Thrombosis Research 238 (2024) 1–10

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Oral anticoagulant therapy in older adults

J. Stuby [a,*], M. Haschke [a,b], T. Tritschler [a], D. Aujesky [a]

[a] Department of General Internal Medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland
[b] Clinical Pharmacology & Toxicology, Department of General Internal Medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland

ARTICLE INFO

Keywords:
Atrial fibrillation
Venous thromboembolism
Anticoagulants
Older patients

ABSTRACT

Patients aged ≥65 years not only account for the majority of patients with atrial fibrillation (AF) and venous thromboembolism (VTE), they are also at a higher risk of morbidity, mortality, and undertreatment than younger patients. Several age-related physiological changes with effects on drug pharmacokinetics/−dynamics and blood vessel fragility as well as the higher prevalence of geriatric conditions such as frailty, multimorbidity, polypharmacy, fall risk, dementia, and malnutrition make older persons more vulnerable to disease- and anticoagulation-related complications. Moreover, because older patients with AF/VTE are underrepresented in oral anticoagulation (OAC) trials, evidence on OAC in older adults with AF/VTE is mainly based on subgroup analyses from clinical trials and observational studies. A growing body of such limited evidence suggests that direct oral anticoagulants (DOACs) may be superior in terms of efficacy and safety compared to vitamin K antagonists in older persons with AF/VTE and that specific DOACs may have a differing risk-benefit profile. In this narrative review, we summarize the evidence on epidemiology of AF/VTE, impact of age-related physiological changes, efficacy/safety of OAC, specifically considering individuals with common geriatric conditions, and review OAC guideline recommendations for older adults with AF/VTE. We also propose a research agenda to improve the evidence basis on OAC older individuals with AF/VTE, including the conduct of advanced age-specific and pragmatic studies using less restrictive eligibility criteria and patient-reported health outcomes, in order to compare the effectiveness and safety of different DOACs, and investigate lower-dose regimens and optimal OAC durations in older patients.

1. Epidemiology

About one of six persons aged ≥65 years is treated with oral anticoagulants (OACs) [1]. The most common reasons for OAC therapy are atrial fibrillation (AF) and venous thromboembolism (VTE), which represent almost 90 % of indications for OAC [2]. The incidence of both new AF and VTE increases with age, probably due to structural fibrotic changes in the atria induced by age-related cardiomyocyte loss and the exposure to comorbidities on one hand [3], and age-related endothelial dysfunction, venous stasis, and hypercoagulability on the other [4]. About 85 % of patients with AF and two-thirds of those with VTE are aged ≥65 years [5,6].

Older patients with AF and VTE have a worse prognosis compared to their younger counterparts [7,8]. The incidence of ischemic stroke/systemic embolism (SSE) increases from 0.75 events/100 patient-years in patients with AF aged <65 years to 2.2 events/100 patient-years in those aged ≥75 years [7]. Patients with AF aged ≥65 years have a 1.4-fold increased risk for OAC-related major bleeding (MB) [9], and those aged ≥80 years an approximately 2-fold increased risk for intracranial hemorrhage (ICH) compared to younger patients [10]. Similarly, patients with VTE aged ≥65 years and those aged ≥80 years carry an about 2-fold higher risk of MB and fatal bleeding, respectively [8,11]. The initiation of OAC within 12 months of AF diagnosis in persons aged ≥65 years has increased from 20 % to 33 % between 2010 and 2020 following the introduction of safer and easy-to-use DOACs [12]. However, older age, frailty, multimorbidity, falls/fall risk, and cognitive impairment/dementia are common reasons for OAC non-initiation/discontinuation, and OAC use remains suboptimal in older adults with AF and VTE [12–14].

2. Age-related physiologic changes

Age is characterized by several physiological organ changes, which may impact pharmacokinetics/−dynamics of OACs (Table 1). Skeletal muscle mass, reflected by the total body weight, decreases with age, with a reduction in total body water content by 10–15 % until the age of

* Corresponding author at: Inselspital Bern, Freiburgstrasse 18, 3010 Bern, Switzerland.
E-mail address: johann.stuby@insel.ch (J. Stuby).

https://doi.org/10.1016/j.thromres.2024.04.009
Received 13 December 2023; Received in revised form 6 March 2024; Accepted 11 April 2024
Available online 14 April 2024

Table 1
Age-related physiologic changes/geriatric conditions with potential impact on OAC or outcomes in older adults.

Age-related physiologic changes	Potential impact on OAC or outcomes
Decrease in skeletal muscle mass and total body water by 10–15 % until age of 80 years	• Increased plasma concentrations of apixaban and edoxaban if body weight is low (<50–60 kg) • Increased risk of MB with edoxaban if body weight is ≤60 kg • Decreased hepatic clearance of warfarin
Decline in glomerular filtration rate by 25–50 % from ages 20 to 90 years	• Increased plasma concentrations of dabigatran > edoxaban > rivaroxaban > apixaban, especially if CrCl <30 ml/min
Decrease in liver size by 25–35 % and blood flow by 40 % in old age	• Effect on DOAC plasma concentrations negligible if less than moderate (rivaroxaban) or severe hepatic dysfunction (apixaban, edoxaban, dabigatran) • Reduced warfarin clearance
Reduced activity of the vitamin K redox recycling system	• Increased warfarin sensitivity with about 20 % lower warfarin dose requirements
Increased prevalence of cerebral leukoaraiosis, amyloid angiopathy, and cerebral atrophy	• Increased risk of ICH
Increased prevalence of diverticular and peptic ulcer disease	• Increased risk of gastrointestinal bleeding

Geriatric conditions	Potential impact on OAC or outcomes
Frailty	• Increased risk of thromboembolic events, MB, and overall mortality in patients
Multimorbidity	• Decrease in OAC control • Increased risk of SSE, MB, and overall mortality in patients with AF • Increased risk of recurrent VTE and MB in patients with VTE
Polypharmacy	• Decrease in OAC control • Increased risk of drug-drug interactions (e.g., with antiplatelet agents) • Increased risk of SSE, MB, and overall mortality in patients with AF • Increase of risk of MB in patients with VTE
Fall risk	• Small increase in absolute risk of fall-related bleeding (controversial)
Cognitive impairment/ dementia	• Decrease in OAC adherence/control • OAC may reduce risk of cognitive impairment/ dementia in patients with AF • Increased risk of fatal pulmonary embolism and significant bleeding in patients with VTE
Malnutrition	• Increased risk of SSE, MB, and overall mortality in patients with AF

Abbreviations: AF, atrial fibrillation; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; ICH, intracranial hemorrhage; MB, major bleeding; OAC, oral anticoagulation; SSE, stroke/systemic embolism; VTE, venous thromboembolism.

80 years and a relative increase of body fat [15]. DOACs are hydrophilic drugs and their volume distribution may decrease and their plasma concentration increase as muscle mass declines [16]. A body weight below <50–60 kg in healthy volunteers or patients with AF seems to result in up to 27 % higher apixaban [17,18] and 40 % higher edoxaban plasma levels [19,20], while the impact on rivaroxaban and dabigatran levels appears clinically negligible [21–24]. A phase II study in patients with AF treated with edoxaban showed a statistically significantly increased bleeding risk in patients weighing ≤60 kg vs. >60 kg [25]. Thus, a body weight ≤ 60 kg is a dose reduction criterion for apixaban and edoxaban [17,19]. Body weight is also independently associated with warfarin clearance [26].

All DOACs are to varying degrees renally eliminated (dagibatran >80 %, edoxaban 50 %, rivaroxaban 33 %, apixaban 25 %) [27]. Rivaroxaban and apixaban are also metabolized by cytochrome P450 (CYP) 3A4 enzymes in the liver/gut [27], whereas VKAs are primarily metabolized by CYP2C9 (warfarin, acenocoumarol) or CYP2C9/3A4 (phenprocoumon) (Table 2) [28]. The glomerular filtration rate declines by 25–50 % from the ages of 20 to 90, due to progressive glomerulosclerosis [15]. There is ample evidence that kidney function predicts DOAC exposure in older adults [29]. Severe renal impairment, defined as a creatinine clearance (CrCl) <30 ml/min, is associated with increased DOAC plasma levels, ranging from +44 % for apixaban to about +500 % for dabigatran, corresponding to their extent of renal elimination [17,19,21,23]. Thus, all DOACs have dose reductions based on renal function or are contraindicated below a given CrCl threshold (Table 2).

Liver size decreases by 25–35 % and liver blood flow by about 40 % in old age [15], leading to a reduction in first-pass and oxidative phase I metabolism [30]. As the pharmacokinetics of DOACs, except for rivaroxaban, are not affected in patients with moderate hepatic impairment [31], an age-related decrease in liver function is unlikely to be clinically relevant. Hepatic warfarin clearance may also decline with age [32].

Because older persons are more likely to have comorbid conditions, including renal and hepatic diseases, as well as polypharmacy [33,34], determining whether age-related physiologic changes per se increase OAC drug levels is challenging. Phase I studies in healthy volunteers indicate that exposure to rivaroxaban (+41 %) [27], apixaban (+32 %) [35], and dabigatran (+40–60 %) [36] is higher in healthy older adults than in the young, which was attributed to the age-related reduction in renal function. After accounting for renal function, age has no independent effect on edoxaban exposure in healthy volunteers [37]. Evidence from the RE-LY AF trials shows that patients aged ≥75 years have a 68 % higher trough dabigatran concentration than those aged <65 years, and that dabigatran exposure is significantly associated with bleeding risk [38].

It is well known that the sensitivity to warfarin increases with age, possibly due to a reduced activity of the vitamin K redox recycling system in older individuals [39]. Thus, individuals aged >70 years have about 20 % lower warfarin dose requirements to achieve an international normalized ratio (INR) in the therapeutic range than those aged <50 years [40]. In patients who are aged >70 years, the often-suggested warfarin initiation dose of 5 mg/d may be excessive for 82 % of women and 65 % of men [41].

Age-related tissue and blood vessel changes may also result in an increased fragility/vulnerability and a greater risk of bleeding in older adults. The prevalence of cerebral leukoaraiosis, amyloid angiopathy, and cerebral atrophy rises with age and is associated with an increased risk of spontaneous and traumatic ICH, including subdural hematoma [12,42]. Reduced colonic motility and changes in the colonic wall may lead to diverticular disease, while a higher prevalence of *H. pylori* infections with subsequent atrophic changes in the gastric mucosa may result in peptic ulcer disease – both common sources of gastrointestinal bleeding in older individuals [12,43,44].

3. OACs in older patients

DOACs are the recommended first-line therapy for AF/VTE, while VKAs are considered as the treatment of choice for specific indications, including mechanical heart valves, moderate/severe mitral stenosis, end-stage renal failure, and the antiphospholipid antibody syndrome [45–47]. Older patients are overproportionally excluded from OAC trials due to co-morbidities, co-medications, or simply advanced age, and such excluded patients have an increased MB risk [48,49]. In a cohort of 993 patients aged ≥65 years with acute VTE, 25 % would have been excluded from key VKA trials and 43 % from key DOAC trials [49]. Similarly, when applying the eligibility criteria of key AF trials to 83,898 patients representative of the AF population in the UK, 32–49 % would have been excluded from study participation [50]. In pivotal phase III trials evaluating DOACs for acute or extended VTE treatment, the proportion of patients aged >75 years was only 9–16 % [27], whereas it

Table 2
Dose adjustment for DOACs and VKAs for treatment of AF and acute VTE.

	Apixaban	Edoxaban	Dabigatran	Rivaroxaban	VKAs
Pharmakokinetics					
Half-life, hours	8–15	9–14	12–14[2]	9-13	8-160[6]
Metabolism/ transport	CYP3A4/P-pg	Minimal (CYP3A4)/P-gp	Glucuronidation (to active metabolites)/P-gp	CYP3A4/P-pg	CYP2C9/ 3A4
Renal elimination, %	25	50	>80	33	0
AF					
Standard dose	2 × 5 mg	1 × 60 mg	2 × 150 mg	1 × 20 mg	INR 2–3
Reduced dose	2 × 2.5 mg	1 × 30 mg	2 × 110 mg	1 × 15 mg	INR 2–3
Indications for reduction	If ≥2 of the following: • Age ≥ 80 years • Body weight ≤ 60 kg • Serum creatinine ≥133 μmol/l	If ≥1 of the following: • CrCl 15–50 ml/min • Body weight ≤ 60 kg • Concomitant use of potent P-gp inhibitor[1]	If ≥1 of the following:[3] • CrCl 30–50 ml/min • Age ≥ 80 years • Concomitant use of moderate P-gp inhibitor[4] • Increased bleeding risk	If CrCl 15–50 ml/min	–
Acute VTE					
Standard dose	First 7 days: 2 × 10 mg After: 2 × 5 mg	First 5 days: LMWH After: 1 × 60 mg	First 5 days: LMWH After: 2 × 150 mg	First 3 weeks: 2 × 15 mg After: 1 × 20 mg	INR 2–3
Reduced dose	None	1 × 30 mg	None[5]	None	INR 2–3
Indications for reduction	–	If ≥1 of the following: • CrCl 15–50 ml/min • Body weight ≤ 60 kg • Concomitant use of potent P-gp inhibitor[1]	–	–	–

Abbreviations: AF, atrial fibrillation; CrCl, creatinine clearance; INR, international normalized ratio; LMWH, low-molecular-weight heparin; P-gp, P-glycoprotein; VKAs, vitamin K antagonists; VTE, venous thromboembolism.

[1] Potent P-gp inhibitors: e.g., cyclosporine, dronedarone, erythromycin, ketoconazole.

[2] CrCl <30 ml/min: 28 h.

[3] United States: 2 × 75 mg if CrCl 15–30 ml/min.

[4] Moderate P-gp inhibitors: e.g., amiodarone, quinidine, verapamil.

[5] Some countries (e.g., Switzerland, Canada) recommend dose reduction: 2 × 110 mg if age ≥ 80 years or if at higher risk of bleeding (age ≥ 75 years with ≥1 risk factor for bleeding).

[6] Acenocoumarol: 8–11 h, phenprocoumon: 110–160 h, warfarin: 25–60 h.

varied from 35 to 40 % in AF trials [51]. Thus, older patients are underrepresented in guideline-defining OAC trials, the results of which may not necessarily be generalizable to the older adults.

3.1. Atrial fibrillation

The evidence for the efficacy/safety of DOACs vs. VKAs in older patients with AF relies mostly on subgroup analyses from randomized-controlled trials (RCTs) and observational studies (OSs) that were not specifically designed to investigate outcomes in older persons [52]. Thus, the results must be interpreted with caution. To decrease the threat to internal validity posed by lack of power and confounding, meta-analyses of RCT subgroups and adjusted risk estimates from OSs may be the best method to study the effect of DOACs vs. VKAs in older patients with AF. One of the most recent and largest study-level meta-analysis of 5 RCT subgroups and 27 high-quality OSs using nationwide databases and adjusted/matched data included 547,419 patients aged ≥75 years with AF [53]. Compared to VKAs, DOACs reduced the risk of SSE (OSs: HR 0.87, 95%CI 0.81–0.94; RCTs: RR 0.82, 95%CI 0.67–0.96), ICH (OSs: 0.47, 95%CI 0.37–0.57; RCTs: 0.47, 95%CI, 0.31–0.63), and to a lesser degree MB (OSs: 0.87, 95%CI 0.77–0.98; RCTs: 0.89, 95%CI 0.66–1.12). In another meta-analysis including 22 RCTs/OSs enrolling 440,281 AF patients aged ≥75 years, DOACs were associated with a lower risk of SSE (HR 0.79, 95%CI 0.70–0.89) and ICH (HR 0.46, 95%CI 0.38–0.58) compared to VKAs, whereas no differences were found for overall MB (HR 0.94, 95%CI 0.85–1.05) [54]. A recent study-level meta-analysis of 11 RCT subgroups found that older patients with AF treated with DOACs may also potentially have a lower mortality risk than those treated with VKAs (HR 0.89, 95%CI 0.77–1.02) [55].

Because head-to-head comparisons of different DOACs are lacking, several study-level network meta-analyses have indirectly compared the efficacy/safety of individual DOACs in patients aged ≥75 years with AF [56–59]. In general, efficacy in terms of SSE prevention was comparable across DOACs [56–58], but both apixaban and edoxaban were associated with a lower risk of MB compared to dabigatran (both doses) and rivaroxaban, with a comparable MB risk observed between edoxaban and dabigatran 110 mg [56,58,60]. No significant differences in MB were shown between apixaban and edoxaban or between dabigatran and rivaroxaban [56,58–60]. Apixaban ranked best among the various DOACs in terms of safety and either first or second in terms of efficacy in three network meta-analyses [56,58,59]. In the ELDERCARE-AF trial that compared a once-daily dose of 15 mg of edoxaban vs. placebo in 984 patients aged ≥80 years with AF who would not have qualified for standard OAC (i.e., CrCl 15–30 ml/min., history of MB, low body weight ≤ 45 kg, concomitant antiplatelet therapy, etc.), low-dose edoxaban was associated with a significant 66 % risk reduction in SSE and a 87 % (albeit statistically not significant) risk increase in MB [61], a benefit that was also maintained in frail patients [62]. In a network meta-analysis of patients aged ≥80 years with AF, edoxaban and apixaban ranked first and second, respectively, in terms of net clinical benefit among the various DOACs [63].

Unexpectedly, the recent FRAIL-AF trial showed that switching from VKAs to DOACs in frail older patients with AF resulted in more clinically relevant bleedings (HR 1.69, 95%CI 1.23–2.32) without reducing embolic events (HR 1.26, 95%CI 0.60–2.61) [64]. Hence, for older adults with AF who have been on long-term VKA treatment, it may be

reasonable to consider its continuation, particularly among those with well-controlled INRs (i.e., >70 % time in the therapeutic range) and no adverse effects [65].

3.2. Venous thromboembolism

There are no RCTs designed to compare the efficacy/safety of DOACs vs. VKAs or specific DOACs in older patients with acute VTE, and the best available evidence mainly relies on subgroup analyses of RCTs and OSs [66–69]. In a study-level meta-analysis of six phase III trials, the subgroup of patients aged ≥75 years treated with DOACs had a lower risk of recurrent VTE than those treated with VKAs (RR 0.56, 95%CI 0.38–0.82), a result not observed in patients below the age of 75 years [66]. DOACs were also associated with a lower risk of MB than VKAs in patients aged ≥75 years (RR 0.49, 95%CI 0.25–0.96), just as they were in younger patients [66]. Two large population-based OSs showed similar efficacy/safety profiles of DOACs vs. VKAs in older patients with acute VTE [68]. Whether older patients with cancer-related VTE benefit from DOAC treatment is currently unclear. In a nationwide OS with propensity matching, DOACs were associated with a somewhat lower risk of recurrent VTE requiring hospitalization than warfarin, with similar risks of MB and mortality in cancer patients aged ≥75 years during chemotherapy [70]. In subgroup analyses of RCTs, apixaban or edoxaban did not offer any clinical benefits over dalteparin in patients aged ≥65 years with cancer-associated VTE [71,72]. In a study-level network meta-analysis of RCTs comparing rivaroxaban, apixaban, and edoxaban in the subgroup of patients aged ≥75 years with acute VTE, all DOACs were similarly effective, but edoxaban showed a higher risk for clinically relevant bleeding than rivaroxaban and apixaban [57].

In VTE extended treatment trials comparing DOACs with placebo, aspirin, or reduced DOAC doses, patients aged >75 years treated with DOACs usually had significantly lower VTE recurrence rates when compared with placebo but not compared with active controls (aspirin or reduced DOAC dose) [27]. Bleeding risks did not differ significantly by treatment arm in older patients. In one large population-based OS, apixaban was associated with a lower bleeding risk compared to warfarin during extended OAC in older patients with VTE but in another this was not the case [67,69].

Determining the optimal treatment duration for older patients remains a challenge, with a delicate balance between the risk of bleeding and recurrent VTE both during and after OAC therapy. While the risk of MB was consistently demonstrated to be higher in older individuals, it remains controversial whether the risk of recurrent VTE after discontinuing OAC is also elevated in older patients [27]. A cost-utility analysis showed that a 3-month OAC duration with warfarin was less costly and more effective than longer-duration strategies in patients aged ≥80 years with unprovoked VTE, but the results were influenced by the risk of MB (which is lower for DOACs) [73]. Many clinical bleeding risk scores (HEMORR2HAGES, ATRIA, HAS-BLED, OBRI, Kuijer, ACCP, VTE-Bleed, Seiler) do not perform well in older patients with AF/VTE, with the areas under the receiver operating characteristic curve for MB varying between 0.47 and 0.70 [74,75]. Clinical prediction rules developed to identify patients with unprovoked VTE who may not require extended OAC have either not been specifically validated in older adults (Men continue and HERDOO2) or lack discriminative power in older patients (updated Vienna Prediction Model) [76]. Current guidelines do not provide age-specific recommendations for OAC duration, but they indirectly consider age by advising against extended OAC in individuals with unprovoked VTE who are at a high risk of bleeding [46,77,78].

In summary, limited evidence indicates that DOACs as a drug class appear to be more effective and safer than VKAs for treating both AF and acute VTE in older persons. Even more limited data suggest that apixaban and edoxaban might have a better risk-benefit profile than rivaroxaban or dabigatran in older adults.

4. OAC in common geriatric conditions

Several common geriatric conditions, including frailty, multimorbidity, polypharmacy, fall risk, cognitive impairment/dementia, and malnutrition are associated with a worse prognosis in older persons with AF or VTE (Table 1). Evidence on OACs for treating AF/VTE in patients with such geriatric conditions is essentially based on subgroup analyses from RCTs and OSs and must be cautiously interpreted.

4.1. Frailty

About one in ten persons aged ≥65 years suffers from *frailty* [79], defined as "a clinically recognizable state of increased vulnerability resulting from aging-associated decline in reserve and function across multiple physiologic systems" [79]. Its clinical phenotype is characterized by weight loss, muscular weakness, and a low physical activity [80,81]. Some degree of frailty is very common in older adults with AF (up to 80 %, depending on the definition) or acute VTE (about 60 %) and is associated with an increased risk of OAC-related bleeding and mortality in patients with AF/VTE [81–83].

In a post-hoc analysis of the ENGAGE AF-TIMI 48 RCT [84], edoxaban was associated with similar efficacy to warfarin in every frailty category, and a lower risk of bleeding than warfarin in all but those with severe frailty. In a meta-analysis of patients with AF, frail individuals had an about 1.5-fold higher risk of stroke and MB, and an about 6-fold higher risk of overall mortality compared to non-frail individuals [85]. A low physical activity level is associated with a 2-fold increased risk of MB in patients aged ≥65 years with acute VTE [86]. Frailty also negatively affects OAC prescription/maintenance in AF [87]. In an OS using nationwide data from 71,638 anticoagulated frail patients with AF, DOACs, particularly apixaban followed by edoxaban, had better benefit-risk profiles than VKAs [88]. Another OS including 653,412 Medicare beneficiaries with AF who initiated use of dabigatran, rivaroxaban, apixaban, or warfarin, suggested that only apixaban was associated with lower rates of a composite endpoint of death, ischemic stroke, or MB among frail patients compared to warfarin (HR 0.73, 95%CI 0.67–0.80) [89]. Based on US MarketScan claims data from 10,754 frail patients with AF, rivaroxaban (HR 0.68, 95%CI 0.49–0.95), but not apixaban or dabigatran, was associated with a reduced risk of SSE, with similar MB risks compared to warfarin [90]. Other OSs suggest that specific DOACs may be more effective (rivaroxaban, apixaban) and safer (apixaban) than warfarin for preventing recurrent VTE [91,92].

Almost no studies evaluated patient-reported outcomes, such as home time, health-related quality of life, and function. In an OS of 136,551 Medicare beneficiaries with AF, apixaban was associated with increased home time and lower rates of clinical events than rivaroxaban or warfarin, especially in those with frailty [93].

4.2. Multimorbidity

The prevalence of multimorbidity, defined as the presence of at least two chronic morbidities, rises with age [33], and about 3 out of 4 patients aged ≥65 years with AF or acute VTE are multimorbid [94,95]. Many of these morbidities represent risk factors for AF-/VTE-related complications as well as bleeding [75,96–98]. The most common clinical risk factors for bleeding in AF/VTE include older age, active cancer, anemia, thrombocytopenia, renal impairment, history of prior bleeding, (uncontrolled) hypertension, and cerebrovascular disease [75,96–98].

In multimorbid older patients with AF, the number of comorbidities is inversely associated with the time spent in the therapeutic INR range [99]. Moreover, multimorbid older patients with AF have an about 2.5-fold increased risk of SSE and MB and an about 2-fold higher risk of death than those without multimorbidity [94,99]. Similarly, multimorbidity is associated with a decreased OAC quality and an about 1.5-fold increased risk of recurrence and MB in older patients with VTE [95].

In an OS using propensity-matched insurance claims data from

155,959 multimorbid patients with AF, apixaban and rivaroxaban were associated with a lower risk of SSE compared to warfarin (−37 % and −30 %, respectively) [100]. Apixaban (−39 %) and dabigatran (−25 %) were also associated with a lower risk of MB. In another propensity-matched OS using data from 85,365 multimorbid Medicare recipients with AF, apixaban (−37 %) and rivaroxaban (−30 %) were associated with a lower risk of SSE than warfarin. Apixaban was associated with a lower risk of SSE and MB than dabigatran or rivaroxaban [101].

4.3. Polypharmacy

Polypharmacy, defined as the use of ≥5 medications [102], is present in about a third of patients aged ≥65 years with AF and in about half of patients with acute VTE [94,103,104]. Older patients with polypharmacy who are treated with VKAs spend less time in the therapeutic INR range than those without polypharmacy [103,105]. In individuals aged ≥65 years with AF/VTE, polypharmacy is associated with an about 1.3- to 1.8-fold increased risk of MB [103,104,106], and with an increased risk of SSE and overall mortality in patients with AF [104,106]. Possible underlying mechanisms are pharmacological interactions, its association with multimorbidity, and falls [103,104]. Drug-drug interactions are responsible for around 60 % of hemorrhagic adverse drug events in older patients treated with OACs [107]. One of the most common and potentially reversible interaction in older patients is the additive bleeding risk of antiplatelet therapy and nonsteroidal anti-inflammatory drugs [108]. About one third of older patients anticoagulated for AF/acute VTE receive concomitant antiplatelet treatment [109]. The combination of DOACs or warfarin with antiplatelet therapy results in an about 1.5- to 4-fold increased risk of MB in patients with AF/VTE [109–111].

In a study-level meta-analysis of 12 studies (9 OS, 3 subgroups from RCTs) including 767,544 patients and a nationwide OS including 167,847 patients with AF and polypharmacy, use of DOACs was associated with an about 20–30 % reduced risk of SSE and ICH compared to VKAs, with a less marked reduction in MB [106,112]. Between-DOAC comparisons indicated the lowest MB risk with apixaban [106]. In subgroup analyses from the Hokusai-VTE (edoxaban) and EINSTEIN-VTE (rivaroxaban) trials, clinically relevant bleeding rates did not differ between DOAC and warfarin in patients with polypharmacy [113,114].

4.4. Fall risk

About half of patients aged ≥65 years with AF/acute VTE have an increased risk of falls [115,116], and the presence of AF itself may increase the fall risk [117]. Falls and the fear of fall-related bleeding are the most common reason to refrain from OAC [74,118]. However, whether falls (or minor head injury) convey a higher risk of MB and ICH in anticoagulated older patients remains controversial [74,115,119–123], and the increase in the absolute risk of fall-related bleeding is small [124]. Consequently, the risk of falls is included only in two bleeding risk scores, the HEMORR2HAGES and the ACCP score [75]. Overall, in patients with AF, the risk of SSE and the benefit from OAC appears to outweigh the risk of bleeding in patients with a high fall risk [124,125], and falls should only rarely be a contraindication to OAC [126]. According to the 2016 ACCP guidelines [78], patients aged >65 years with VTE with frequent falls have a high risk of bleeding and may not be candidates for extended OAC (>3 months).

In a study-level meta-analysis of 10 studies (5 OS, 5 subgroups from RCTs) of patients with AF who were at risk of falls, DOACs were significantly more effective in preventing SSE (−18 %) and safer regarding ICH (−47 %) than VKAs [127]. In a nationwide OS including 18,947 patients with AF at risk of falls, DOACs were associated with a lower risk of SSE (−30 %) and mortality (−17 %) than warfarin, with comparable bleeding risks [128]. Apixaban was associated with a lower MB risk than the other DOACs. In a retrospective cohort, falls resulted in −30 % bleeding complications and − 40 % ICH in patients under DOACs compared to VKAs [129].

4.5. Cognitive impairment/dementia

About a third of patients aged ≥65 years with AF suffer from cognitive impairment/dementia [116]. Evidence indicates that AF is a risk factor for developing cognitive impairment/dementia independent of clinical stroke, possibly due to cerebral microinfarctions [130]. While OAC use and higher OAC quality appear to decrease the risk of dementia in older patients with AF [131], those with dementia treated with warfarin have a poorer OAC control [132]. Dementia itself may also negatively impact patient OAC adherence in AF [133], which may deteriorate patient outcomes [134]. In patients with VTE, dementia is associated with an increased risk of fatal pulmonary embolism and significant bleeding [135,136].

In a large OS assessing the comparative effectiveness and safety of specific OACs in 1,160,462 propensity score-matched patients aged ≥65 years with or without dementia, those with dementia using warfarin (HR 1.5, 95%CI 1.3–1.7), dabigatran (HR 1.5, 95%CI 1.2–2.0), and rivaroxaban (HR 1.3, 95%CI 1.1–1.5) showed a higher risk of a composite endpoint of stroke or MB compared to apixaban users [137]. In a study-level meta-analysis of five OS including 21,962 patients with AF and dementia, DOAC therapy was associated with a lower risk of all-cause mortality (HR 0.79, 95%CI 0.68–0.92) compared to warfarin, without significant differences in the risk for ischemic stroke or MB [138]. A nationwide OS including 237,012 persons with AF suggested that DOACs, especially apixaban and edoxaban, may have a protective effect on the development of dementia compared to VKAs (HR 0.91, 95%CI 0.85–0.98) [139].

4.6. Malnutrition

Older adults are at risk of malnutrition, which can be explained by their higher rate of comorbidities and impairments [140]. Almost half of patients with AF aged ≥80 years have some degree malnutrition, which was shown to be independently associated with an increased risk of MB (SHR 1.29, 95%CI 1.02–1.64), ischemic stroke (SHR 1.37, 95%CI 1.10–1.69), and overall-mortality (SHR 1.36, 95%CI 1.24–1.49) [140]. According to an OS [141], the incidence of MB in adults ≥80 years with AF and moderate malnutrition was increased when treated with warfarin compared to those without or mild malnutrition (12.1/10 vs. 0.6/100 person-years, $p < 0.01$), but not when treated with DOACs (1.6/100 vs. 0.8/100 person-years, $p = 0.54$), possibly due to a poorer INR-control in malnourished patients.

5. Current recommendations for treating AF and VTE in the older adults

Both general and geriatric guidelines recommend DOACs over VKAs for the treatment of both AF and VTE (Table 3) [45,46,65,77]. Given the possibly higher risk of MB with rivaroxaban and dabigatran in older adults compared to apixaban and edoxaban, the American Geriatrics Society has added them to their list of potentially inappropriate medications that should be used with caution in patients aged ≥75 years [65].

Dose reductions based on age are recommended for two DOACs for AF, dabigatran and apixaban (Table 2). In patients aged ≥80 years, the recommended dose reduction for dabigatran is from 2 × 150 mg to 2 × 110 mg daily [23,45]. As advanced age, low body weight, and reduced CrCl individually have only a modest effect on apixaban exposure, a dose reduction from 2 × 5 mg to 2 × 2.5 mg daily is only warranted if at least two risk factors (age ≥ 80 years, weight ≤ 60 kg, or creatinine ≥133 μg/l) are present [17,45]. There is no evidence indicating that rivaroxaban or edoxaban require a dose reduction based on advanced age alone. In older adults, a lower warfarin starting dose of ≤5 mg is

Table 3
Recommendations/statements in contemporary key AF/VTE practice guidelines regarding OAC use in patients with advanced age, frailty, multimorbidity, fall risk, or cognitive impairment/dementia.

Guidelines	Recommendations/statements
AF	
ACC/AHA 2023 [143]	• Long-term OAC is contraindicated in the context of serious bleeding related to recurrent falls when cause of falls is not felt to be treatable.
ACCP 2018 [144]	• In frail patients and those at high risk of falls, an individual risk assessment needs to be undertaken prior to OAC initiation. • The benefits of ischemic stroke reduction generally outweigh the risk of harm from serious bleeding with OAC use. • In patients with cognitive impairment or dementia, OAC should only be withheld if there is no available caregiver who can guarantee medication adherence.
CCS 2020 [145]	• OAC should be prescribed for most frail older patients with AF (strong recommendation; moderate-quality evidence).
ESC 2020 [45]	• Frailty, comorbidities, and increased risk of falls do not outweigh the benefits of OAC. • DOACs appear to have a better overall risk-benefit profile compared with warfarin in older and frail patients.
NICE 2021 [146]	• Do not withhold OAC solely because of a person's age or their risk of falls (age is factored into the [ORBIT] bleeding risk score and falls are rarely a cause of major hemorrhage). The benefits/harms [of OAC] should be discussed with the person.
VTE	
ACCP 2021 [47]	• No specific recommendation/statement
ASCO 2023 [147]	• No specific recommendation/statement
ASH 2020 [46]	• No specific recommendation/statement
ASH Cancer 2021 [148]	• No specific recommendation/statement
ESC 2019 [77]	• Warfarin may be started at a dose ≤5 mg in older patients.
ESMO 2023 [149]	• No specific recommendation/statement
ESVS 2021 [150]	• No specific recommendation/statement
ITAC-CME 2022 [151]	• No specific recommendation/statement
NICE 2020, update 2023 [152]	• No specific recommendation/statement
THANZ 2019 [153]	• No specific recommendation/statement
AF and VTE	
AGS 2023 [65]	• Avoid starting warfarin as initial therapy for the treatment of nonvalvular AF/VTE unless alternative options [DOACs] are contraindicated or there are substantial barriers to their use. • Avoid rivaroxaban for long-term treatment of non-valvular AF/VTE in favor of safer OAC alternatives. • Use caution in selecting dabigatran over other DOACs (e.g., apixaban) for long-term treatment of nonvalvular AF/VTE.

Abbreviations: ACC, American College of Cardiology; ACCP, American College of Chest Physicians; AF, atrial fibrillation; AGS, American Geriatrics Society; AHA, American Heart Association; ASCO, American Society of Clinical Oncology; ASH, American Society of Hematology; CCS, Canadian Cardiovascular Society; DOACs, direct oral anticoagulants; ESMO, European Society of Medical Oncology; ESC, European Society of Cardiology; ESVS, European Society for Vascular Surgery; ITAC-CME, International Initiative on Thrombosis and Cancer; NICE, National Institute for Health and Care Excellence; OAC, oral anticoagulation; THANZ, Thrombosis and Haemostasis Society of Australia and New Zealand; VTE, venous thromboembolism.

recommended because of their greater sensitivity to warfarin [28,77].

6. Future research

Almost no specific treatment trials exist in older adults who are also underrepresented in existing landmark OAC studies. As a result, there is a paucity of age-specific OAC guideline recommendations/statements (Table 3) and trial results from younger, healthier individuals are extrapolated to older, sicker patients. To increase the generalizability of study findings to the older population and considering that the risk-benefit profile of specific DOACs may differ in older patients, there is a need for advanced age-specific, pragmatic prospective, especially randomized studies with less restrictive eligibility criteria, including patients with common geriatric conditions such as frailty. Future studies should directly compare the effectiveness and safety of different DOACs, evaluate risks and benefits of lower-dose regimens, and investigate the optimal OAC durations in older patients with different risk profiles (e.g., after unprovoked or cancer-related VTE) (Table 4). Especially comparative RCTs are necessary. As older persons may value independence over longevity, these studies should not only evaluate traditional morbidity and mortality but also patient-reported health outcomes, such as health-related quality of life and function, and active life expectancy (e.g., home time) [142]. Such comparative effectiveness research would not only provide an evidence base for specific OAC recommendations for older adults with AF/VTE, but would also help identify subgroups of older patients who would particularly benefit from OAC and those who would not. A next step towards this goal could be the foundation of a consortium/working group (e.g., under the leadership of the International Society of Thrombosis and Haemostasis) to establish a research agenda for OAC therapy in older adults, including the identification of specific research questions and the definition of study designs and appropriate outcome measures. On a regulatory level, potential measures such as the mandatory inclusion of a sufficient sample size of older patients in OAC studies or the requirement of funding/conducting post-marketing studies in older persons treated with OAC should also be discussed.

7. Conclusions

Although the majority of patients with AF/VTE are older adults at increased risk of SSE and bleeding, specific treatment trials are scarce, resulting in a notable underrepresentation of older adults in landmark OAC trials and practice guidelines. A growing body of evidence from RCT subgroups and OSs indicates that DOACs as a drug class may be

Table 4
Goals, design characteristics, and themes of potential future studies on anticoagulant therapy in older adults.

Study goals	Study characteristics and study ideas
• To increase the generalizability of study findings to older patients • To provide an evidence base for specific OAC recommendations in terms of OAC intensity and duration for older patients with AF/VTE • To help identify subgroups of older patients for whom OAC therapy is beneficial (or not)	• Study characteristics: • Enrolment of older adults, such as persons aged ≥65 years, the very old (80+), or the oldest old (85+) • Pragmatic, prospective, and preferably randomized design, with less restrictive eligibility criteria • Use of patient-reported health outcomes (e.g., health-related quality of life, active life expectancy, function) • Study ideas: • Direct comparison of the effectiveness and safety of different DOACs in older patients, including specific subgroups (e.g., frail patients) • Direct comparison of effectiveness and safety of lower-dose vs. normal-dose regimens in older patients • Direct comparison of effectiveness and safety different OAC durations in older patients, including patients with different risk profiles (e.g., after unprovoked or cancer-related VTE)

Abbreviations: AF, atrial fibrillation; DOACs, direct oral anticoagulants; OAC, oral anticoagulation; VTE, venous thromboembolism.

more effective and safer than VKAs in older persons with AF/VTE and may have a positive effect on cognitive function in patients with AF. The available evidence also suggests that apixaban and edoxaban might have the most favorable risk-benefit profile among DOACs in older adults including those with typical geriatric conditions such as frailty, multimorbidity, polypharmacy, fall risk, cognitive impairment/dementia, and potentially also those with malnutrition. In older and frail patients with AF, there is currently no evidence of benefit for switching OAC from VKAs to DOACs and even some evidence of an increased bleeding risk. Advanced age-specific and pragmatic comparative effectiveness studies using patient-reported outcomes are needed to expand our knowledge on optimal OAC strategies in the growing population of older multimorbid patients with AF/VTE. Considering patient specific characteristics, treatment decisions should be tailored to the individual, and shared decision making with evaluation of the potential outcomes of both continuing and discontinuing OAC, as well as consideration of individual preferences should be encouraged.

CRediT authorship contribution statement

J. Stuby: Writing – review & editing, Writing – original draft, Conceptualization. **M. Haschke:** Writing – review & editing. **T. Tritschler:** Writing – review & editing. **D. Aujesky:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Q. Chen, K. Lapane, A.P. Nunes, J. Tjia, J. Hugunin, M. Alcusky, Prevalence and the factors associated with oral anticoagulant use among nursing home residents, J. Clin. Pharm. Ther. 46 (6) (2021) 1714–1728.

[2] C.M. Eschler, B.K. Woitok, G.C. Funk, P. Walter, V. Maier, A.K. Exadaktylos, et al., Oral anticoagulation in oatients in the emergency department: high rates of off-label doses, no difference in bleeding rates, American Journal of Medicine. 133 (5) (2020) 599–604.

[3] K. Wasmer, L. Eckardt, G. Breithardt, Predisposing factors for atrial fibrillation in the elderly, J. Geriatr. Cardiol. 14 (3) (2017) 179–184.

[4] Akrivou D, Perlepe G, Kirgou P, Gourgoulianis KI, Malli F. Pathophysiological Aspects of Aging in Venous Thromboembolism: An Update. Medicina (Kaunas). 2022;vol. 58(8).

[5] J. Heeringa, D.A.M. van der Kuip, A. Hofman, J.A. Kors, G. van Herpen, B.H. C. Stricker, et al., Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study, Eur. Heart J. 27 (8) (2006) 949–953.

[6] A.S. Go, E.M. Hylek, K.A. Phillips, Y. Chang, L.E. Henault, J.V. Selby, et al., Prevalence of diagnosed atrial aibrillation in adults national implications for rhythm management and stroke prevention: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study, JAMA 285 (18) (2001) 2370–2375.

[7] M. Esato, Y. An, H. Ogawa, H. Wada, K. Hasegawa, H. Tsuji, et al., Age-dependent risk for thromboembolism in atrial fibrillation: the Fushimi AF registry, International Journal of Cardiology: Heart & Vasculature. 41 (2022) 101055.

[8] L. Lopez-Jimenez, M. Montero, J.A. Gonzalez-Fajardo, J.I. Arcelus, C. Suarez, J. L. Lobo, et al., Venous thromboembolism in very elderly patients: findings from a prospective registry (RIETE), Haematologica 91 (8) (2006) 1046–1051.

[9] G.Y. Lip, A. Banerjee, I. Lagrenade, D.A. Lane, S. Taillandier, L. Fauchier, Assessing the risk of bleeding in patients with atrial fibrillation: the loire valley atrial fibrillation project, Circ. Arrhythm. Electrophysiol. 5 (5) (2012) 941–948.

[10] M.C. Fang, A.S. Go, E.M. Hylek, Y. Chang, L.E. Henault, N.G. Jensvold, et al., Age and the risk of warfarin-associated hemorrhage: the anticoagulation and risk factors in atrial fibrillation study, J. Am. Geriatr. Soc. 54 (8) (2006) 1231–1236.

[11] F. Khan, T. Tritschler, M. Kimpton, P.S. Wells, C. Kearon, J.I. Weitz, et al., Long-term risk for major bleeding during extended oral anticoagulant therapy for first unprovoked venous thromboembolism : a systematic review and meta-analysis, Ann. Intern. Med. 174 (10) (2021) 1420–1429.

[12] D. Ko, K.J. Lin, L.G. Bessette, S.B. Lee, A.J. Walkey, S. Cheng, et al., Trends in use of oral anticoagulants in older adults with newly diagnosed atrial fibrillation, 2010-2020, JAMA Netw. Open 5 (11) (2022) e2242964.

[13] L.A. Ritchie, S.L. Harrison, P.E. Penson, A. Akbari, F. Torabi, J. Hollinghurst, et al., Prevalence and outcomes of atrial fibrillation in older people living in care homes in wales: a routine data linkage study 2003–2018, Age Ageing 51 (12) (2022).

[14] J.C. Coons, A. Wang, D. Latremouille-Viau, C. Russ, D. Cheng, R. Stellhorn, et al., Oral anticoagulant (OAC) use among Medicare patients newly diagnosed with venous thromboembolism (VTE): factors associated with treatment status, Blood 142 (2023) 2363.

[15] K. Turnheim, When drug therapy gets old: pharmacokinetics and pharmacodynamics in the elderly, Exp. Gerontol. 38 (8) (2003) 843–853.

[16] M. Bendayan, V. Mardigyan, D. Williamson, A. Chen-Tournoux, S. Eintracht, L. Rudski, et al., Muscle mass and direct oral anticoagulant activity in older adults with atrial fibrillation, J. Am. Geriatr. Soc. 69 (4) (2021) 1012–1018.

[17] Bristol-Myers-Squibb-Canada. Apixaban summary of product characteristics [Available from: https://www.ema.europa.eu/en/documents/product-information/eliquis-epar-product-information_en.pdf.

[18] V.V. Upreti, Y. Song, J. Wang, W. Byon, R.A. Boyd, J.M. Pursley, et al., Effect of Famotidine on the Pharmacokinetics of Apixaban, an Oral Direct Factor Xa Inhibitor, Advances and Applications, Clinical Pharmacology, 2013, pp. 59–66.

[19] Daiichi-Sankyo. Edoxaban summary of product characteristics [Available from: https://www.ema.europa.eu/en/documents/product-information/lixiana-epar-product-information_en.pdf.

[20] E.T. Kato, R.P. Giugliano, C.T. Ruff, Y. Koretsune, T. Yamashita, R.G. Kiss, et al., Efficacy and safety of edoxaban in elderly patients with atrial fibrillation in the ENGAGE AF-TIMI 48 trial, J. Am. Heart Assoc. 5 (5) (2016).

[21] Bayer. Rivaroxaban summary of product characteristics [Available from: https://www.ema.europa.eu/en/documents/product-information/xarelto-epar-product-information_en.pdf.

[22] D. Kubitza, M. Becka, M. Zuehlsdorf, W. Mueck, Body weight has limited influence on the safety, tolerability, pharmacokinetics, or pharmacodynamics of rivaroxaban in healthy subjects, J. Clin. Pharmacol. 47 (2) (2007) 218–226.

[23] Boehringer-Ingelheim. Dabigatran summary of product characteristics [Available from: https://www.ema.europa.eu/en/documents/product-information/pradaxa-epar-product-information_en.pdf.

[24] C. Dansirikul, T. Lehr, K.-H. Liesenfeld, S. Haertter, A. Staab, A combined pharmacometric analysis of dabigatran etexilate in healthy volunteers and patients with atrial fibrillation or undergoing orthopaedic surgery, Thromb. Haemost. 107 (04) (2012) 775–785.

[25] T. Yamashita, Y. Koretsune, M. Yasaka, H. Inoue, Y. Kawai, T. Yamaguchi, et al., Randomized, multicenter, warfarin-controlled phase II study of edoxaban in japanese patients with non-valvular atrial fibrillation, Circ. J. 76 (8) (2012) 1840–1847.

[26] S. Lane, S. Al-Zubiedi, E. Hatch, I. Matthews, A.L. Jorgensen, P. Deloukas, et al., The population pharmacokinetics of R- and S-warfarin: effect of genetic and clinical factors, Br. J. Clin. Pharmacol. 73 (1) (2012) 66–76.

[27] T. Tritschler, L.A. Castellucci, N. Van Es, D. Aujesky, G. Le Gal, Treatment of venous thromboembolism in elderly patients in the era of direct oral anticoagulants, Polish Archives of Internal Medicine. 130 (6) (2020) 529–538.

[28] Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American college of chest physicians evidence-based clinical practice guidelines (8th edition). Chest. 2008;133(6 Suppl):160s–98s.

[29] A.E. Edwina, N. Dia, E. Dreesen, T. Vanassche, P. Verhamme, I. Spriet, et al., Insights into the pharmacokinetics and pharmacodynamics of direct oral anticoagulants in older adults with atrial fibrillation: a structured narrative review, Clin. Pharmacokinet. 62 (3) (2023) 351–373.

[30] A.A. Mangoni, S.H. Jackson, Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications, Br. J. Clin. Pharmacol. 57 (1) (2004) 6–14.

[31] J. Graff, S. Harder, Anticoagulant therapy with the oral direct factor Xa inhibitors rivaroxaban, apixaban and edoxaban and the thrombin inhibitor dabigatran etexilate in patients with hepatic impairment, Clin. Pharmacokinet. 52 (4) (2013) 243–254.

[32] B.P. Jensen, P.K. Chin, R.L. Roberts, E.J. Begg, Influence of adult age on the total and free clearance and protein binding of (R)- and (S)-warfarin, Br. J. Clin. Pharmacol. 74 (5) (2012) 797–805.

[33] K. Barnett, S.W. Mercer, M. Norbury, G. Watt, S. Wyke, B. Guthrie, Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study, The Lancet. 380 (9836) (2012) 37–43.

[34] M. Delara, L. Murray, B. Jafari, A. Bahji, Z. Goodarzi, J. Kirkham, et al., Prevalence and factors associated with polypharmacy: a systematic review and meta-analysis, BMC Geriatr. 22 (1) (2022) 601.

[35] C.E. Frost, Y. Song, A. Shenker, J. Wang, Y.C. Barrett, A. Schuster, et al., Effects of age and sex on the single-dose pharmacokinetics and pharmacodynamics of apixaban, Clin. Pharmacokinet. 54 (6) (2015) 651–662.

[36] J. Stangier, A. Clemens, Pharmacology, pharmacokinetics, and pharmacodynamics of dabigatran etexilate, an oral direct thrombin inhibitor, Clin. Appl. Thromb. Hemost. 15 (Suppl. 1) (2009) 9s–16s.

[37] D.A. Parasrampuria, K.E. Truitt, Pharmacokinetics and pharmacodynamics of edoxaban, a non-vitamin K antagonist oral anticoagulant that inhibits clotting factor Xa, Clin. Pharmacokinet. 55 (6) (2016) 641–655.

[38] P.A. Reilly, T. Lehr, S. Haertter, S.J. Connolly, S. Yusuf, J.W. Eikelboom, et al., The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the RE-LY trial (randomized evaluation of long-term anticoagulation therapy), J. Am. Coll. Cardiol. 63 (4) (2014) 321–328.

[39] H. Wynne, L. Cope, P. Kelly, T. Whittingham, C. Edwards, F. Kamali, The influence of age, liver size and enantiomer concentrations on warfarin requirements, Br. J. Clin. Pharmacol. 40 (3) (1995) 203–207.

[40] A. Shendre, G.M. Parmar, C. Dillon, T.M. Beasley, N.A. Limdi, Influence of age on warfarin dose, anticoagulation control, and risk of hemorrhage, Pharmacotherapy 38 (6) (2018) 588–596.
[41] D. Garcia, S. Regan, M. Crowther, R.A. Hughes, E.M. Hylek, Warfarin maintenance dosing patterns in clinical practice: implications for safer anticoagulation in the elderly population, Chest 127 (6) (2005) 2049–2056.
[42] J. Rosand, E.M. Hylek, H.C. O'Donnell, S.M. Greenberg, Warfarin-associated hemorrhage and cerebral amyloid angiopathy: a genetic and pathologic study, Neurology 55 (7) (2000) 947–951.
[43] G. Bassotti, F. Chistolini, A. Morelli, Pathophysiological aspects of diverticular disease of colon and role of large bowel motility, World J. Gastroenterol. 9 (10) (2003) 2140.
[44] A. Pilotto, M. Franceschi, Helicobacter pylori infection in older people, World J. Gastroenterol. 20 (21) (2014) 6364–6373.
[45] G. Hindricks, T. Potpara, N. Dagres, E. Arbelo, J.J. Bax, C. Blomström-Lundqvist, et al., 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the european association for cardio-thoracic surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the european society of cardiology (ESC) developed with the special contribution of the european heart rhythm association (EHRA) of the ESC, Eur. Heart J. 42 (5) (2020) 373–498.
[46] T.L. Ortel, I. Neumann, W. Ageno, R. Beyth, N.P. Clark, A. Cuker, et al., American society of hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism, Blood Adv. 4 (19) (2020) 4693–4738.
[47] S.M. Stevens, S.C. Woller, L.B. Kreuziger, H. Bounameaux, K. Doerschug, G.-J. Geersing, et al., Antithrombotic therapy for VTE disease: second update of the CHEST guideline and expert panel report, Chest 160 (6) (2021) e545–e608.
[48] M. Levi, G.K. Hovingh, S.C. Cannegieter, M. Vermeulen, H.R. Büller, F. R. Rosendaal, Bleeding in patients receiving vitamin K antagonists who would have been excluded from trials on which the indication for anticoagulation was based, Blood, The Journal of the American Society of Hematology. 111 (9) (2008) 4471–4476.
[49] C. Schenker, O. Stalder, M. Mean, T. Tritschler, M. Righini, N. Rodondi, et al., Bleeding risk in elderly patients with venous thromboembolismwho would have been excluded from anticoagulation trials, Thromb. Haemost. 123 (4) (2023) 427–437.
[50] S. Lee, B.U. Monz, A. Clemens, M. Brueckmann, G.Y. Lip, Representativeness of the dabigatran, apixaban and rivaroxaban clinical trial populations to real-world atrial fibrillation patients in the United Kingdom: a cross-sectional analysis using the general practice research database, BMJ Open 2 (6) (2012) e001768.
[51] C.T. Ruff, R.P. Giugliano, E. Braunwald, E.B. Hoffman, N. Deenadayalu, M. D. Ezekowitz, et al., Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials, Lancet 383 (9921) (2014) 955–962.
[52] A. Mitchell, M.C. Watson, T. Welsh, A. McGrogan, Effectiveness and safety of direct oral anticoagulants versus vitamin K antagonists for people aged 75 years and over with atrial fibrillation: a systematic review and meta-analyses of observational studies, J. Clin. Med. 8 (4) (2019) 554.
[53] N.-N. Shen, Y. Wu, N. Wang, L.-C. Kong, C. Zhang, J.-L. Wang, et al., Direct oral anticoagulants vs. vitamin-K antagonists in the elderly with atrial fibrillation: a systematic review comparing benefits and harms between observational studies and randomized controlled trials, Frontiers in Cardiovascular Medicine. 7 (2020) 132.
[54] A. Silverio, M. Di Maio, C. Prota, E. De Angelis, I. Radano, R. Citro, et al., Safety and efficacy of non-vitamin K antagonist oral anticoagulants in elderly patients with atrial fibrillation: systematic review and meta-analysis of 22 studies and 440 281 patients, European Heart Journal - Cardiovascular Pharmacotherapy. 7 (FI1) (2019) f20–f29.
[55] K. Doni, S. Bühn, A. Weise, N.-K. Mann, S. Hess, A. Sönnichsen, et al., Safety outcomes of direct oral anticoagulants in older adults with atrial fibrillation: a systematic review and meta-analysis of (subgroup analyses from) randomized controlled trials, GeroScience (2023) 1–22.
[56] L. Lin, W.S. Lim, H.J. Zhou, A.L. Khoo, K.T. Tan, A.P. Chew, et al., Clinical and safety outcomes of oral antithrombotics for stroke prevention in atrial fibrillation: a systematic review and network meta-analysis, J. Am. Med. Dir. Assoc. 16(12): 1103 (2015) e1 (e19).
[57] A.H. Sadlon, D.A. Tsakiris, Direct oral anticoagulants in the elderly: systematic review and meta-analysis of evidence, current and future directions, Swiss Med. Wkly. 146(3940):w14356-w (2016).
[58] A.H. Malik, S. Yandrapalli, W.S. Aronow, J.A. Panza, H.A. Cooper, Meta-analysis of direct-acting oral anticoagulants compared with warfarin in patients >75 years of age, Am. J. Cardiol. 123 (12) (2019) 2051–2057.
[59] X. Wang, T. Wang, X. Chen, W. Tian, D. Ma, J. Zhang, et al., Efficacy and safety of oral anticoagulants in older adult patients with atrial fibrillation: pairwise and network meta-analyses, J. Am. Med. Dir. Assoc. 24 (8) (2023), 1233-9.e26.
[60] M. Grymonprez, T.L. De Backer, X. Bertels, S. Steurbaut, L. Lahousse, Long-term comparative effectiveness and safety of dabigatran, rivaroxaban, apixaban and edoxaban in patients with atrial fibrillation: a nationwide cohort study, Front. Pharmacol. 14 (2023) 1125576.
[61] K. Okumura, M. Akao, T. Yoshida, M. Kawata, O. Okazaki, S. Akashi, et al., Low-dose edoxaban in very elderly patients with atrial fibrillation, New England Journal of Medicine. 383 (18) (2020) 1735–1745.
[62] S. Akashi, M. Oguri, E. Ikeno, M. Manita, J. Taura, S. Watanabe, et al., Outcomes and safety of very-low-dose edoxaban in frail patients with atrial fibrillation in the ELDERCARE-AF randomized clinical trial, JAMA Netw. Open 5(8):e2228500-e (2022).
[63] K.-H. Lee, Y.-F. Chen, W.-Y. Yeh, J.-T. Yeh, T.-H. Yang, C.-Y. Chou, et al., Optimal stroke preventive strategy for patients aged 80 years or older with atrial fibrillation: a systematic review with traditional and network meta-analysis, Age Ageing 51(12):afac292 (2022).
[64] L.P. Joosten, S. van Doorn, P.M. van de Ven, B.T. Köhlen, M.C. Nierman, H. L. Koek, et al., Safety of switching from a vitamin K antagonist to a non-vitamin K antagonist oral anticoagulant in frail older patients with atrial fibrillation: results of the FRAIL-AF randomized controlled trial, Circulation 149 (4) (2023) 279–289.
[65] AGS, American geriatrics society 2023 updated AGS beers criteria® for potentially inappropriate medication use in older adults, J. Am. Geriatr. Soc. 71 (7) (2023) 2052–2081.
[66] N. Van Es, M. Coppens, S. Schulman, S. Middeldorp, H.R. Büller, Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials, Blood, The Journal of the American Society of Hematology. 124 (12) (2014) 1968–1975.
[67] K. Glise Sandblad, S. Schulman, A. Rosengren, J. Sörbo, J. Philipson, P. O. Hansson, Association of type of oral anticoagulation with risk of bleeding in 45,114 patients with venous thromboembolism during initial and extended treatment - a nationwide register-based study, J. Intern. Med. 294 (6) (2023) 743–760.
[68] A. Douros, F. Basedow, Y. Cui, J. Dimakos, J. Walker, D. Enders, et al., Effectiveness and safety of direct oral anticoagulants among octogenarians with venous thromboembolism: an international multidatabase cohort study, Am. J. Med. 136 (1) (2023) 79–87.e7.
[69] A. Pawar, J.J. Gagne, C. Gopalakrishnan, G. Iyer, H. Tesfaye, G. Brill, et al., Association of type of oral anticoagulant dispensed with adverse clinical outcomes in patients extending anticoagulation therapy beyond 90 days after hospitalization for venous thromboembolism, JAMA 327 (11) (2022) 1051–1060.
[70] C. Iwai, T. Jo, T. Konishi, R. Kumazawa, H. Matsui, K. Fushimi, et al., Comparative safety and effectiveness of direct oral anticoagulants and warfarin during chemotherapy in cancer patients with venous thromboembolismaged 75 years or older: a nationwide inpatient database study, Gerontology 69 (5) (2023) 561–570.
[71] G. Agnelli, C. Becattini, G. Meyer, A. Muñoz, M.V. Huisman, J.M. Connors, et al., Apixaban for the treatment of venous thromboembolism associated with cancer, N. Engl. J. Med. 382 (17) (2020) 1599–1607.
[72] G.E. Raskob, N. van Es, P. Verhamme, M. Carrier, M. Di Nisio, D. Garcia, et al., Edoxaban for the treatment of cancer-associated venous thromboembolism, New England Journal of Medicine. 378 (7) (2017) 615–624.
[73] D. Aujesky, K.J. Smith, M.S. Roberts, Oral anticoagulation strategies after a first idiopathic venous thromboembolic event, American Journal of Medicine. 118 (6) (2005) 625–635.
[74] J. Donzé, C. Clair, B. Hug, N. Rodondi, G. Waeber, J. Cornuz, et al., Risk of falls and major bleeds in patients on oral anticoagulation therapy, American Journal of Medicine. 125 (8) (2012) 773–778.
[75] A.N. Frei, O. Stalder, A. Limacher, M. Méan, C. Baumgartner, N. Rodondi, et al., Comparison of bleeding risk scores in elderly patients receiving extended anticoagulation with vitamin K antagonists for venous thromboembolism, Thromb. Haemost. 121 (11) (2021) 1512–1522.
[76] T. Tritschler, D. Aujesky, Venous thromboembolism in the elderly: a narrative review, Thromb. Res. 155 (2017) 140–147.
[77] S.V. Konstantinides, G. Meyer, C. Becattini, H. Bueno, G.-J. Geersing, V.-P. Harjola, et al., 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the european respiratory society (ERS): the task force for the diagnosis and management of acute pulmonary embolism of the european society of cardiology (ESC), Eur. Heart J. 41 (4) (2019) 543–603.
[78] C. Kearon, E.A. Akl, J. Ornelas, A. Blaivas, D. Jimenez, H. Bounameaux, et al., Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report, Chest 149 (2) (2016) 315–352.
[79] M.-V. Castell, M. Sánchez, R. Julián, R. Queipo, S. Martín, Á. Otero, Frailty prevalence and slow walking speed in persons age 65 and older: implications for primary care, BMC Fam. Pract. 14 (1) (2013) 86.
[80] L.P. Fried, C.M. Tangen, J. Walston, A.B. Newman, C. Hirsch, J. Gottdiener, et al., Frailty in older adults: evidence for a phenotype, J. Gerontol. A Biol. Sci. Med. Sci. 56 (3) (2001) M146–M157.
[81] C. Wilkinson, A. Clegg, O. Todd, K. Rockwood, M.E. Yadegarfar, C.P. Gale, et al., Atrial fibrillation and oral anticoagulation in older people with frailty: a nationwide primary care electronic health records cohort study, Age Ageing 50 (3) (2021) 772–779.
[82] M. Candeloro, M. Di Nisio, N. Potere, L. Di Pizio, E. Secinaro, C. De Flaviis, et al., Frailty phenotype as a predictor of bleeding and mortality in ambulatory patients receiving direct oral anticoagulants, J. Am. Geriatr. Soc. 70 (12) (2022) 3503–3512.
[83] P.L. Lutsey, B.G. Windham, J.R. Misialek, M. Cushman, A. Kucharska-Newton, S. Basu, et al., Long-term association of venous thromboembolismwith frailty, physical functioning, and quality of life: the atherosclerosis tisk in communities study, J. Am. Heart Assoc. 9 (12) (2020) e015656.
[84] C. Wilkinson, J. Wu, S.D. Searle, O. Todd, M. Hall, V. Kunadian, et al., Clinical outcomes in patients with atrial fibrillation and frailty: insights from the ENGAGE AF-TIMI 48 trial, BMC Med. 18 (1) (2020) 401.
[85] M. Proietti, G.F. Romiti, V. Raparelli, I. Diemberger, G. Boriani, L.A. Dalla Vecchia, et al., Frailty prevalence and impact on outcomes in patients with atrial

fibrillation: a systematic review and meta-analysis of 1,187,000 patients, Ageing Res. Rev. 79 (2022) 101652.
[86] E. Ferrazzini, M. Méan, O. Stalder, A. Limacher, N. Rodondi, D. Aujesky, Incidence and clinical impact of bleeding events in older patients with acute venous thromboembolism, Blood Adv. 7 (2) (2023) 205–213.
[87] V. Perera, B.V. Bajorek, S. Matthews, S.N. Hilmer, The impact of frailty on the utilisation of antithrombotic therapy in older patients with atrial fibrillation, Age Ageing 38 (2) (2009) 156–162.
[88] M. Grymonprez, M. Petrovic, T.L. De Backer, S. Steurbaut, L. Lahousse, Impact of frailty on the effectiveness and safety of non-vitamin K antagonist oral anticoagulants (NOACs) in patients with atrial fibrillation: a nationwide cohort study, European Heart Journal - Quality of Care and Clinical Outcomes 10 (1) (2023) 55–56.
[89] D.H. Kim, A. Pawar, J.J. Gagne, L.G. Bessette, H. Lee, R.J. Glynn, et al., Frailty and clinical outcomes of direct oral anticoagulants versus warfarin in older adults with atrial fibrillation: a cohort study, Ann. Intern. Med. 174 (9) (2021) 1214–1223.
[90] B.K. Martinez, N.A. Sood, T.J. Bunz, C.I. Coleman, Effectiveness and safety of apixaban, dabigatran, and rivaroxaban versus warfarin in frail patients with nonvalvular atrial fibrillation, J. Am. Heart Assoc. 7 (8) (2018) e008643.
[91] C.I. Coleman, A.G.G. Turpie, T.J. Bunz, J. Beyer-Westendorf, Effectiveness and safety of rivaroxaban versus warfarin in frail patients with venous thromboembolism, American Journal of Medicine. 131 (8) (2018), 933-8.e1.
[92] J.D. Guo, P. Hlavacek, L. Rosenblatt, A. Keshishian, C. Russ, J. Mardekian, et al., Safety and effectiveness of apixaban compared with warfarin among clinically-relevant subgroups of venous thromboembolism patients in the United States medicare population, Thromb. Res. 198 (2021) 163–170.
[93] K.J. Lin, D.E. Singer, D. Ko, R. Glynn, M. Najafzadeh, S.B. Lee, et al., Frailty, home time, and health care costs in older adults with atrial fibrillation receiving oral anticoagulants, JAMA Netw. Open 6(11):e2342264-e (2023).
[94] A. Kotalczyk, Y. Guo, Y. Wang, G.Y.H. Lip, Investigators obotCR., Impact of multimorbidity and polypharmacy on clinical outcomes of elderly chinese patients with atrial fibrillation. Journal of, Clin. Med. 11(5):1370 (2022).
[95] N. Lange, M. Mean, O. Stalder, A. Limacher, T. Tritschler, N. Rodondi, et al., Anticoagulation quality and clinical outcomes in multimorbid elderly patients with acute venous thromboembolism, Thromb. Res. 177 (2019) 10–16.
[96] T.-F. Chao, C.-E. Chiang, Y.-H. Chan, J.-N. Liao, T.-J. Chen, G.Y.H. Lip, et al., Oral anticoagulants in extremely-high-risk, very elderly (>90 years) patients with atrial fibrillation, Heart Rhythm 18 (6) (2021) 871–877.
[97] M.A. De Winter, H.R. Büller, M. Carrier, A.T. Cohen, J.-B. Hansen, K.A. H. Kaasjager, et al., Recurrent venous thromboembolism and bleeding with extended anticoagulation: the VTE-PREDICT risk score, Eur. Heart J. 44 (14) (2023) 1231–1244.
[98] J.L.I. Burggraaf, N. van Rein, F.A. Klok, S.C. Cannegieter, How to predict recurrent venous thromboembolism and bleeding? A review of recent advances and their implications. Polish, Arch. Intern. Med. 133 (5) (2023).
[99] M. Proietti, M.A. Esteve-Pastor, J.M. Rivera-Caravaca, V. Roldán, I.R. Rabadán, J. Muñiz, et al., Relationship between multimorbidity and outcomes in atrial fibrillation, Exp. Gerontol. 153 (2021) 111482.
[100] S. Deitelzweig, A. Keshishian, A. Kang, A.D. Dhamane, X. Luo, C. Klem, et al., Use of non-vitamin K antagonist oral anticoagulants among patients with nonvalvular atrial fibrillation and multimorbidity, Adv. Ther. 38 (6) (2021) 3166–3184.
[101] A.D. Dhamane, M. Ferri, A. Keshishian, C. Russ, N. Atreja, C. Gutierrez, et al., Effectiveness and safety of direct oral anticoagulants among patients with non-valvular atrial fibrillation and multimorbidity, Adv. Ther. 40 (3) (2023) 887–902.
[102] N. Masnoon, S. Shakib, L. Kalisch-Ellett, G.E. Caughey, What is polypharmacy? A systematic review of definitions, BMC Geriatr. 17 (1) (2017) 230.
[103] W. Leiss, M. Méan, A. Limacher, M. Righini, K. Jaeger, H.-J. Beer, et al., Polypharmacy is associated with an increased risk of bleeding in elderly patients with venous thromboembolism, J. Gen. Intern. Med. 30 (2015) 17–24.
[104] L. Martínez-Montesinos, J.M. Rivera-Caravaca, S. Agewall, E. Soler, G.Y.H. Lip, F. Marín, et al., Polypharmacy and adverse events in atrial fibrillation: main cause or reflection of multimorbidity? Biomed. Pharmacother. 158 (2023) 114064.
[105] L. Eggebrecht, M. Nagler, S. Göbel, H. Lamparter, K. Keller, B. Wagner, et al., Relevance of polypharmacy for clinical outcome in patients receiving vitamin K antagonists, J. Am. Geriatr. Soc. 67 (3) (2019) 463–470.
[106] M. Grymonprez, M. Petrovic, T.L. De Backer, S. Steurbaut, L. Lahousse, The impact of polypharmacy on the effectiveness and safety of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation, Thromb. Haemost. 124 (02) (2023) 135–148.
[107] J.Y. Lee, I.Y. Oh, J.H. Lee, S.Y. Kim, S.S. Kwon, H.J. Yang, et al., The increased risk of bleeding due to drug-drug interactions in patients administered direct oral anticoagulants, Thromb. Res. 195 (2020) 243–249.
[108] S.R. Vazquez, Drug-drug interactions in an era of multiple anticoagulants: a focus on clinically relevant drug interactions, Blood, The Journal of the American Society of Hematology. 132 (21) (2018) 2230–2239.
[109] S. Kumar, S.B. Danik, R.K. Altman, C.D. Barrett, G.Y. Lip, S. Chatterjee, et al., Non-vitamin K antagonist oral anticoagulants and antiplatelet therapy for stroke prevention in patients with atrial fibrillation: a meta-analysis of randomized controlled trials, Cardiol. Rev. 24 (5) (2016) 218–223.
[110] B.A. Steinberg, S. Kim, J.P. Piccini, G.C. Fonarow, R.D. Lopes, L. Thomas, et al., Use and associated risks of concomitant aspirin therapy with oral anticoagulation in patients with atrial fibrillation: insights from the outcomes registry for better informed treatment of atrial fibrillation (ORBIT-AF) registry, Circulation 128 (7) (2013) 721–728.
[111] E. Valeriani, E. Porreca, J.I. Weitz, S. Schulman, M. Candeloro, M. Di Nisio, Impact of concomitant antiplatelet therapy on the efficacy and safety of direct oral anticoagulants for acute venous thromboembolism: systematic review and meta-analysis, J. Thromb. Haemost. 18 (7) (2020) 1661–1671.
[112] Y. Zheng, S. Li, X. Liu, G.Y.H. Lip, L. Guo, W. Zhu, Effect of oral anticoagulants in atrial fibrillation patients with polypharmacy: a meta-analysis, Thromb. Haemost. (2023).
[113] T. Vanassche, P. Verhamme, P.S. Wells, A. Segers, W. Ageno, M.P.A. Brekelmans, et al., Impact of age, comorbidity, and polypharmacy on the efficacy and safety of edoxaban for the treatment of venous thromboembolism: an analysis of the randomized, double-blind hokusai-VTE trial, Thromb. Res. 162 (2018) 7–14.
[114] I.M. Bistervels, R. Bavalia, M. Gebel, A.W.A. Lensing, S. Middeldorp, M.H. Prins, et al., Effect of polypharmacy on bleeding with rivaroxaban versus vitamin K antagonist for treatment of venous thromboembolism, J. Thromb. Haemost. 20 (6) (2022) 1376–1384.
[115] P. Kämpfen, M. Méan, A. Limacher, M. Righini, K. Jaeger, H.J. Beer, et al., Risk of falls and bleeding in elderly patients with acute venous thromboembolism, J. Intern. Med. 276 (4) (2014) 378–386.
[116] S.J. Shah, M.C. Fang, S.Y. Jeon, S.E. Gregorich, K.E. Covinsky, Geriatric syndromes and atrial fibrillation: prevalence and association with anticoagulant use in a national cohort of older americans, J. Am. Geriatr. Soc. 69 (2) (2021) 349–356.
[117] V. Malik, C. Gallagher, D. Linz, A.D. Elliott, M. Emami, K. Kadhim, et al., Atrial fibrillation is associated with syncope and falls in older adults: a systematic review and meta-analysis, Mayo Clin. Proc. 95 (4) (2020) 676–687.
[118] D. Pugh, J. Pugh, G.E. Mead, Attitudes of physicians regarding anticoagulation for atrial fibrillation: a systematic review, Age Ageing 40 (6) (2011) 675–683.
[119] D. Poli, E. Antonucci, S. Testa, A. Tosetto, W. Ageno, G. Palareti, et al., Bleeding risk in very old patients on vitamin K antagonist treatment: results of a prospective collaborative study on elderly patients followed by italian centres for anticoagulation, Circulation 124 (7) (2011) 824–829.
[120] H. Minhas, A. Welsher, M. Turcotte, M. Eventov, S. Mason, D.K. Nishijima, et al., Incidence of intracranial bleeding in anticoagulated patients with minor head injury: a systematic review and meta-analysis of prospective studies, Br. J. Haematol. 183 (1) (2018) 119–126.
[121] L. Uccella, C. Zoia, D. Bongetta, P. Gaetani, F. Martig, C. Candrian, et al., Are antiplatelet and anticoagulants drugs a risk factor for bleeding in mild traumatic brain injury? World Neurosurg. 110 (2018) e339–e345.
[122] A. Lampart, T. Kuster, C.H. Nickel, R. Bingisser, V. Pedersen, Prevalence and severity of traumatic intracranial hemorrhage in older adults with low-energy falls, J. Am. Geriatr. Soc. 68 (5) (2020) 977–982.
[123] D. Caldeira, P. Alves da Silva, F.J. Pinto, Clinical outcomes of anticoagulated patients with atrial fibrillation after falls or head injury: insights from RE-LY, Stroke 54 (6) (2023) 1656–1659.
[124] T. Hagerty, M.W. Rich, Fall risk and anticoagulation for atrial fibrillation in the elderly: a delicate balance, Cleve. Clin. J. Med. 84 (1) (2017) 35–40.
[125] G.Y. Lip, N. Clementy, L. Pericart, A. Banerjee, L. Fauchier, Stroke and major bleeding risk in elderly patients aged≥ 75 years with atrial fibrillation: the loire valley atrial fibrillation project, Stroke 46 (1) (2015) 143–150.
[126] A.S. Volgman, G. Nair, R. Lyubarova, F.M. Merchant, P. Mason, A.B. Curtis, et al., Management of atrial fibrillation in patients 75 years and older: JACC state-of-the-art review, J. Am. Coll. Cardiol. 79 (2) (2022) 166–179.
[127] T. Galvain, R. Hill, S. Donegan, P. Lisboa, G.Y.H. Lip, G. Czanner, Efficacy and safety of anticoagulants in patients with atrial fibrillation and history of falls or risk of falls: a systematic review and multilevel meta-analysis, Drug Saf. 45 (11) (2022) 1349–1362.
[128] M. Grymonprez, M. Petrovic, T.L. De Backer, S. Steurbaut, L. Lahousse, Clinical outcomes in patients with atrial fibrillation and a history of falls using non-vitamin K antagonist oral anticoagulants: a nationwide cohort study, International Journal of Cardiology: Heart & Vasculature. 47 (2023) 101223.
[129] M. Müller, I. Chanias, M. Nagler, A.K. Exadaktylos, T.C. Sauter, Falls in ED patients: do elderly patients on direct oral anticoagulants bleed less than those on vitamin K antagonists? Scandinavian journal of trauma, Resuscitation and Emergency Medicine. 29 (1) (2021) 1–9.
[130] L. Rivard, L. Friberg, D. Conen, J.S. Healey, T. Berge, G. Boriani, et al., Atrial fibrillation and dementia: a report from the AF-SCREEN international collaboration, Circulation 145 (5) (2022) 392–409.
[131] A.A. Rahman, J. Michaud, S. Dell'Aniello, E.E.M. Moodie, J.M. Brophy, M. Durand, et al., Oral anticoagulants and the risk of dementia in patients with nonvalvular atrial fibrillation: a population-based cohort study, Neurology 100 (12) (2023) e1309–e1320.
[132] A.J. Rose, D.R. Miller, A. Ozonoff, D.R. Berlowitz, A.S. Ash, S. Zhao, et al., Gaps in monitoring during oral anticoagulation: insights into care transitions, monitoring barriers, and medication nonadherence, Chest 143 (3) (2013) 751–757.
[133] M. Grymonprez, A. Capiau, S. Steurbaut, E. Mehuys, K. Boussery, T.L. De Backer, et al., Adherence and persistence to oral anticoagulants in patients with atrial fibrillation: a belgian nationwide cohort study, Frontiers in Cardiovascular Medicine. 9 (2022) 994085.
[134] Y. Komatsu, S. Yokoyama, K. Hosomi, M. Takada, Impact of medication adherence on the association between oral anticoagulant use and risk of dementia: a retrospective cohort study using the japanese claims database, Drugs-Real World Outcomes. 9 (3) (2022) 437–449.
[135] C. Martinez, A. Katholing, C. Wallenhorst, A.T. Cohen, Prediction of significant bleeding during vitamin K antagonist treatment for venous thromboembolism in outpatients, Br. J. Haematol. 189 (3) (2020) 524–533.

[136] M.J. Nuñez, J.C. Villalba, E. Cebrián, A. Visoná, L. Lopez-Jimenez, M. Núñez, et al., Venous thromboembolism in immobilized patients with dementia. Findings from the RIETE registry, Thromb. Res. 130 (2) (2012) 173–177.
[137] K.J. Lin, D.E. Singer, K. Bykov, L.G. Bessette, J.M. Mastrorilli, A. Cervone, et al., Comparative effectiveness and safety of oral anticoagulants by dementia status in older patients with atrial fibrillation, JAMA Netw. Open 6(3):e234086-e (2023).
[138] D. Wang, X. Xu, X. Han, J. Xie, H. Zhou, W. Peng, et al., Clinical benefits of oral anticoagulants in atrial fibrillation patients with dementia: a systematic review and meta-analysis, Frontiers in Cardiovascular Medicine. 10 (2023) 1265331.
[139] M. Grymonprez, M. Petrovic, T.L. De Backer, M.A. Ikram, S. Steurbaut, L. Lahousse, Comparing the risk of dementia in subjects with atrial fibrillation using non-vitamin K antagonist oral anticoagulants versus vitamin K antagonists: a belgian nationwide cohort study, Age Ageing 52(3):afad038 (2023).
[140] S. Raposeiras-Roubín, E. Abu-Assi, R.C. Paz, X. Rosselló, C. Barreiro Pardal, M. Piñón Esteban, et al., Impact of malnutrition in the embolic–haemorrhagic trade-off of elderly patients with atrial fibrillation, EP Europace. 22 (6) (2020) 878–887.
[141] M. Shinohara, R. Wada, K. Yano, K. Akitsu, H. Koike, T. Kinoshita, et al., Relationship between the nutritional status and safety and efficacy outcomes in atrial fibrillation patients aged 80 years and over receiving oral anticoagulants, J. Cardiol. 77 (2) (2021) 147–153.
[142] C.M.M. De Jong, R.P. Rosovsky, F.A. Klok, Outcomes of venous thromboembolism care: future directions, J. Thromb. Haemost. 21 (5) (2023) 1082–1089.
[143] W.C. Members, J.A. Joglar, M.K. Chung, A.L. Armbruster, E.J. Benjamin, J. Y. Chyou, et al., ACC/AHA/ACCP/HRS guideline for the diagnosis and management of atrial fibrillation: a report of the american college of cardiology/american heart association joint committee on clinical practice guidelines, J. Am. Coll. Cardiol. 149 (2023) e1–e156.
[144] G.Y.H. Lip, A. Banerjee, G. Boriani, Chiang Ce, R. Fargo, B. Freedman, et al., Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report, Chest 154 (5) (2018) 1121–1201.
[145] J.G. Andrade, M. Aguilar, C. Atzema, A. Bell, J.A. Cairns, C.C. Cheung, et al., The 2020 Canadian cardiovascular society/Canadian geart rhythm cociety comprehensive guidelines for the management of atrial fibrillation, Can. J. Cardiol. 36 (12) (2020) 1847–1948.
[146] NICE. Atrial fibrillation: diagnosis and management 2021 [Available from: https://www.nice.org.uk/guidance/ng196.
[147] N.S. Key, A.A. Khorana, N.M. Kuderer, K. Bohlke, A.Y. Lee, J.I. Arcelus, et al., Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO guideline update, J. Clin. Oncol. 41 (16) (2023) 3063–3071.
[148] G.H. Lyman, M. Carrier, C. Ay, M. Di Nisio, L.K. Hicks, A.A. Khorana, et al., American society of hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer, Blood Adv. 5 (4) (2021) 927–974.
[149] A. Falanga, C. Ay, M. Di Nisio, G. Gerotziafas, L. Jara-Palomares, F. Langer, et al., Venous thromboembolism in cancer patients: ESMO clinical practice guideline, Ann. Oncol. 34 (5) (2023) 452–467.
[150] S.K. Kakkos, M. Gohel, N. Baekgaard, R. Bauersachs, S. Bellmunt-Montoya, S. A. Black, et al., European society for vascular surgery (ESVS) 2021 clinical practice guidelines on the management of venous thrombosis, Eur. J. Vasc. Endovasc. Surg. 61 (1) (2021) 9–82.
[151] D. Farge, C. Frere, J.M. Connors, A.A. Khorana, A. Kakkar, C. Ay, et al., 2022 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer, including patients with COVID-19, Lancet Oncol. 23 (7) (2022) e334–e347.
[152] NICE. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing 2023 [Available from: https://www.nice.org.uk/guidance/ng158.
[153] H.A. Tran, H. Gibbs, E. Merriman, J.L. Curnow, L. Young, A. Bennett, et al., New guidelines from the thrombosis and haemostasis society of Australia and New Zealand for the diagnosis and management of venous thromboembolism, Med. J. Aust. 210 (5) (2019) 227–235.