, dabigatran ≥80 years), low body weight (apixaban ≤60 kg if ≥80 years and/or creatinine ≥ 133 micromol/liter, edoxaban <61 kg) and impaired renal function (apixaban creatinine clearance [CrCl] 15-29 ml/min, rivaroxaban CrCl 15-49 ml/min, edoxaban CrCl 15-50 ml/min, dabigatran CrCl 30-50 ml/min) are indications for reduced dosing [28]. Inappropriate NOAC over- or under-dosing outside of product licensing may result in adverse events [29,30]. In people with antiphospholipid syndrome, moderate/severe mitral stenosis or mechanical heart valve(s), VKA therapy should be prescribed and time in therapeutic range (TTR) maintained at ≥70% [13]. For people with advanced CKD (CrCl <15 ml/min), VKA remains the first-line treatment but the decision whether or not to prescribe anticoagulation must be individualized and multidisciplinary team discussions with a nephrologist should be held to inform an assessment of thrombotic and bleeding risk; there are conflicting data on the net clinical benefit of OAC prescription in this cohort [31].

The efficacy and safety of NOACs vs. warfarin in people aged ≥75 years has been verified by secondary analyses of data from the original Phase III NOAC RCTs [23–26,32–36] (Table 1). Apixaban was more effective than warfarin for stroke/systemic embolism reduction (hazard ratio [HR] 0.71, 95% CI 0.53–0.95) [33], and rivaroxaban and edoxaban were non-inferior [32,34,35]. In one analysis [36], dabigatran 150 mg was more effective than warfarin for prevention of stroke/systemic embolism (relative risk [RR] 0.67, 95% 0.49–0.90), but there was no reported difference in another analysis [35]. Apixaban and edoxaban were associated with a significant reduction in major bleeding compared to warfarin [33,34], and there was no significant difference between warfarin and dabigatran or rivaroxaban for this outcome [32,35,36] (Table 1). RE-LY, ROCKET-AF and ENGAGE-AF reported sub-analyses on the risk of gastrointestinal (GI) bleeding [32,34,36]; dabigatran, edoxaban and rivaroxaban were associated with a higher risk of GI bleeding compared to warfarin in patients aged ≥75 years (Table 1). One systematic review [37] identified three retrospective observational studies reporting on GI bleeding risk with apixaban compared to VKA in older people identified from German (n = 70,501) [38] and United States (US) (n = 423,450 [39] and n = 88,582 [40]) claims databases. In two studies, the risk of GI bleeding was lower in older people receiving apixaban (5/2.5 mg) compared to VKA (HR 0.64, 95% CI 0.50–0.81 [38] and 0.62, 0.53–0.72 [40]), and in another study there was no difference in risk (HR 0.93, 95% CI 0.80–1.07) [39]. The risk of residual confounding by indication in these studies limits the conclusions that can be drawn.

Observational studies have become increasingly important to compare the representativeness of clinical trial populations to real-world populations [41]. One network meta-analysis compiled direct (head-to-head comparisons) and indirect (studies with a shared comparator) evidence from 25 RCTs and 24 non-randomized studies on 897,748 people with AF to compare clinical outcomes of NOACs vs. warfarin and between individual NOACs for stroke prevention in younger (65–74 years) vs. older (≥75 years) populations [42]. In people aged ≥75 years, apixaban 5 mg bid (rate ratio 0.69, 95% CI 0.53–

Table 1. Secondary analyses of phase III trials comparing non-vitamin K antagonist oral anticoagulants vs. warfarin in people aged ≥75 years.

Drug name, trial name	Participant characteristics* [a] Sample size [b] Proportion of females, n (%) [c] Age (mean [SD] or median [IQR]) [d] NOAC dose	Clinical efficacy and safety outcomes (effect measure, 95% CI)					
		Stroke/systemic embolism		Major bleeding		Gastrointestinal bleeding	
Dabigatran RE-LY¥ [23,35,36]	[a] 7,258 [b] 3,062 (42.2) [c] ≥75 to <80 years: 76.8 [1.4]/≥80 to <85 years: 81.7 [1.4]/≥85 years: 86.8 [2.2] [d] 110mg/150mg bid (random allocation)	*150mg bid* *≥75 years* **RR 0.67** **(0.49–0.90)** *≥75 to <80 years* HR 0.65 (0.42–1.01) *≥80 to <85 years* HR 0.67 (0.41–1.10) *≥85 years* HR 0.70 (0.31–1.57)	*110mg bid* *≥75 years* RR 0.88 (0.66–1.17) *≥75 to <80 years* HR 1.08 (0.73–1.60) *≥80 to <85 years* HR 0.75 (0.46–1.23) *≥85 years* HR 0.52 (0.21–1.29)	*150mg bid* *≥75 years* RR 1.18 (0.98–1.42) *≥75 to <80 years* HR 1.04 (0.81–1.35) *≥80 to <85 years* **HR 1.41** **(1.02–1.94)** *≥85 years* HR 1.22 (0.74 to 2.02)	*110mg bid* *≥75 years* RR 1.01 (0.83–1.23) *≥75 to <80 years* HR 0.93 (0.71–1.21) *≥80 to <85 years* HR 1.18 (0.84–1.65) *≥85 years* HR 1.01 (0.59–1.73)	*150mg bid* *≥75 years* **RR 1.79** **(1.35–2.37)**	*110mg bid* *≥75 years* **RR 1.39** **(1.03–1.98)**
Rivaroxaban ROCKET-AF [26,32]	[a] 3,120/3,109 [b] 1,446 (46.4)/1432 (46.1) [c] 79.0 [76.0–82.0]/79.0 [76.0–82.0] [d] 20mg qd (15mg qd if CrCl <50ml/min)	HR 0.80 (0.63–1.02)		HR 1.11 (0.92–1.34)		Event rate per 100 person-years (rivaroxaban 2.81 vs. warfarin 1.66, p=0.0002)	
Apixaban ARISTOTLE [25,33]	[a] 5,678 [b] 2,396 (42.2) [c] ∞ [d] 5mg bid (2.5mg bid if two or more of: age ≥80 years, bodyweight ≤60 kg, serum creatinine ≥133 µmol/L)	**HR 0.71** **(0.53–0.95)**		**HR 0.64** **(0.52–0.79)**		∞	
Edoxaban ENGAGE AF-TIMI 48 [24,34]	[a] 8,474 [b] 3,777 (45.0%) [c] 79.0 [76.0–82.0] [d] 60mg qd (30mg qd if CrCl ≤50ml/min, weight ≤60 kg, or concomitant use of potent P-glycoprotein inhibitor)	HR 0.83 (0.66–1.04)		**HR 0.83** **(0.70–0.99)**		**HR 1.32** **(1.01–1.72)**	

ARISTOTLE, apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation trial; bid, twice daily; CI, confidence interval; CrCl, creatinine clearance; ENGAGE-TIMI 48, effective anticoagulation with factor Xa next generation in atrial fibrillation – thrombolysis in myocardial infarction 48 trial; HR, hazard ratio; IQR, interquartile range; RE-LY, the randomized evaluation of long-term anticoagulation trial; ROCKET-AF, the rivaroxaban once daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation; RR, risk ratio; SD, standard deviation; qd, once daily.

Significant results highlighted in **bold**.

*reported for NOAC and warfarin groups separately where data is available, otherwise reported for entire study cohort or relevant specified subgroups.

¥results from two sub-analyses of RE-LY reported for dabigatran 110/150mg bid in different age categories (≥75 years [36] and ≥75 to <80 years, ≥80 to <85 years and ≥85 years [35]).

∞not reported.

0.90) and dabigatran 150 mg bid (rate ratio 0.74, 95% CI 0.55–0.98) had a lower risk of stroke and systemic embolism compared to warfarin [42]. When individual NOACs were compared, no differences were identified in risk of stroke/systemic embolism [42]. There was no significant difference in major bleeding observed between warfarin and dabigatran 110/150 mg, edoxaban 60 mg or rivaroxaban 20 mg [42], whereas apixaban 5 mg bid was associated with a significantly lower risk of major bleeding (rate ratio 0.67, 95% CI 0.55–0.82) compared to warfarin [42]. The risk of major bleeding in older people was reported to be lower with apixaban and edoxaban when compared to dabigatran 150 mg bid (rate ratio 0.57, 95% CI 0.44–0.75 and 0.71, 0.55–0.92, respectively) and rivaroxaban (rate ratio 0.60, 95% CI 0.45–0.79 and 0.74, 0.57–0.97, respectively) [42].

More recent observational studies on 2,881 US nursing home residents (median age 84 [IQR 77–89] years) [43] and 17,971 people (mean age 76.5 [SD 7.4] years) identified from US claims databases [39] prescribed apixaban corroborate findings from the network meta-analysis [39,42,43]. In both studies, apixaban was associated with a lower risk of major bleeding compared to VKA (HR 0.86, 95% CI 0.80–0.93 [39] and HR 0.66, 95% CI 0.49–0.88 [43]). Choice of NOAC should be evidence-based according to an individual's risk of stroke/systemic embolism and their risk of major and GI bleeding on OAC (Table 2).

Irrespective of age, antiplatelet therapy should not be prescribed and is not an appropriate stroke prevention strategy. This is supported by a multicentre RCT [BAFTA; Birmingham Atrial Fibrillation Treatment of the Aged Study] of 973 older people ≥75 years (mean age 81.5, standard deviation [SD, 4.2] years) comparing dose-adjusted warfarin vs. aspirin 75 mg/daily [56]. The relative risk of stroke was significantly lower in the warfarin group (RR 0.52, 95% CI 0.33–0.80), and there was no significant difference in the risk of major hemorrhage (RR 0.96, 95% CI 0.53–1.75) [56]. Other RCTs have been undertaken to selectively investigate warfarin vs. aspirin in older people [57–60]. A meta-analysis of these studies [56–60] reported a significantly lower risk of stroke/thromboembolism with warfarin therapy compared to aspirin (5 studies, 2,347 participants, RR 0.44, 95% CI 0.24–0.64, $I^2 = 0.0\%$) [61]. Reassuringly, there was no significant different in major bleeding (RR 1.20, 95% CI 0.91–1.50) [61].

3. Multiple chronic conditions

Multiple chronic conditions, defined as the presence of two or more chronic health conditions [63], is a high priority global public health concern. Prevalence is increasing as a result of the aging population, and it is reported to affect between 55 to 98% of older people with AF [7,9,64]. Multiple chronic conditions are associated with under-prescription of anticoagulant therapy, poor anticoagulation control and a higher risk of adverse health outcomes, presenting a major challenge to AF management [11,65].

People with AF and multiple chronic conditions, classified using the Charlson Co-morbidity Index (CCI), were identified in two retrospective studies using administrative health data in Lombardy ($n = 24,040$, mean age 76.1 years, 49.8% female) [11] and the FANTASIIA registry in Spain ($n = 1,956$, mean age 73.8 years, 44.5% female) [65]. One study reported an inverse association between increasing CCI and the likelihood of OAC prescription (OR 0.91, 95% CI 0.89–0.92) [11]. The other study reported an inverse association between multimorbidity (increasing CCI) and high-quality anticoagulation control (defined as TTR ≥ 70%) where mean TTR in 202 people with a CCI ≥ 3 was 54.7% [SD 24.2] compared to 63.1% [SD 24.5], 62.0% [25.3] and 62.2% [SD 25.7] in people with a CCI of 0, 1 and 2, respectively [65]. In both studies, an increasing number of chronic conditions was independently associated with a greater risk of adverse health outcomes including stroke (aHR 1.04, 95% CI 1.02–1.06) [11], major bleeding (aHR 1.03, 95% CI 1.01–1.06 [11] and aHR 1.18, 95% CI 1.02–1.38 [65]) and all-cause mortality (HR 1.10, 95% CI 1.09–1.11 [11] and aHR 1.26, 95% CI 1.13–1.40 [65]).

More recently, observational research using Medicare data has examined the safety and effectiveness of NOACs in people aged ≥65 years with AF and ≥ 6 chronic conditions [66]. After propensity score matching for apixaban-dabigatran ($n = 12,567$), apixaban-rivaroxaban ($n = 60,287$) and dabigatran-rivaroxaban ($n = 12,567$) groups, apixaban was associated with a lower risk of stroke/systemic embolism (HR 0.90, 95% CI 0.81–1.00) and major bleeding (HR 0.62, 95% CI 0.59–0.65) when compared to rivaroxaban [66]. Risk of major bleeding was also lower when apixaban was compared to dabigatran (HR 0.81, 95% CI 0.72–0.90). There was no significant difference in risk of stroke/systemic embolism when rivaroxaban and dabigatran were compared (HR 1.04, 95% CI 0.84–1.28), but dabigatran was associated with a lower risk of major bleeding compared to rivaroxaban (HR 0.78, 95% CI 0.71–0.87) [66].

International research programs are currently underway, including the atrial fibrillation integrated approach in frail, multimorbid and polymedicated older people (AFFIRMO) [67], and European Heart Rhythm Association (EHRA) member survey of current management practices and clinical priorities (EHRA-Paths) [68]. Their aim is to systematically analyze the management of people with AF and multiple chronic conditions, specifically the effectiveness of person-centered care and interdisciplinary approaches [67,68]. Findings from these programs will be critical to shape clinical practice and management of this high-risk cohort.

3.1. Chronic kidney disease

Atrial fibrillation and CKD are interconnected conditions, described as having a bidirectional relationship [69]. Mortality rates are higher in people with AF and CKD, attributed to an increased incidence of stroke and heightened bleeding risk [70]. There are no RCT data on the use of VKA in people with severe CKD (CrCl 15-29 ml/min) or on dialysis. People with a CrCl <30 ml/min were excluded from all landmark NOAC trials except ARISTOTLE [23–26,31]. This makes treatment decisions in the sub-population of older adults with AF and CKD inherently more complex. In severe CKD (CrCl 15-29 ml/min), reduced dose NOAC (apixaban 2.5 mg twice daily, rivaroxaban 15 mg once daily, edoxaban 30 mg

Table 2. Non-vitamin K antagonist oral anticoagulant prescribing aid for older people and high-risk subgroups, based on product licensing and available randomized and observational data.

Clinical scenarios	Apixaban	Edoxaban	Rivaroxaban	Dabigatran
Required dispensing into blister pack [44]	✓	✓	✓	X
Dietary intake unpredictable (unlikely to take medication with food) [45–48]	✓	✓	X	✓
Preference for once daily preparation [45–48]	X	✓	✓	X
Required crushing for oral/enteral tube administration [49,50]	✓ Licensed	✓ Licensed	✓ Licensed	X
Severe chronic kidney disease (creatinine clearance 15-29ml/min) [45–48]	✓ Reduced dose	✓ Reduced dose	✓ Reduced dose	X
Evidence presented below to guide NOAC choice in high-risk older subpopulations should be interpreted cautiously Prescribing decisions should consider a person's preference and local prescribing guidelines				
High risk of major bleeding - consider NOAC(s) with evidence of lowest major bleeding risk in older people (≥75 years) compared to VKA[Π]	✓ [25,33,39,42,43]	✓ [24,34]		
High risk of gastrointestinal bleeding - consider NOAC(s) with evidence of lowest gastrointestinal bleeding risk in older people compared to VKA∞	✓ [37,38,40]			
High risk of stroke/systemic embolism - consider NOAC(s) with evidence of highest risk reduction in older people (≥75 years) compared to VKA[†]	✓ [25,33,42]			✓ [36,42] 150mg twice daily, if person qualifies for lower dose dabigatran, consider another NOAC
High risk of dementia/cognitive impairment* - consider NOAC(s) with evidence of highest risk reduction compared to VKA	✓ [51]		✓ [51]	
Frailty - consider NOAC(s) with evidence of equivalent/higher risk reduction of stroke/systemic embolism and bleeding compared to VKA	✓ [37,38]			
Low body weight (≤60kg) – consider NOAC(s) with RCT evidence of safety and efficacy compared to VKA	✓ [52]	✓ [53]		
High falls risk – consider NOAC(s) with RCT evidence of safety and efficacy compared to VKA	✓ [37,54]	✓ [37,55]		

NOAC, non-vitamin K antagonist oral anticoagulant; RCT, randomized controlled trial; VKA, vitamin K antagonist. Images taken from flaticon.com.
Table key: ✓[supporting references] = NOAC with most evidence to support prescribing in high-risk sub-group.
Πevidence from secondary analyses of phase III NOAC randomized controlled trials in favor of apixaban and edoxaban [24,25,34,35], additional evidence from real world studies in favor of apixaban [39,42,43].
∞observational data only.
†evidence from secondary analyses of phase III NOAC randomized controlled trials and real-world studies in favor of apixaban and dabigatran 150mg [25,33,36,42].
*people with risk factors according to stage of life: early life (age <18 years) - less education; mid-life (age 45–65 years) - hearing loss, hypertension, obesity; and later life (age >65 years) - smoking, depression, physical inactivity, social isolation and diabetes [62].

once daily) or VKA can be prescribed with caution, but nephrology input is advocated [28,45–47,71]. Outside the US, dabigatran is generally contraindicated in severe CKD with CrCl <30 ml/min, although the 75 mg bid dose is licensed in the US for people with CrCl 15-29 ml/min [28,48].

Data exist from small-scale studies comparing VKA to rivaroxaban, edoxaban and apixaban in severe CKD [72–74]. An exploratory, observational study of 46 people (mean age 84.6 [SD 6.9] years, 63.0% female) prescribed edoxaban 30 mg daily reported no major bleeding or thrombotic events over a mean follow-up of 9.13 [SD 3.0] months [72]. In a secondary analysis of 269 people (median age 81 [IQR 76–85] years, 60.6% female) enrolled into the ARISTOTLE trial with a CrCl of 25-30 ml/min [25,73], the risk of major bleeding was lower with apixaban compared to warfarin (HR 0.34, 95% CI 0.14–0.80). However, there was no statistically significant difference between treatments for stroke or systemic embolism (HR 0.55, 95% CI 0.20–1.51) [73]. Apixaban dosing was reduced to 2.5 mg bid in 173/269 people with ≥ 2 of the following: age ≥80 years; body weight ≤60 kg; serum creatinine ≥1.5 mg/dL [73]. It is noteworthy that apixaban dose reduction based on a CrCl of 15-29 ml/min alone (as per UK and European licensing) was not followed in this analysis. When stratified by apixaban dose, there was no difference in the risk of major bleeding between apixaban 2.5 mg bid (HR 0.34, 95% CI 0.11–1.07) or 5 mg bid (HR 0.34, 95% CI 0.09–1.29) vs. warfarin [73]. In another study, 2,317 people (mean age 79.9 [SD 8.2] years, 60.5% female) were identified from electronic records with severe CKD who initiated warfarin or rivaroxaban [74]. Among rivaroxaban users ($n = 781$, 33.7%), 469 people (60.1%) were prescribed a reduced dose of 15 mg as per UK and European licensing. There was no statistically significant difference in the risk of ischemic stroke/systemic embolism (HR 1.34, 95% CI 0.51–3.53, $p = 0.55$) or major bleeding (HR 1.00, 95% CI 0.63–1.57, $p = 0.99$) reported between rivaroxaban 15 mg vs. warfarin [74]. Data from these studies must be interpreted cautiously because of the risk of residual confounding. Nevertheless, they indicate that apixaban, edoxaban and rivaroxaban are safe and efficacious alternatives to VKA in older people with severe CKD (Table 2).

There is a paucity of strong evidence to guide the decision whether to anticoagulate people with end-stage CKD (CrCl <15 ml/min) or on dialysis, and if so, which OAC to choose. Treatment decisions must be highly individualized [31]. The use of rivaroxaban, apixaban and edoxaban is not recommended. Frequent international normalized ration (INR) monitoring is required if VKA therapy is prescribed, and prescribers should be aware of the risk of calciphylaxis [31,71].

3.2. Cognitive impairment

Atrial fibrillation and dementia commonly co-exist and disproportionately affect older populations [75]. However, cognitive impairment and dementia are not reasons to preclude OAC prescription in older people with AF [13]. Indeed, rigorous assessment for stroke prevention with consideration of OAC initiation is mandatory in this sub-group who are at high-risk of disability and institutionalization after stroke events [31,76]. In addition to reducing the risk of stroke, there is also evidence to suggest that OAC therapy may protect against cognitive decline [51,77–80].

In the Atherosclerosis Risk in Communities Neurocognitive study (ARIC-NCS), the association between incident AF and dementia was explored in 12,515 people (mean age 56.9 [SD 5.7] years, 56% women) [81]. Over a 20-year follow-up, 2,106 and 1,157 people developed AF and dementia, respectively [81]. After adjusting for cardiovascular risk factors and ischemic stroke, a positive association was reported between incident AF and an increased dementia risk (HR 1.23, 95% CI 1.04–1.45) [81]. A recent systematic review and meta-analysis [82] also reported AF to be associated with dementia (8 studies, aOR 1.6, 95% CI 1.3–2.1, $I^2 = 31\%$ and 17 studies, aHR 1.4, 95% CI 1.2–1.5, $I^2 = 92\%$) and the combined outcome of dementia or cognitive impairment (15 studies, aOR 1.5, 95% CI 1.4–1.8, $I^2 = 34\%$ and 18 studies, aHR 1.4, 95% CI 1.2–1.5, $I^2 = 92\%$) after pooling different effect measures separately [82]. Positive associations persisted in sensitivity analyses when people with a history of stroke were excluded (11 studies, aOR 2.2, 95% CI 1.4–3.5, $I^2 = 96\%$ and 7 studies, aHR 1.4, 95% CI 1.1–1.7, $I^2 = 87\%$) [82].

The most familiar pathophysiological mechanism proposed to explain this association is hypoperfusion secondary to ischemic stroke. In the absence of stroke, other alterations to brain perfusion resulting from beat-to-beat variability and cerebral microinfarcts, known as 'silent strokes,' are thought to be responsible for AF-related cognitive decline [83]. This has been a catalyst to examine OAC prescription and the risk of cognitive impairment or dementia in people with AF, with or without a history of stroke. To date, the available evidence is inconclusive. Different meta-analyses have found OAC use to be associated with a reduced risk of dementia (6 studies, 448,418 participants, risk ratio 0.79, 95% CI 0.67–0.93, $p = 0.005$, $I^2 = 59.7\%$ [80] and 8 studies, 217,767 participants, HR 0.68, 95% CI 0.55–0.82, $I^2 = 87.7\%$ [79]) and cognitive impairment (8 studies, 452,661 participants, HR 0.71, 95% CI 0.69–0.74, $I^2 = 0\%$ [77]) compared to no OAC use, but another meta-analysis (3 studies, 5,899 participants) reported no association [78] (Table 3). Sub-group analyses have demonstrated the positive effects of OAC to persist in a mixed cohort of people with and without prior stroke history [80] and in people without prior stroke history [79] (Table 3).

Three meta-analyses of observational studies [77,79] and a combination of observational studies and RCTs [51] compared the effects of NOAC vs. VKA on dementia [51,77,79] and all suggested a benefit for NOACs (HR 0.87, 95% CI 0.79–0.95 [79], HR 0.51, 95% CI 0.37–0.71, $p < 0.00001$ [60] and OR 0.56, 95% CI 0.34–0.94, $p = 0.03$ [51]) (Table 3). When those with a prior history of stroke were excluded from one subgroup analysis, the effect was nullified (HR 0.90, 95% CI 0.71–1.15 [79] (Table 2). In another subgroup analysis individual NOACs were compared [51]. There was no statistically significant difference between dabigatran vs. VKA and composite dementia outcomes. However, apixaban (OR 0.58, 95% CI 0.50–0.67, $p = 0.00001$, $I^2 = 0\%$) and rivaroxaban (OR 0.67, 95% CI 0.61–0.75, $p = 0.00001$, $I^2 = 44\%$) had a significantly lower risk of dementia compared to VKA (Table 3) [51]. Based on the available evidence, it is unclear if NOACs offer enhanced cognitive protection compared to VKA, or whether different NOACs offer

Table 3. Key findings from meta-analyses investigating the effect of oral anticoagulant use (vs. nonuse) and choice of oral anticoagulant (NOAC vs. VKA) on dementia or cognitive impairment in AF.

Author (Year)	Number of studies included in meta-analysis (study design)	Population, n	Average age (mean/median) range (years) of participants in included studies (where reported)	Prior history of dementia or stroke specified as exclusion criteria	Main findings (*p* value reported if provided)
OAC vs. No OAC					
Wang [79]	8 (retrospective observational [84–91])	217, 767	60.0–76.4	Studies including individuals with prior events of moderate to severe cognitive impairment or dementia were excluded	OAC use associated with reduced dementia risk vs. no OAC use (HR 0.68, 95% CI 0.55–0.82, p=0.005, I^2=87.7%) Protective effects of OAC use on dementia risk persisted when people with prior history of stroke were excluded (HR 0.60, 95% CI 0.54–0.66, I^2=44.9%, n=4 studies 59,533 participants)
Mongkhon [80]	4 (n=2 retrospective observational [84,85], n=2 prospective observational [92,93])	448, 418	71.0–75.7	Studies including individuals with a prior history of dementia were excluded	OAC use associated with reduced dementia risk vs. no OAC use (risk ratio 0.79, 95% CI 0.67–0.93, p=0.005, I^2=59.7%) Protective effects of OAC use on dementia risk persisted in subgroup analysis including people with and without history of prior stroke (risk ratio 0.77, 95% CI 0.64–0.93, I^2=58.2%)
Cheng [77]	5 (n=3 retrospective observational [84,85,94], n=2 prospective observational [92,95])	452, 661	71.0–74.8	Studies including individuals with dementia history excluded	OAC use associated with reduced risk of dementia vs. no OAC use (HR 0.71, 95% CI 0.69–0.74, p <0.00001, I^2=0%)
Moffit [78]	3 (prospective observational [92,95,96])	5, 899	Not reported for individual studies	No	No significant difference between OAC vs. no OAC on incident cognitive syndromes (OR 0.89, 95% CI 0.47–1.69, p=0.73, I^2=66%) Planned subgroup analysis to explore the effect of stroke history but unable to perform with available data
NOAC vs. VKA					
Wang [79]	9 (retrospective observational [85,86,89,90,97–101])	809, 467	60.0–73.9	Studies including individuals with prior events of moderate to severe cognitive impairment or dementia excluded	NOAC use associated with reduced dementia risk vs. VKA (HR 0.87, 95% CI 0.79–0.95, I^2=72%) No statistically significant difference between NOAC vs. VKA when people with prior history of stroke excluded (HR 0.90, 95% CI 0.71–1.15, I^2=76.6%, n=6 studies 96,534 participants)
Lee [51]	9 (n=5 retrospective observational [81,85,86,98,102], n=4 randomized controlled trials [23–26])	611, 069	Not reported for individual studies	No	NOAC use associated with reduced risk of composite dementia outcomes vs. VKA (OR 0.56, 95% CI 0.34–0.94, p=0.03, I^2=97%) When individual NOACs were considered, there was no statistically significant difference between dabigatran vs. VKA and composite dementia outcomes (OR 0.97, 95% CI 0.88–1.08, p=0.61, I^2=29%), whereas apixaban (OR 0.58, 95% CI 0.50–0.67, p=0.00001, I^2=0%) and rivaroxaban (OR 0.67, 95% CI 0.61–0.75, p=0.00001, I^2=44%) had a significantly lower risk compared to VKA
Cheng [77]	2 (retrospective observational [85,102])	208, 740	72.4–74.8	Studies including individuals with dementia history excluded	NOAC use associated with reduced risk of dementia vs. VKA (HR 0.51, 95% CI 0.37–0.71, p < 0.00001, I^2=0%)

CI, confidence interval; HR, hazard ratio; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; OR, odds ratio; VKA, vitamin K antagonist.

better protection than others. In people with risk factors for dementia according to their stage of life: early life (age <18 years) – less education; mid-life (age 45–65 years) – hearing loss, hypertension, obesity; and later life (age >65 years) – smoking, depression, physical inactivity, social isolation and diabetes [62], choosing a NOAC with most evidence of protective benefit may be appropriate (Table 2).

The importance of maintaining a high TTR with warfarin therapy has been highlighted in two meta-analyses [77,80]. When results from two retrospective cohort studies (total 13,142 participants) were pooled [103,104], the risk of cognitive impairment was lower with increasing TTR (<25% vs. >75%; HR 3.02, 95% CI 1.12–8.91, $p = 0.03$); 25%–50% vs. >75% (HR 2.44, 95% CI 0.95–6.22, $p = 0.06$); 50%–75% vs.

>75% (HR 1.75, 95% CI 0.90–3.99, $p = 0.1$) [77]. In the other meta-analysis [80], results from one of these studies [104] was pooled with an observational study of 2,800 participants (mean age 71.2 years, 47% female) with incident AF [84]. A higher TTR was associated with a lower risk of dementia (risk ratio 0.38, 95% CI 0.22–0.64, $p < 0.001$) [80]. Close monitoring of INR is critical to maintain high TTR, and accessibility and persistence to attend anticoagulation clinics for monitoring are important practical considerations when choosing OAC therapy, especially in older people with dementia or cognitive impairment (Figure 1).

As previously alluded to, cognitive impairment is a recognized barrier to OAC prescription for stroke prevention in AF [15,105]. This is likely owing to multiple concerns about persistence with therapy, ability to fulfill monitoring requirements for both VKA (INR testing) and NOAC therapy (full blood count, liver and renal function testing), and concerns of a heightened bleeding risk resulting from unintentional overdosing, encountering environmental hazards or falls [106,107] (Figure 1). In the context of these concerns, NOAC therapy boasts some advantages over VKA; edoxaban, apixaban and rivaroxaban can be dispensed into a blister pack to support therapy adherence and mitigate the risk of overdose. The availability of once daily regimens (edoxaban and rivaroxaban) can also support therapy adherence. Further, NOAC therapy is devoid of intensive monitoring requirements like VKA, and depending on a person's age, frailty status and renal function may only require annual blood test monitoring once therapy is established (Figure 1). Food intake is essential for rivaroxaban absorption, so if a person's eating pattern is variable and unpredictable, an alternative OAC is required. It is prudent to consider if an individual with cognitive impairment or dementia has support with medication administration from family or carers, and whether they live at home or in long-term care facilities. This information will inform the risk assessment of initiating OAC therapy (Figure 1). Above all, treatment decisions must be person-centered and steps must be taken to discuss with an individual's next of kin or Power of Attorney for Health in the event they do not have capacity.

3.3. History of previous stroke/transient ischemic attack and intracranial hemorrhage

Anticoagulant approaches for secondary stroke prevention will be considered in older people with AF and a history of prior stroke/TIA or intracranial hemorrhage. In people with a history of stroke/TIA despite OAC treatment, assessment of the quality of OAC therapy (TTR ≥70% if on VKA, NOAC dosed appropriately according to age, body weight and renal function) and adherence is paramount [13]. It may be necessary to switch between therapies (VKA to NOAC, NOAC to NOAC) and introduce additional monitoring (increased frequency of INR testing, plasma Xa levels for NOAC therapy).

NOACs are recommended in preference to VKA in people with AF and a history of ischemic stroke/TIA or intracranial hemorrhage [13]. Sub-group analysis of the RE-LY trial comparing dabigatran to warfarin for secondary stroke prevention [108] was restricted to people aged ≥75 years or at least 65 years with hypertension, diabetes or coronary artery disease [108]. There was no significant difference in relative risk of

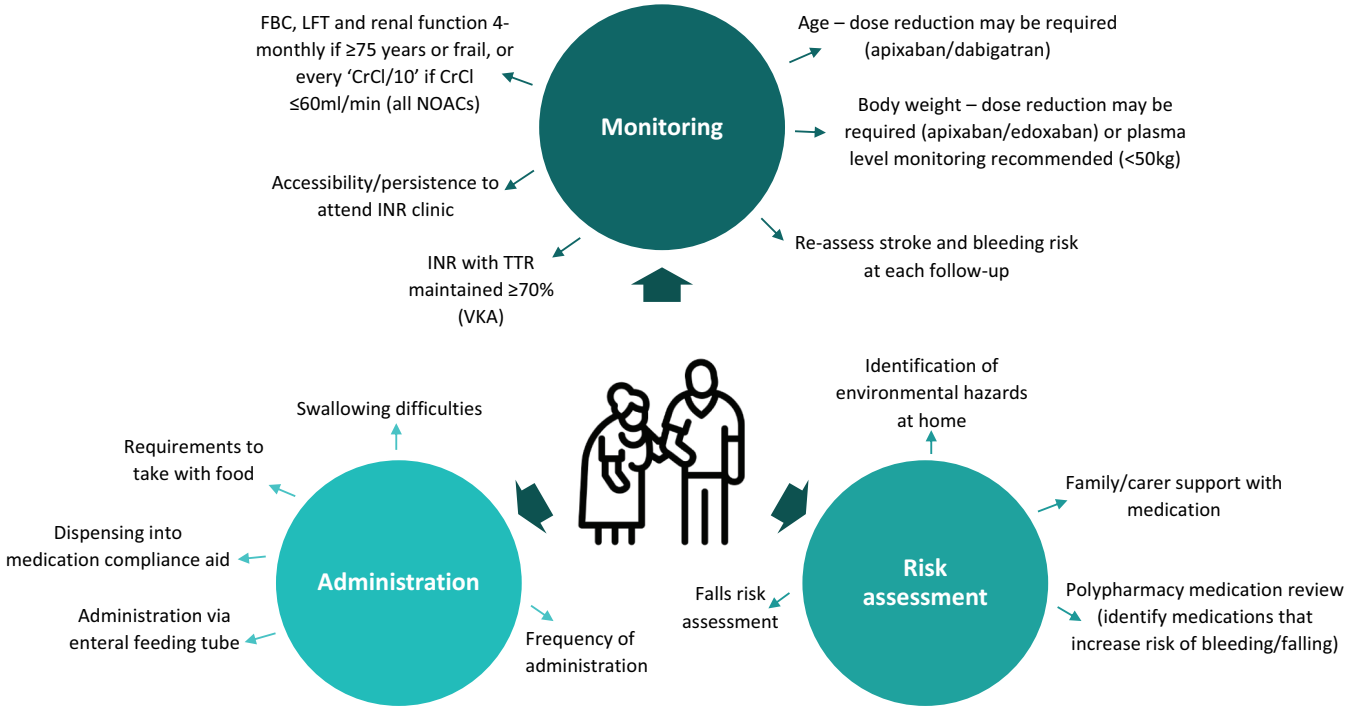

Figure 1. Practical considerations when prescribing oral anticoagulant therapy for stroke prevention in AF in older people.

CrCl, creatinine clearance; FBC, full blood count; INR, international normalized ratio; LFT, liver function tests; NOAC, non-vitamin K antagonist oral anticoagulant; TTR, time in therapeutic range; VKA, vitamin K antagonist. Images taken from flaticon.com.

stroke or systemic embolism in people with prior stroke/TIA taking dabigatran 110 mg (RR 0.84, 95% CI 0.58–1.20) or 150 mg (RR 0.75, 95% CI 0.52–1.08) compared to warfarin [108], but the relative risk of hemorrhagic stroke was significantly lower with dabigatran treatment (110 mg: RR 0.11, 95% CI 0.03–0.47 and 150 mg: RR 0.27, 95% CI 0.10–0.72) [108]. Both doses of dabigatran were similar to warfarin in terms of safety, but the risk of major bleeding was significantly lower with dabigatran 110 mg (RR 0.66, 95% CI 0.48–0.90) [108]. Similarly, there was no significant difference in risk of stroke or systemic embolism in 3,436 people (mean age 70.1 years [SD 9.5]) with prior stroke/TIA on apixaban vs. warfarin (HR 0.76, 95% CI 0.56–1.03), but the risk of hemorrhagic stroke (HR 0.40, 95% CI 0.21–0.78) and major bleeding (HR 0.73, 95% CI 0.55–0.98) was significantly lower [109]. From 7,468 people with a history of previous stroke/TIA included in the ROCKET trial, 3,754 (median age 75 years [IQR 68–79]) were randomized to rivaroxaban and 3,714 (median age 75 years [IQR 69–79]) to warfarin. There was no significant difference between rivaroxaban and warfarin for any efficacy and safety outcome [110].

When RCT data from landmark NOAC AF trials [23–26] on 20,500 people with AF and previous stroke/TIA was pooled, NOACs (apixaban 5 mg, edoxaban 60 mg, rivaroxaban 20 mg, dabigatran 150 mg) were associated with a significantly lower odds of stroke/systemic embolism (OR 0.86, 95% CI 0.75–0.98, $p = 0.02$), hemorrhagic stroke (OR 0.51, 95% CI 0.38–0.69, $p < 0.0001$) and any stroke (OR 0.86, 95% CI 0.75–0.99, $p = 0.04$) compared to VKA [111]. There was no difference between NOACs vs. VKA for other adverse health outcomes including disabling or fatal stroke, ischemic or unknown stroke, cardiovascular or all-cause mortality and myocardial infarction [111]. Generalisability of these findings to older people is often refuted because people aged ≥75 years were under-represented in the RCTs. Despite this, real-world observational data appears to corroborate these findings in older people with AF and previous stroke/TIA or intracranial hemorrhage [112]. A systematic review and meta-analysis [112] (10 observational studies, 114, 735 participants [99,113–121]) compared NOACs to VKA for stroke prevention in AF in people with prior history of stroke/TIA [113–116,118,119,121] or intracranial hemorrhage [113,117,120,122] (Table 4). From pooled analyses, NOAC use was associated with a lower risk (HR [95% CI]) of all adverse health outcomes compared to VKA therapy in people with prior stroke/TIA (stroke: 0.82 [0.69–0.97], $p = 0.02$; systemic embolism: 0.73 [0.61–0.87], $p = 0.0003$, all-cause mortality: 0.87 [0.81–0.94], $p = 0.0005$; major bleeding: 0.77 [0.64–0.92], $p = 0.004$ and intracranial hemorrhage: 0.54 [0.38–0.77], $p = 0.0006$) [112]. There was no significant difference between NOACs and VKA for gastrointestinal bleeding (1.13 [0.95–1.35], $p = 0.17$) [112]. Improved outcomes with NOAC therapy were also observed for people with AF and a history of intracranial hemorrhage [112]. When compared to VKA therapy, NOACs were associated with a lower risk (HR [95% CI]) of stroke (0.81 [0.68–0.95], $p = 0.009$), all-cause mortality (0.68 [0.49–0.94], $p = 0.02$), and recurrent intracranial hemorrhage (0.66 [0.51–0.84], $p = 0.0008$) [112] (Table 4).

Although only one study included in the meta-analyses had older age (≥65 years) as an inclusion criteria [115], the average age was >70 years in all studies except one (median age [IQR] in dabigatran 150 mg subgroup 69 [9,64–73] years) [114] (Table 4). One study conducted a subgroup analysis comparing the effects of NOAC vs. VKA in people aged ≥ 80 vs. <80 years with a history of stroke/TIA [116] and concluded there was no significant interaction between treatment effects (Table 4).

In four studies, NOAC-specific data were reported for stroke [114,118,119,121], bleeding [118,119,121], thromboembolism [118] and all-cause-mortality outcomes [121] (Table 4). Dabigatran and rivaroxaban were associated with a greater reduction in risk of recurrent stroke compared to warfarin (aHR 0.64 [0.48–0.85] and 0.73 [0.63–0.85], respectively) and apixaban (0.61 [0.44–0.85] and 0.70 [0.56–0.87], respectively) in people with a history of stroke/TIA on both regular and low-dose NOACs [118] (Table 4). In another study, no significant differences were reported between dabigatran 150 mg, rivaroxaban 20 mg or apixaban 5 mg vs. warfarin for the outcome of recurrent ischemic stroke/intracranial hemorrhage [119]. Among people with a history of stroke, all NOACs prescribed at regular doses showed a significantly lower risk of recurrent stroke, major bleeding (except dabigatran 150 mg), the composite outcome of recurrent stroke and major bleeding, fatal recurrent stroke, fatal major bleeding, fatal composite outcome and all-cause mortality [121] (Table 3). People with AF and a history of stroke/TIA were stratified by prior warfarin prescription [114] and switching to dabigatran was associated with an increased risk of stroke/TIA compared to warfarin in people who had previously been on warfarin. In contrast, there was a reduced risk of stroke/TIA in warfarin-naïve participants associated with low dose dabigatran (110 mg) when compared to warfarin, but no significant difference with dabigatran 150 mg (Table 4) [114].

More recently, an international, prospective observational cohort study of 5,984 people with AF and prior ischemic stroke (<3 months) has compared NOAC vs. VKA therapy [123]. Treatment with OAC was initiated three months after the index event in people aged ≥ 85 ($n = 1,380$, median age 88 [IQR 86–90] years, 63.8% female) vs. <85 years ($n = 4,604$, median age 75 [IQR 69–80] years, 42.9% female) [123]. Over 6,874 person-years follow-up, NOAC therapy was associated with a reduced risk of the composite of recurrent stroke, intracranial hemorrhage and all-cause death vs. VKA (HR 0.74, 95% CI 0.63–0.86, $p < 0.001$) [123], irrespective of age group (aged ≥85 years HR 0.65, 95% CI 0.52–0.81 and <85 years 0.79, 95% CI 0.66–0.95) [123].

Older people with AF who have swallowing difficulties post-stroke/TIA must be identified. This is crucial to inform the decision of which OAC to (re)-initiate in eligible people. Apixaban, edoxaban and rivaroxaban tablets are licensed to be crushed for oral, or enteral tube, administration [49]. Dabigatran capsules should not be opened to facilitate administration; increases in bioavailability can increase the risk of bleeding [48]. Warfarin tablets can be crushed and dispersed in water or given with soft food, but this is off-label use [49] (Table 2).

Table 4. Summary characteristics and outcomes of individual studies included in a systematic review and meta-analysis by Guo et al [112] comparing non-vitamin K antagonist oral anticoagulant vs. vitamin K antagonist therapy in people with AF and prior history of stroke, transient ischemic attack and intracranial hemorrhage.

				Main outcomes *aHR (95% CI) reported for all outcomes unless otherwise stated*		
Author (Year)	[a] Sample size, n [b] Mean [SD]/median [IQR] age (years) [c] Proportion (%) female	NOACs	VKAs	Stroke	Bleeding	Other
NOAC vs. VKA in people with AF and prior history of stroke/transient ischemic attack						
Yang [118]	[a] Apix 494/Dab 247/Riva 1,104/Warf 3,082 [b] Apix 80.3 [8.3]/Dab 78.3 [8.4]/Riva 78.8 [8.6]/Warf 77.9 [10.0] [c] Apix 65.0/Dab 56.3/Riva 62.7/Warf 60.7	Dab, Riva, Apix	Warfarin	*Analysis included a mixture of people on low-dose (Dab 110mg, Riva 15mg, Apix 2.5mg) and regular dose NOACs* *Ischaemic stroke* Apixaban vs. Warfarin 1.04 (0.86–1.27) Dabigatran vs. Warfarin **0.64 (0.48–0.85)** Rivaroxaban vs. Warfarin **0.73 (0.63–0.85)** Dabigatran vs. Apixaban **0.61 (0.44–0.85)** Rivaroxaban vs. Apixaban **0.70 (0.56–0.87)** Rivaroxaban vs. Dabigatran 1.14 (0.85–1.54)	*Major bleeding* Apixaban vs. Warfarin 0.78 (0.60–1.01) Dabigatran vs. Warfarin 1.03 (0.78–1.36) Rivaroxaban vs. Warfarin 0.98 (0.84–1.15) Dabigatran vs. Apixaban 1.32 (0.92–1.89) Rivaroxaban vs. Apixaban 1.25 (0.95–1.67) Rivaroxaban vs. Dabigatran 0.95 (0.71–1.28) *Gastrointestinal bleeding* Apixaban vs. Warfarin 0.71 (0.44–1.14) Dabigatran vs. Warfarin 1.41 (0.92–2.15) Rivaroxaban vs. Warfarin 1.21 (0.94–1.56) Dabigatran vs. Apixaban **2.00 (1.09–3.57)** Rivaroxaban vs. Apixaban **1.70 (1.04–2.78)** Rivaroxaban vs. Dabigatran 0.86 (0.55–1.35)	*Thromboembolism* Apixaban vs. Warfarin **0.62 (0.43–0.90)** Dabigatran vs. Warfarin **0.62 (0.39–0.99)** Rivaroxaban vs. Warfarin **0.73 (0.58–0.93)** Dabigatran vs. Apixaban 1.00 (0.57–1.75) Rivaroxaban vs. Apixaban 1.18 (0.79–1.75) Rivaroxaban vs. Dabigatran 1.18 (0.72–1.92)
Coleman [119]	[a] Apix vs. Warf 2,514/Dab vs. Warf 1,962/Riva vs. Warf 5,208* [b] Apix vs. Warf 74 [9,63–81], 74 [9,63–81]/Dab vs. Warf 73 [9,63–79], 73 [9,64–81]/ Riva vs. Warf 72 [9,63–80], 72 [9,63–81]* [c] Apix vs. Warf 46.00, 44.2/Dab vs. Warf 48.2, 47.7/Riva vs. Warf 46.9, 46.3	Dab, Riva, Apix	Warfarin	*Analysis included people on regular dose NOACs only* *HR (95% CI) reported for each propensity score matched NOAC vs. warfarin comparison* *Ischemic stroke/intracranial hemorrhage* Apixaban vs. Warfarin 0.70 (0.33–1.48) Dabigatran vs. Warfarin 0.53 (0.26–1.07) Rivaroxaban vs. Warfarin **0.45 (0.29–0.72)**	*Major bleeding* Apixaban vs. Warfarin 0.79 (0.38–1.64) Dabigatran vs. Warfarin 0.58 (0.26–1.27) Rivaroxaban vs. Warfarin 1.07 (0.71–1.61)	

(*Continued*)

Table 4. (Continued).

Author (Year)	[a] Sample size, n [b] Mean [SD]/median [IQR] age (years) [c] Proportion (%) female	NOACs	VKAs	Main outcomes *aHR (95% CI) reported for all outcomes unless otherwise stated*		
				Stroke	Bleeding	Other
Larsen [114]	No prior warfarin therapy [a] Warf 1,825/Dab 110mg 793/ Dab 150mg 646 [b] Warf 76 [68–81]/Dab 110mg 83 [77–84,103,104]/Dab 150mg 69 [9,64–73] [c] Warf 44.0/Dab 110mg 56.2/ Dab 150mg 35.9 Prior Warfarin therapy [a] Warf 1,918/Dab 110mg 547/ Dab 150mg 412 [b] Warf 75 [68–81]/Dab 110mg 82 [77–83,103,104]/Dab 150mg 70 [9,65–73] [c] Warf 38.7/Dab 110mg 55.0/ Dab 150mg 38.0	Dab	Warfarin	No prior VKA therapy: *Stroke* Dabigatran 110mg vs. Warfarin **0.74 (0.56–0.97)** Dabigatran 150mg vs. Warfarin 1.10 (0.83–1.44) *Transient ischemic attack* Dabigatran 110mg vs. Warfarin **0.48 (0.28–0.83)** Dabigatran 150mg vs. Warfarin 0.79 (0.49–1.28) Prior VKA therapy: *Stroke* Dabigatran 110mg vs. Warfarin **1.73 (1.21–2.47)** Dabigatran 150mg vs. Warfarin **1.79 (1.18–2.72)** *Transient ischemic attack* Dabigatran 110mg vs. Warfarin 1.30 (0.68–2.50) Dabigatran 150mg vs. Warfarin 1.72 (0.92–3.22)		
Seiffge [116]	[a] Warf 2,256/NOAC 2,656 [b] Warf 78.00 [70–83]/NOAC 77 [70–83] [c] Warf 47.00/NOAC 48.00	NOACs (all)	Warfarin, phenprocoumon			*Composite of ischemic stroke, intracerebral hemorrhage and mortality* NOACs vs. VKA 0.82 (0.66–1.00) No significant interactions between treatment effects in subgroup analysis comparing people NOAC vs. VKA in people aged ≥80 vs. <80 years
NOAC vs. VKA in people with AF and prior history of ischemic stroke						
Xian [115]	[a] Warf 7,621/NOAC 4,041 [b] Warf 80 [73–83,103,104]/ NOAC 80 [73–83,103,104] [c] Warf 56.3/NOAC 56.3	NOACs (Dab, Riva, Apix)	Warfarin			Number of days at home in first year post-discharge NOACs vs. warfarin: mean 287.2 [SD 114.7] vs. 263.0 [127.3] days; adjusted difference, 15.6 [99% CI 9.0–22.1] days *Major adverse cardiovascular events* NOACs vs. Warfarin **0.89 (99% CI 0.83–0.96)**
Komen [113]	[a] Warf 1,229/NOAC 454 [b] Warf 80.62 [8.45]/NOAC 79.25 [9.35] [c] Warf 46.9/NOAC 52.2	NOACs (all)	Warfarin			Mortality NOACs vs. Warfarin 0.84 (0.63–1.12)

(*Continued*)

Table 4. (Continued).

Author (Year)	[a] Sample size, n [b] Mean [SD]/median [IQR] age (years) [c] Proportion (%) female	NOACs	VKAs	Main outcomes *aHR (95% CI) reported for all outcomes unless otherwise stated*		
				Stroke	Bleeding	Other
Park [121]	[a] Warf 28,839/NOAC 32.729 [b] Warf 73.1 [9.4]/NOAC 75.2 [9.1] [c] Warf 46.8/NOAC 49.0	NOACs (all)	Warfarin	*HR reported after inverse probability of treatment weighting* *Analysis included people on regular dose NOACs only* *Recurrent stroke* NOACs vs. Warfarin 0.67 (0.62–0.72) Rivaroxaban 20mg vs. Warfarin **0.63 (0.57–0.70)** Dabigatran 150mg vs. Warfarin **0.71 (0.62–0.80)** Apixaban 5mg vs. Warfarin **0.70 (0.63–0.79)** Edoxaban 60mg vs. Warfarin **0.65 (0.55–0.76)** *Fatal recurrent stroke* NOACs vs. Warfarin **0.69 (0.59–0.79)** Rivaroxaban 20mg vs. Warfarin **0.77 (0.63–0.93)** Dabigatran 150mg vs. Warfarin **0.78 (0.60–0.99)** Apixaban 5mg vs. Warfarin **0.64 (0.50–0.81)** Edoxaban 60mg vs. Warfarin **0.43 (0.29–0.62)**	*Major bleeding* NOACs vs. Warfarin **0.73 (0.66–0.80)** Rivaroxaban 20mg vs. Warfarin **0.80 (0.70–0.92)** Dabigatran 150mg vs. Warfarin 0.87 (0.73–1.02) Apixaban 5mg vs. Warfarin **0.59 (0.49–0.70)** Edoxaban 60mg vs. Warfarin **0.54 (0.42–0.70)** *Fatal major bleeding* NOACs vs. Warfarin **0.50 (0.37–0.68)** Rivaroxaban 20mg vs. Warfarin **0.67 (0.45–0.97)** Dabigatran 150mg vs. Warfarin **0.30 (0.13–0.58)** Apixaban 5mg vs. Warfarin **0.44 (0.25–0.74)** Edoxaban 60mg vs. Warfarin **0.45 (0.19–0.90)**	*Composite outcome (recurrent stroke and major bleeding)* **NOACs vs. Warfarin** **0.69 (0.65–0.73)** Rivaroxaban 20mg vs. Warfarin **0.69 (0.64–0.75)** Dabigatran 150mg vs. Warfarin **0.75 (0.67–0.83)** Apixaban 5mg vs. Warfarin **0.67 (0.61–0.74)** Edoxaban 60mg vs. Warfarin **0.62 (0.54–0.71)** *Fatal composite outcome* NOACs vs. Warfarin **0.65 (0.57–0.74)** Rivaroxaban 20mg vs. Warfarin **0.74 (0.62–0.88)** Dabigatran 150mg vs. Warfarin **0.68 (0.53–0.86)** Apixaban 5mg vs. Warfarin **0.60 (0.48–0.75)** Edoxaban 60mg vs. Warfarin **0.44 (0.31–0.60**) All-cause mortality NOACs vs. Warfarin **0.84 (0.80–0.89)** Rivaroxaban 20mg vs. Warfarin **0.93 (0.86–0.99)** Dabigatran 150mg vs. Warfarin **0.78 (0.70–0.86)** Apixaban 5mg vs. Warfarin **0.85 (0.77–0.93)** Edoxaban 60mg vs. Warfarin **0.71 (0.63–0.81)**
NOAC vs. VKA in people with AF and prior history of intracranial hemorrhage						
Tsai [117]	[a] 4,540 [b] 76.00 [10.50] [c] 41.6	NOACs (Dab, Riva, Apix)	Warfarin	*Intracranial hemorrhage* NOACs vs. Warfarin **0.56 (0.39–0.80)** *Ischemic stroke* NOACs vs. Warfarin 0.88 (0.68–1.14)	*Major bleeding* NOACs vs. Warfarin **0.65 (0.53–0.79)**	*All-cause mortality* NOACs vs. Warfarin **0.52 (0.46–0.59)**

(*Continued*)

Table 4. (Continued).

Author (Year)	[a] Sample size, n [b] Mean [SD]/median [IQR] age (years) [c] Proportion (%) female	NOACs	VKAs	Main outcomes *aHR (95% CI) reported for all outcomes unless otherwise stated*		
				Stroke	Bleeding	Other
Lee [122]	[a] 5,712 [b] 72.40 [10.00] [c] 43.10	NOACs (all)	Warfarin	*HR reported after inverse probability of treatment weighting* *Ischemic stroke* NOACs vs. Warfarin **0.77 (0.61–0.97)** *Intracranial hemorrhage* NOACs vs. Warfarin **0.66 (0.47–0.92)**		*Composite (ischemic stroke and intracranial hemorrhage)* NOACs vs. Warfarin **0.73 (0.60–0.88)**
Nielsen [120]	[a] 622 [b] 76.10 [9.20] [c] 39.10	NOACs (Dab, Riva, Apix)	Warfarin	*Weighted risk ratio (95% CI) reported* *Ischemic stroke at 1 year* NOACs vs. Warfarin 0.52 (0.27–1.00) *Ischemic stroke at 3 years* NOACs vs. Warfarin 0.72 (0.44–1.17) *Intracerebral hemorrhage at 1 year* NOACs vs. Warfarin 0.72 (0.38–1.38) *Intracerebral hemorrhage at 3 years* NOACs vs. Warfarin 0.94 (0.53–1.64)		
Komen [113]	[a] Warf 1,028/NOAC 311 [b] Warf 79.62 [8.75]/NOAC 80.02 [9.12] [c] Warf 40.4/NOAC 42.40	NOACs (all)	Warfarin			*Mortality* NOACs vs. Warfarin **1.36 (1.04–1.78)**

aHR, adjusted hazard ratio; CI, confidence interval; IQR, interquartile range; NOAC, non-vitamin K antagonist oral anticoagulant; SD, standard deviation; VKA, vitamin K antagonist.
Significant results highlighted in **bold**.
*numbers reported in article as 1:1 propensity score–matched cohorts.

4. Frailty

Frailty is defined as a reduction in homeostatic reserve that leads to increased vulnerability and disproportionate changes in health in response to stressor events [124]. Frailty is often typified by advanced age, polypharmacy and dementia/cognitive impairment [106] which are addressed individually in this review. It is increasingly acknowledged that treatment decisions in older people should be guided by assessment of frailty rather than chronological age [125]. There are a variety of frailty assessment tools available for use in clinical practice. Implications on anticoagulant management approaches for stroke prevention in older people with frailty and AF must be considered; there is evidence of reduced OAC prescription in cohorts with frailty possibly due to misperception of risk [126,127].

The prevalence of AF in people who are frail has previously been reported to range from 48.2% to 75.4% [128]. A recent systematic review of 33 studies (1,187,951 participants) reported a pooled frailty prevalence of 39.7% (95% CI 29.9%-50.5%) in people with AF [129]. Meta-analyses showed an association between frail people with AF and a higher odds of all-cause death (OR 5.56, 95% CI 3.46–8.94), ischemic stroke (OR 1.59, 95% CI 1.00–2.52) and bleeding (OR 1.64, 95% CI 1.11–2.41) when compared to people without frailty [129]. This is corroborated by an observational study of 10,177 people (mean age 69.0 [SD 11.4] years, 40.3% females) with AF identified from the European Society of Cardiology and EHRA EURObservational Research Programme (EORP) atrial fibrillation general long-term registry [127]. Increasing frailty was associated with a higher risk of all-cause mortality (pre-frail HR 2.13, 95% CI 1.60–2.84 vs. frail HR 3.54, 95% CI 2.56–4.89), major adverse cardiovascular events [MACEs] (pre-frail HR 1.80, 95% CI 1.35–2.40 vs. frail HR 3.41, 95% CI 2.44–4.77) and major bleeding (pre-frail HR 2.25, 95% CI 1.32–3.85 vs. frail HR 2.87, 95% CI 1.55–5.29) [101]. This study also found that the clinical benefit of OAC in terms of reduced risk of all-cause death and MACEs was maintained across a spectrum of frailty, except in people with very high (frailty index > 0.36) or extreme frailty (frailty index > 0.44) [127]. Phase III RCTs on NOACs did not specifically examine safety or efficacy of NOAC therapy vs. warfarin in older people with AF and frailty [23–26], however, observational data supports OAC prescription in this high risk subpopulation [37,38,130,131]. The EHRA consensus document on arrhythmia management in frailty syndrome states that frailty itself should not preclude anticoagulant prescription [106]. In one study, 190 hospitalized older people (aged ≥75 years) with AF and frailty (defined using the FRESH screening instrument [132]) were stratified by anticoagulant prescription ($n = 119$, mean age [SD] 84.7 [4.8] years, 49.6% female) or non-prescription ($n = 71$, mean age [SD] 88.4 [4.6] years, 66.2% female) [130]. The risk of the composite of ischemic stroke and/or bleeding was significantly higher in frail people with AF not prescribed anticoagulation (HR 4.54, 95% CI 1.83–1.25, $p = 0.001$) [130].

In two other retrospective observational studies [38,131], frail people with AF were identified from administrative healthcare claims databases using the John Hopkins Claims-based Frailty Indicator algorithm [38,131,133]. In one study, among 36,267 frail people with AF (mean [SD] age 76.7 [9.5] years) prescribed a NOAC (dabigatran, rivaroxaban, apixaban) or phenprocoumon, NOAC use was associated with a significantly lower risk of major extracranial bleeding (HR 0.73, 95% CI 0.60–0.89) and intracerebral bleeding (HR 0.52, 95% CI 0.41–0.67) [37,38]. There was no significant difference between NOACs vs. phenprocoumon for other clinical outcomes (stroke/systemic embolism: 0.91 [0.77–1.07]; gastrointestinal bleeding: 1.09 [0.93–1.28]) [37,38]. NOAC-specific data was reported for major extracranial and gastrointestinal bleeding. Dabigatran (HR 0.53, 95% CI 0.39–0.73) and apixaban (HR 0.54, 95% CI 0.32–0.89) were associated with a significantly lower risk of major extracranial bleeding compared to phenprocoumon, and apixaban was also associated with a significantly lower risk of GI bleeding (HR 0.68, 95% CI 0.53–0.87) [37,38]. There was no significant difference between rivaroxaban and phenprocoumon in terms of major extracranial bleeding risk, but rivaroxaban was associated with a significantly higher risk of gastrointestinal bleeding (HR 1.38, 95% CI 1.16–1.64) [37,38]. In the other study, similar outcomes were reported for three 1:1 propensity score matched cohorts ($n = 1,350$ dabigatran vs. warfarin; $n = 2,635$ rivaroxaban vs. warfarin; $n = 1,392$ apixaban vs. warfarin) [131]. The median age was reported as 85 or 86 years for each cohort after matching. At two years, no significant difference between apixaban or dabigatran vs. warfarin and the risk of stroke/systemic embolism (HR 0.78, 95% CI 0.46–1.35 and 0.94, 0.60–1.45, respectively), major bleeding (HR 0.72, 95% CI 0.49–1.06 and 0.87, 0.63–1.19, respectively), intracranial bleeding (HR 0.97, 95% CI 0.28–3.33 and 0.14, 0.02–1.11, respectively) or gastrointestinal bleeding (HR 0.76, 95% CI 0.48–1.21 and 0.94, 0.66–1.35, respectively) was found [131]. Results were similar for rivaroxaban with no significant difference in the hazard of major, intracranial, or gastrointestinal bleeding when compared to warfarin. However, rivaroxaban was associated with a lower risk of stroke/systemic embolism compared to warfarin at two years (HR 0.68, 95% CI 0.49–0.95) [131]. Available data suggest apixaban may be preferable to prescribe in older people with frailty; there is most evidence in support of equivalent stroke/systemic embolism risk reduction and higher bleeding risk reduction compared to VKA (Table 2) [37,38].

The decision to switch between OAC therapy from INR-guided VKA to NOAC in older frail people should be carefully considered [134]. In an open-label RCT including 1,330 older people (mean age 83 [SD 5.1] years) with frailty (median Groningen Frailty Indicator [135] of 4), 661 were randomized to remain on INR-guided VKA and 662 switched to a NOAC chosen at the discretion of the treating physician [134]. Switching from VKA to NOAC was associated with a higher risk of major or clinically relevant non-major bleeding complications (HR 1.69, 95% CI 1.23–2.32) over a mean follow up of 344 days [134]. However, the study was not powered for the primary clinical endpoints. Individual TTR measurements were not available, but the TTR range for clinical practices taking part in the study was reported between 65.3% and 74.0% during years of study. Dosing of NOAC was in accordance with licensing in 93.4% ($n = 618$) of people [134]. Post-hoc

subgroup analyses suggested there was no significant difference in risk of major or clinically relevant non-major bleeding complications between VKA and dabigatran (HR 1.52, 95% CI 0.68–3.38) or edoxaban (HR 1.10, 95% CI 0.57–2.13), but the risk was higher with apixaban (HR 2.17, 95% CI 1.28–3.68) and rivaroxaban (HR 1.95, 95% CI 1.36–2.79) [134]. It is important to note that the EHRA NOAC practical guide highlights that there may be no benefit to OAC in people with severe frailty or where predicted life expectancy is limited [31].

Additional considerations when choosing an OAC in an older person with AF and frailty include low body weight and falls risk. Low body weight, defined as a body mass index (BMI) of <18.5 kg/m^2 [31], has been associated with an increased risk of bleeding from OAC therapy [136,137]. Dose adjustments to warfarin, dabigatran or rivaroxaban are not required in people with low body weight [45,48,71]. In people ≤60 kg, reduced doses of edoxaban (30 mg once daily) and apixaban (2.5 mg twice daily if a person is aged ≥80 years and/or has a serum creatinine ≥133 mmol/liter) should be prescribed [46,47]. In a meta-analysis of weight-specific data from NOAC RCTs [23–26], NOACs were more effective than warfarin in reducing the odds of stroke/systemic embolism (OR 0.73, 95% CI 0.56–0.97, $p = 0.03$) and no different to warfarin in terms of major bleeding risk (OR 0.62, 95% CI 0.37–1.05, $p = 0.01$) in people with low BMI [138]. When choosing between NOACs, the EHRA NOAC practical guide proposes that apixaban and edoxaban may be preferred choices in people ≤60 kg based on results of sub-analyses of phase III trials (Table 2) [31,52,53]. It recommends plasma level measurements are considered for people on rivaroxaban or dabigatran [31]. Plasma level monitoring may also be warranted for all NOACs prescribed in people <50 kg to check for drug accumulation [31].

Falls are common in older people with frailty and AF; a falls risk assessment should be considered in the context of polypharmacy to identify medications that increase the risk of falls and bleeding with de-prescribing as appropriate. Other modifiable bleeding risk factors such as uncontrolled hypertension and excessive alcohol intake should also be identified and addressed where possible. Falls risk can be minimized with home modifications and the provision of walking aids. Falls are not an independent predictor of OAC-related bleeding [106]. The risk of severe bleeding from falls does not outweigh the benefit of stroke risk reduction in older people with AF [31,106]. Falling should not be a barrier to OAC prescription. In people with high falls risk, NOACs are preferable owing to their lower relative risk of intracranial hemorrhage (0.48, 95% CI 0.39–0.59, $p < 0.0001$) [27]. Observational data supports this; from 162 people older people aged >65 years hospitalized with traumatic intracranial hemorrhage whilst on OAC ($n =$ 101 on warfarin, $n = 61$ on NOAC), NOAC use was associated with lower mortality (4.9% vs. 20.8%, $p < 0.008$) and operative intervention (8.2% vs. 26.7%, $p = 0.023$) compared to warfarin [139]. In another study, data were collected on 1,365 people aged ≥65 years presenting to hospital with head trauma on antithrombotic therapy. Those receiving NOAC had lower rates of intracranial hemorrhage progression (9.1% vs. 29.6%) and functional dependence (classified as Glasgow Outcome Scale-Extended [140] [GOSE] ≤4) at discharge (25% vs. 46.8%) compared to those on warfarin [141]. Sub analyses of edoxaban and apixaban RCTs have verified their use in people at risk of falls [54,55]. There was no significant difference in major bleeding (HR 0.81, 95% CI 0.48–1.36) or hemorrhagic stroke (HR 0.32, 95% CI 0.03–3.09) risk in people with a history of falls within one year prescribed apixaban ($n = 386$) vs. warfarin ($n =$ 367), and the risk of intracranial bleeding was lower in apixaban users (HR 0.19, 95% CI 0.04–0.88) [54]. Edoxaban had a lower risk of intracranial hemorrhage (aHR 0.16, 95% CI 0.04–0.71) and life-threatening bleeding (aHR 0.32, 95% CI 0.10–0.98) compared to VKA in people at increased falls risk (Table 2) [55]. The availability of NOAC reversal agents, idarucizumab which reverses dabigatran, and andexanet which reverses edoxaban [unlicensed, subject to local prescribing guidance], rivaroxaban and apixaban is also reassuring when prescribing in older people at risk of falling.

5. Polypharmacy

Polypharmacy, most commonly defined as prescription of five or more medications [142], must be considered when prescribing OACs for stroke prevention in older people with AF. The prevalence of polypharmacy has been reported to be as high as 95% in this cohort [143], and is associated with a higher risk of adverse events including all-cause mortality (HR 1.36, 95% CI 1.20–1.54, $p < 0.001$) and major bleeding (HR 1.32, 95% CI 1.14–1.52, $p < 0.001$) [144]. In accordance with the Atrial fibrillation Better Care pathway, pharmacotherapy is the cornerstone of AF management to reduce stroke risk, control AF symptoms and optimize management of cardiovascular and related co-morbidities [13,145]. This presents the difficult challenge of person-centered medicines optimization to include prescription and de-prescription of medications to improve health outcomes, mitigate the risk of medication-related adverse effects and empower people to independently manage their complex treatment regimens and persist with therapy.

Anticoagulants are high-risk medications that can have catastrophic consequences such as stroke and major bleeding in the event of drug interactions. As previously highlighted, the risk of GI bleeding is higher with NOAC therapy compared to VKA [27]. Proton pump inhibitors may be considered to reduce this risk in people at advanced age, taking other medications that increase their risk of bleeding, or with a history of GI bleeding or ulcer [31].

Pharmacodynamic drug interactions common to both VKA and NOAC arise from concomitant prescription of drugs that also increase bleeding risk, such as antiplatelets, selective serotonin re-uptake inhibitors and non-steroidal anti-inflammatory drugs [28,45–48,71]. Warfarin, apixaban, edoxaban and rivaroxaban are subject to pharmacokinetic interactions with drugs known to induce or inhibit Cytochrome P450 enzymes (warfarin: CYP3A4, CYP1A2, CYP2C9; apixaban: CYP3A4; rivaroxaban: CYP3A4, CYP2J2; edoxaban: CYP3A4, CYP3A5) [45–47,71]. All NOACs rely on P-glycoprotein (P-gp) mediated renal clearance and gastrointestinal re-secretion, so it is important to be mindful of the prescription of other drugs capable of inhibiting or inducing P-gp [45–48]. There are substantially more drug-drug and drug-food interactions

with VKA compared to NOACs. Manufacturer's documentation for individual drugs can be accessed via the Electronic Medicines Compendium [146]. This provides information on the mechanism of drug metabolism/excretion and any inhibition/induction of CYP450 enzymes and P-gp. The EHRA NOAC Practical guide also contains a comprehensive list of possible drug interactions with NOACs and in-depth practical advice on how to manage them [31]. Medications that increase falls risk should also be reviewed to prevent falls that could result in a bleed. These include psychotropic drugs such as sedatives, hypnotics, antipsychotics and antidepressants, in addition to cardiovascular drugs including antihypertensives and diuretics [147]. Medication reviews should be person-centered and may require multidisciplinary discussions with different specialties and further consultation with the person's family/friends.

6. Conclusions

Oral anticoagulants are fundamental for stroke prevention in older people with AF, and NOACs should be prescribed first-line in those eligible, including people with CKD, dementia/cognitive impairment, prior history of stroke/TIA or intracranial hemorrhage, polypharmacy, frailty, low body weight and high falls risk. Older people with AF are at a higher risk of adverse health outcomes, therefore regular re-assessment of stroke and bleeding risk is required as these are on a continuum and change temporally [148]. There are inconsistencies in results from randomized and observational studies on NOAC prescription in high-risk older adult sub-populations to guide treatment choice, and head-to-head comparisons of NOACs are lacking. A methodical approach to decision making is recommended. Firstly, contraindications to NOAC therapy should be ruled out. Choice of NOAC should be guided by individual risk assessment with consideration of practical aspects of administration, incorporating individual preference. In all cases, processes of shared decision making should be followed.

7. Expert opinion

With population growth and aging, older people with AF and those in high-risk subgroups will increase exponentially. Complex decision making about OAC prescription will be a scenario increasingly encountered by clinicians. This review complements another published review paper [107] and a systemic review and meta-analysis on the effectiveness and safety of OACs in older people with AF [37]. Available data on measures of NNT_{net} and NCB for OAC therapy support their use in older people [18–20]. In older people who are eligible for OAC therapy, NOACs should be considered first-line for stroke prevention in preference to VKA provided there are no absolute contraindications to treatment (e.g. mechanical valve or moderate-severe mitral stenosis) [28]. All NOACs are licensed to be prescribed in older adults with AF. The risk benefit profile of apixaban vs. VKA in people with frailty, low body weight, at high falls risk and advanced age (≥75 years) also appears more favorable than the other NOACs where data was available to compare. Research gaps are most prominent in older people with frailty. Readers are urged to interpret this evidence cautiously and apply it in the context of local prescribing guidelines and the person's individual risk profile and associated socio-demographic factors. Most importantly, NOAC choice should be guided by an individual's preference, and practical considerations regarding monitoring and administration must be considered.

The decision whether to prescribe OAC therapy or not, and if so which OAC to prescribe, involves a complex shared decision-making process and must be based on what outcomes are important to the person with AF. Healthcare professionals must be able to effectively communicate the risks associated with treatment/no treatment, as well as the available evidence base and practical considerations for individual OACs so people can be empowered to articulate their priorities and choose the most appropriate therapy for them. If an individual does not have capacity, conversations should be held with their next of kin or Power of Attorney for Health. Poor patient health literacy including their understanding of AF and the rationale for OAC prescription has been highlighted by research, and structured support from healthcare professionals, carers or family were identified by people with AF as important for optimization and adherence to OAC therapy [17]. This reiterates the need for healthcare professionals to provide high quality education in a standardized way to prevent inequity in care.

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