



Expert review

Anticoagulant Regimen for Nonvalvular Atrial Fibrillation in the Elderly and Frail Population



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ARTICLE INFO

Article History:

Received 26 May 2026

Revised 14 June 2026

Accepted 3 July 2026

Keywords:

atrial fibrillation
anticoagulation
DOACs
elderly
frailty
bleeding risk

Anticoagulant therapy is the cornerstone of stroke prevention in atrial fibrillation (AF), yet its management in elderly and frail patients remains particularly challenging. This review aims to summarize current evidence, guideline recommendations, and future perspectives regarding the optimal anticoagulant strategy in this vulnerable population. A narrative review of pivotal randomized clinical trials and major real-world registries was conducted, focusing on outcomes of direct oral anticoagulants (DOACs) versus vitamin K antagonists (VKAs) in patients aged ≥ 75 years or meeting frailty criteria. Across studies, DOACs consistently demonstrated similar or superior efficacy compared with VKAs for the prevention of stroke and systemic embolism, with a substantially lower risk of intracranial hemorrhage. Apixaban and edoxaban, particularly at adjusted doses, showed the most favorable balance between thromboembolic protection and bleeding risk. Conversely, switching stable elderly patients from long-term VKAs to DOACs, as in the FRAIL-AF trial, was associated with an early excess of clinically relevant nonmajor bleeding. Frailty, multimorbidity, renal impairment, and polypharmacy remain critical modifiers of both efficacy and safety, underlining the need for individualized dosing and regular renal function monitoring. Recent European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) and the American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) guidelines recommend DOACs as the preferred treatment for nonvalvular AF, emphasizing comprehensive risk assessment and shared decision-making. Emerging agents, such as factor XI inhibitors, offer a promising approach to minimizing bleeding risk in the elderly, though confirmation of their efficacy against ischemic events remains to be fully established. In elderly and frail patients with AF, DOACs represent the first-line anticoagulant therapy when appropriately dosed and monitored. A personalized, multidisciplinary approach incorporating frailty assessment, renal evaluation, and patient preference is essential to optimize outcomes. Future trials specifically enrolling very old and severely frail patients are urgently needed to close existing evidence gaps.

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The use of anticoagulant drugs has become a cornerstone in the management of various thrombotic disorders, such as atrial fibrillation, deep vein thrombosis, and pulmonary embolism, where the prevention of blood clot formation is crucial.¹ While these medications offer substantial benefits in terms of reducing the risk of stroke and

other thromboembolic events, their administration in elderly and frail individuals represents a unique and intricate challenge.² This review aims to investigate the role of anticoagulant therapy in the geriatric and frail population, highlighting the multifaceted nature of this issue, its clinical significance, and the pressing need for tailored approaches.

The aging demographic is rapidly expanding across the globe, and with it, the prevalence of chronic medical conditions and cardiovascular diseases.³ As a result, healthcare providers are confronted with

Funding: None.

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<https://doi.org/10.1016/j.amjcard.2026.07.006>

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an increasing number of elderly patients who require anticoagulant therapy. Simultaneously, frailty, characterized by diminished physiologic reserves and heightened vulnerability to stressors, is a common feature of the aging process. The confluence of these factors necessitates a careful examination of the risks and benefits associated with anticoagulant use in this vulnerable population.

The primary objective of anticoagulation therapy is to mitigate the risk of thromboembolic events; yet this pursuit often comes at the cost of increased bleeding tendencies. In the elderly, age-related changes in pharmacokinetics and pharmacodynamics, coupled with the presence of comorbidities and polypharmacy, amplify the potential for adverse outcomes.⁴ Consequently, the delicate balance between preventing clot formation and avoiding hemorrhagic complications becomes remarkably challenging in this demographic.

Moreover, frailty further complicates the clinical landscape. Frail individuals not only exhibit higher baseline risks of falls and injuries but also have diminished physiological reserves to cope with bleeding events.⁵ Therefore, prescribing anticoagulants in these patients demands a comprehensive evaluation of individualized risk factors, functional status, and patient preferences.

This review embarks on a comprehensive view embracing anticoagulant use in the elderly and frail population, analyzing the existing evidence, clinical guidelines, and emerging strategies aimed at optimizing therapeutic outcomes while minimizing harm, shedding light on the critical need for a personalized approach to anticoagulation in this rapidly growing demographic segment.

Methods

This review was performed as a narrative synthesis of the existing literature: a general search strategy was employed using widely accessible biomedical databases, including PubMed, Google Scholar, and Scopus. The search covered publications from 2010 to 2025, focusing on studies addressing anticoagulant therapy in elderly and frail patients with nonvalvular atrial fibrillation. The search terms included combinations of “atrial fibrillation,” “oral anticoagulants,” “direct oral anticoagulants,” “vitamin K antagonists,” “elderly,” and “frailty.” Study selection was based primarily on relevance to the topic, with preference given to widely cited clinical trials, registries, and review articles. No formal inclusion or exclusion criteria were predefined, and no systematic assessment of study quality or risk of bias was undertaken. Case series, narrative reviews, randomized controlled trials, and guideline documents were all considered when deemed pertinent by the authors. In cases of overlapping study populations, the most comprehensive or recent dataset was retained.

Reference lists of relevant articles and reviews were manually screened to identify additional eligible studies. The information gathered was summarized qualitatively, emphasizing clinically meaningful findings and practical implications rather than detailed statistical synthesis. The resulting overview is intended to provide a broad understanding of current evidence and trends, acknowledging potential limitations related to the nonsystematic nature of the search and selection process.

Risk Factors of Frailty and Elderly Clinical Characteristics (Figure 1)

Frailty

Frailty is defined as a clinically recognizable state of increased vulnerability resulting from aging-associated decline in reserve and function across multiple physiologic systems.⁶ Its clinical phenotype is characterized by weight loss, muscular weakness, and a low physical activity which carries an increased risk for poor health outcomes including falls, disability, higher hospitalization rate, and mortality.⁷ Some degree of frailty is very common in older adults with AF (up to 80 %) and is associated with an increased risk of OAC-related bleeding and mortality.⁸

In a meta-analysis including 1,187,651 persons with AF, the frailty pooled prevalence was 39.7% (95% CI = 29.9% to 50.5%, $I^2 = 100\%$).⁹ Frail AF patients were associated with a higher risk of all-cause death (OR = 5.56, 95% CI = 3.46 to 8.94), ischemic stroke (OR = 1.59, 95% CI = 1.00 to 2.52), and bleeding (OR = 1.64, 95% CI = 1.11 to 2.41), when compared to robust individuals. Frailty may influence the prognosis and management of AF patients, thus requiring person-tailored intervention. In a posthoc analysis of the ENGAGE AF-TIMI 48, edoxaban was similarly efficacious to warfarin across the frailty spectrum and was associated with lower rates of bleeding except in those with severe frailty. Overall, with increasing frailty, there was an increase in stroke and bleeding risk, highlighting the need for high-quality, frailty-specific population randomized control trials (RCTs) to guide therapy in this vulnerable population.¹⁰

Frailty can be assessed using several validated instruments, reflecting its multidimensional nature and the absence of a universally accepted definition. The most commonly adopted tools include the Fried Frailty Phenotype, which identifies frailty according to physical characteristics such as weight loss, weakness, exhaustion, slowness, and low physical activity; the Frailty Index, based on the cumulative deficit model; the Clinical Frailty Scale (CFS), a clinician-based assessment of functional status and vulnerability; the

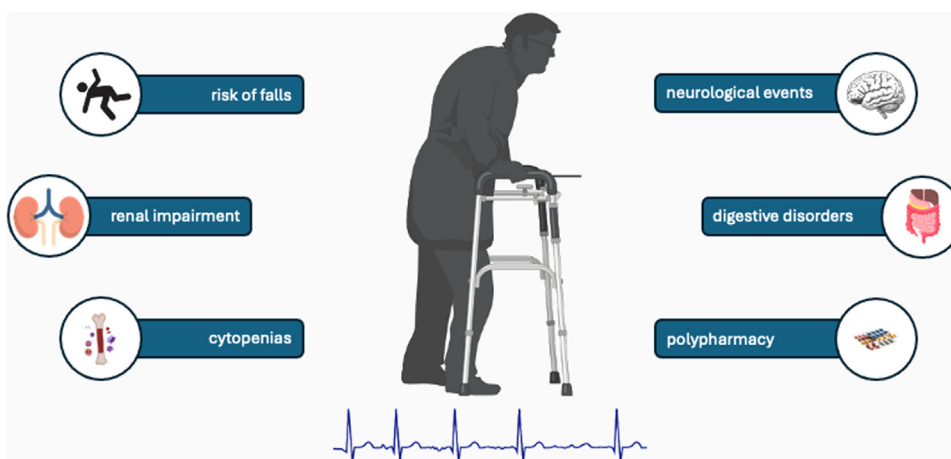


Figure 1. Clinical factors influencing the effectiveness and safety of anticoagulation therapy in elderly and frail patients with atrial fibrillation.

Groningen Frailty Indicator (GFI), a multidomain questionnaire evaluating physical, cognitive, social, and psychological domains; and the Hospital Frailty Risk Score (HFRS), which is derived from administrative data. Importantly, these instruments identify partially overlapping but not identical patient populations, contributing to heterogeneity across studies and potentially influencing estimates of both thromboembolic and bleeding risk in patients with AF.

Comorbidity

Multimorbidity, defined as the coexistence of at least 2 chronic diseases, is associated with adverse outcomes, adds complexity to AF management, and poses a significant burden on healthcare costs. About 3 out of 4 patients aged ≥ 65 years with AF are multimorbid, with many of these morbidities representing risk factors for AF-related complications as bleeding.¹¹

The most common risk factors for bleeding in patients affected from AF in OAC therapy include active cancer, pancytopenia, chronic kidney disease, history of prior bleeding, uncontrolled hypertension, and cerebrovascular disease. In a posthoc analysis from the ARISTOTLE trial, the risk of major bleeding (MB) rises by approximately 15% for each singular comorbidity.¹²

In a propensity-matched retrospective study of 155,959 multimorbid patients with AF, compared to warfarin, apixaban and rivaroxaban were associated with a lower risk of stroke or systemic embolism (HR 0.63, 95% CI 0.54 to 0.74; HR 0.70, 95% CI 0.64 to 0.77, respectively). Apixaban and dabigatran were associated with a lower risk of major bleedings (HR 0.61, 95% CI 0.56 to 0.67; HR 0.75, 95% CI 0.66 to 0.86, respectively).¹³

Risk of falls

More than 25% of older adults fall each year, and falls are the leading cause of injury-related death in persons aged 65 years or older; therefore, about half of patients aged ≥ 65 years with AF have an increased risk of falls.^{14,15} Falls result from age-related physiologic changes intensified by multiple intrinsic and extrinsic risk factors. Major modifiable risk factors include gait and balance disorders, orthostatic hypotension, sensory impairment, medications, and environmental hazards.¹⁶ Falls and the fear of fall-related bleeding are the most common reason to refrain from OAC, even though it remains unclear whether falls (or minor head injury) convey a higher risk of major bleedings and intracranial hemorrhage in anticoagulated older patients, while the increase in the absolute risk of fall-related bleeding is small.¹⁷ Actually, the risk of falls is included only in 2 bleeding risk scores, the HEMORR2HAGES and the ACCP score.¹⁸ In a study-level meta-analysis, DOACs were associated with superior effectiveness compared with VKA for ischemic stroke/systemic embolism (hazard ratio [HR] 0.82, 95% confidence interval [CI] 0.69 to 0.98; $p < 0.05$) and safety (HR 0.53, 95% CI 0.40 to 0.71; $p < 0.05$) for intracranial hemorrhage, in a dataset of patients with AF who were at risk of falls.¹⁹

Drug interactions

Several different drug–drug interactions need to be considered when evaluating the risks associated with anticoagulant therapy. Warfarin has a narrow therapeutic index and has many drug–drug and drug–food interactions that may increase the risk of bleeding or reduce its effectiveness.²⁰

Drug–drug interactions are responsible for around 60% of hemorrhagic adverse drug events in older patients treated with OACs.²¹ Older patients with polypharmacy who are treated with VKAs spend less time in the therapeutic INR range than those without polypharmacy, leading to an about 1.3- to 1.8-fold increased risk of major

bleedings.²² DOACs generally have fewer drug–drug interactions, but some important ones should be considered during prescribing: dabigatran, and to a lesser extent edoxaban, are substrates of the P-glycoprotein (P-gp) efflux transporter, therefore, medications that inhibit P-gp, such as ketoconazole and dronedarone, can increase the concentrations of both agents, raising the risk of bleeding. Conversely, P-gp inducers like rifampicin and carbamazepine may lower their effectiveness.²³ Rivaroxaban and apixaban are metabolised by both CYP3A4 and P-gp: strong inhibitors of either pathway may increase the risk of bleeding. Further agents that can increase the risk of bleeding include selective serotonin reuptake inhibitors (SSRIs) and non-steroidal anti-inflammatories (NSAIDs), so the need for these medications should be carefully pondered when used in addition to anticoagulation.^{24,25}

Clinical Evidence for Anticoagulant Selection in Elderly and Frail Patients With Atrial Fibrillation

The evidence on the efficacy and safety of DOACs versus VKAs in older patients with atrial fibrillation primarily comes from subgroup analyses of RCTs and observational studies, which were not specifically designed to investigate outcomes in this age group. Older patients are regularly excluded from OAC trials due to comorbidities or comedications, even though such cohort of patients are considered at high bleeding risk (Table 1).

The FRAIL-AF trial was a randomized, open-label, pragmatic, superiority trial conducted across 8 centers in the Netherlands, enrolling 1,330 patients >75 years old already on oral anticoagulant therapy with Vitamin K Antagonists (VKAs) for nonvalvular atrial fibrillation and defined as frail due to a Groningen Frailty Indicator (GFI) >3 .²⁶ The GFI is a 15-item questionnaire assessing mobility, cognitive and nutritional status, psychosocial activity, and comorbidities, and has been widely validated in different populations.²⁷

Eligible patients were randomized to either continue a VKA-based anticoagulant strategy with an INR target between 2 and 3 (control group, 661 pts) or to switch to a Direct Oral Anticoagulant (DOAC)–based strategy (switching group, 663 pts). Initially, the switch was performed when $\text{INR} < 2$, but after preliminary analyses suggested more bleeding during the transition, the protocol was amended to switch only when $\text{INR} < 1.3$. The choice and dose of DOAC were left to the investigator's discretion based on patient characteristics and drug labeling. In the switching group, 57 patients (8.6%) switched to dabigatran, 332 (50.2%) to rivaroxaban, 115 (17.4%) to apixaban, and 109 (16.5%) to edoxaban; in 22 cases (3.3%), the switch was not performed despite randomization. Low-dose DOAC use was considered off-label in 44 subjects.

The primary endpoint was major or clinically relevant nonmajor (CRNM) bleeding per ISTH definition;²⁸ secondary endpoints included all-cause mortality, individual bleeding complications, thromboembolic events (stroke, TIA, peripheral embolism), and composite ischemic and hemorrhagic outcomes. Mean follow-up was 344 days, during which 90 deaths occurred (44 in the switching group and 46 in the control group), including 31 cardiovascular deaths (12 vs 19). Fatal bleeding incidence was the same (5 per group). After 163 primary-outcome bleeding events (101 DOAC vs 62 VKA), the trial was stopped early for futility, as superiority of switching to DOACs could not be demonstrated. The switching group showed a 1.69-fold increased risk of major or CRNM bleeding, mainly gastrointestinal and urogenital, with no difference in hemorrhagic stroke. Subgroup analyses found no effect of age, sex, GFI score, or renal function. Bleeding risk varied by DOAC type—higher with rivaroxaban (HR 1.95) and apixaban (HR 2.17), apparently lower with edoxaban (HR 1.10)—though this was a post hoc analysis. The higher bleeding risk was mainly driven by CRNM events (HR 1.77).

Table 1
Summary of major clinical trials and registries evaluating anticoagulation in elderly and frail patients with atrial fibrillation

Study/Registry	Population (age/frailty)	Intervention vs comparator	Frailty assessment	Main results and key findings (overall vs in elderly/frail subgroup)
RE-LY (2009)	18,113 pts; 40% ≥75 years	Dabigatran (150/110 mg) vs Warfarin	No formal frailty scale	Overall: Dabigatran 150 mg superior for stroke prevention; 110 mg noninferior with less bleeding. (110 mg RR 0.80; 150 mg RR 0.93) Elderly ≥75: Marked reduction in ICH at both doses; extracranial/GI bleeding increased with 150 mg in elderly.
ROCKET-AF (2011)	14,264 AF pts; 44% ≥75 years	Rivaroxaban vs Warfarin	No formal frailty scale	Overall: Stroke/SE HR 0.80 (noninferior); major bleeding similar. Elderly ≥75: Subgroup analyses showed consistent efficacy vs warfarin with reduced intracranial hemorrhage but higher gastrointestinal bleeding.
ARISTOTLE (2011)	18,201 AF pts; 31% ≥75 years	Apixaban vs Warfarin	No formal frailty scale	Overall: Stroke/SE HR 0.80 (noninferior); major bleeding similar. Elderly ≥75: Subgroup analyses showed consistent efficacy vs warfarin with reduced intracranial hemorrhage but higher gastrointestinal bleeding.
ENGAGE AF–TIMI 48 (2013)	21,105 AF pts; 40% ≥75 years	Edoxaban (60/30 mg) vs Warfarin	Claims-based Frailty Index	Overall: Stroke/SE HR 0.83; major bleeding HR 0.83. Elderly ≥75/≥80: Reduced ICH across ages; higher GI bleeding with high-dose edoxaban, while low-dose regimen showed favorable bleeding profile in ≥80 years.
ELDERCARE-AF (2020)	984 pts ≥80 years, unsuitable for std DOAC	Edoxaban 15 mg vs Placebo	No formal frailty scale	Overall/Target population: Stroke/SE HR 0.34; no statistically significant increase in major bleeding. Demonstrates efficacy and acceptable safety in very elderly, high-risk patients.
FRAIL-AF (2023)	1,330 frail pts >75 years (GFI >3)	Switch VKA → DOAC vs continue VKA	Groningen Frailty Indicator	Frail subgroup only: Major/CRNM bleeding HR 1.69 with switching; no difference in stroke or mortality. Highlights that frailty-defined subgroup results differ from age-based subgroups.
EORP-AF Registry (2016)	10,000 European AF pts	Observational	40 items-physician-reported frailty classification	Frail vs nonfrail: Frailty reduced likelihood of OAC prescription (OR 0.70, 95% CI 0.55 to 0.89); however, treated frail patients still derived net clinical benefit, attenuated only in extreme frailty.
REPOSI Registry (2019)	Elderly frail AF pts	Real-world DOAC use	Charlson Comorbidity Index	Frail elderly: DOAC therapy associated with lower stroke and mortality when dose-adjusted to renal function; observational HRs refer to frail subgroup only.
ANAFIE Registry (2021)	32,275 pts ≥80 years	DOAC vs Warfarin/No OAC	No formal frailty scale	Elderly ≥80: DOACs use associated with lower stroke/SE (HR 0.53) and mortality (HR 0.65) compared with warfarin or no OAC; benefits consistent across bleeding-risk strata.

AF = atrial fibrillation; CRNM = clinically relevant non-nonmajor bleeding; eGFR = estimated glomerular filtration rate; GFI = Groningen Frailty Indicator; ICH = intracranial hemorrhage; pts = patients; SE = systemic embolism.

Thromboembolic events (HR 1.26), all-cause mortality (HR 0.96), and combined ischemic/hemorrhagic stroke (HR 1.3) were comparable.

The study generated considerable debate, as DOACs have consistently demonstrated excellent safety profiles—even in high bleeding–risk patients—and are considered first-line for anticoagulation initiation. This trial deserves credit for focusing on elderly and frail patients, a group usually excluded from pivotal DOAC trials. However, real-world data support DOAC safety in this setting, particularly in treatment-naïve patients.

A key aspect in interpreting these results is that FRAIL-AF enrolled patients with long-standing VKA therapy (mean AF duration 12 years), who had already shown good adherence, tolerance, and stable INR control (≥70% within range). This population thus represents a “survivor cohort”—frail elderly patients who had already demonstrated the ability to tolerate and manage VKAs over time. As a result, a selection bias is introduced, excluding those frail patients who previously discontinued VKAs due to poor control or

intolerance. This helps explain the discrepancy between the FRAIL-AF findings and real-world data, which generally favor DOACs in anticoagulation-naïve frail patients.

The higher rate of CRNM bleeding—particularly gastrointestinal—might have been mitigated by adequate or intensified gastroprotection. In contrast, there were no significant differences in fatal or intracranial bleeding, which are the events with the greatest prognostic impact. Lastly, the relatively small sample size and early study termination limit the ability to draw definitive conclusions.

The Edoxaban Low-Dose for Elder Care Atrial Fibrillation Patients (ELDERCARE-AF) trial aimed to assess the safety and efficacy of low-dose edoxaban among Japanese patients ≥80 years of age who had nonvalvular AF and in whom standard oral anticoagulants were not recommended.²⁹

A total of 984 patients were randomly assigned in a 1:1 ratio to receive a daily dose of 15 mg of edoxaban (492 patients) or placebo (492 patients). The primary efficacy end point was the composite of

stroke or systemic embolism, and the primary safety end point was major bleeding according to the definition of the International Society on Thrombosis and Haemostasis.

The annualized rate of stroke or systemic embolism was 2.3% in the edoxaban group and 6.7% in the placebo group (hazard ratio, 0.34; 95% confidence interval [CI], 0.19 to 0.61; $p < 0.001$), and the annualized rate of major bleeding was 3.3% in the edoxaban group and 1.8% in the placebo group (hazard ratio, 1.87; 95% CI, 0.90 to 3.89; $p = 0.09$). There were substantially more events of gastrointestinal bleeding in the edoxaban group than in the placebo group. There was no substantial between-group difference in death from any cause (9.9% in the edoxaban group and 10.2% in the placebo group; hazard ratio, 0.97; 95% CI, 0.69 to 1.36).

The findings from this trial demonstrate that a very low dose of edoxaban was more effective than placebo in reducing stroke or systemic embolism among Japanese patients aged 80 years and older with AF. The primary safety outcome was comparable between groups, though overall bleeding events were higher with edoxaban, mainly due to gastrointestinal bleeding. In the placebo group, the incidence of stroke or systemic embolism increased with age, while edoxaban maintained its protective effect across older age categories. Similarly, bleeding risk with edoxaban also increased with advancing age. Mortality rates were high and comparable between the 2 groups, and trial discontinuation was frequent, occurring in nearly one-third of participants.

These participants were extremely elderly, with a high prevalence of frailty—about one-third had experienced a fall in the year before enrolment. The edoxaban dose tested was one-quarter of the standard 60 mg daily dose approved for stroke prevention in AF. Typically, the dose is reduced to 30 mg daily when estimated glomerular filtration rate (eGFR) is below 50 mL/min. The current results suggest that an even lower dose may still be effective and might be an option for selected elderly patients. However, a key limitation is that the median body weight in this cohort was approximately 50 kg and all participants were East Asian, leaving uncertainty about whether similar efficacy would be observed in elderly populations from other world-countries.

A further point that warrants emphasis is that the 15 mg once-daily edoxaban regimen evaluated in ELDERCARE-AF is currently not approved for stroke prevention in patients with atrial fibrillation in either the United States or Europe. Regulatory approval of edoxaban for AF is based on the findings of the ENGAGE AF-TIMI 48 trial, in which dose reduction from 60 mg to 30 mg (or from 30 mg to 15 mg in selected patients) was permitted according to predefined clinical criteria.

Although the study suggests that very-low-dose edoxaban may be a reasonable option in carefully selected, extremely elderly and frail patients who are unsuitable for standard anticoagulation, its use should be considered off-label in Western clinical practice.

The randomized evaluation of long-term anticoagulant therapy (RE-LY) trial enrolled 18,113 patients who were randomly assigned to receive either dabigatran 110 mg or 150 mg twice daily, or warfarin with dosing adjusted to maintain an international normalized ratio (INR) of 2.0 to 3.0, over a median follow-up of 2 years.³⁰ Compared with warfarin, dabigatran 110 mg twice daily resulted in a significantly lower rate of major bleeding (2.87% vs 3.57%; $p = 0.002$), while the 150 mg twice-daily dose showed a comparable bleeding risk (3.31% vs 3.57%; $p = 0.32$). A significant interaction between treatment and age was observed: for patients younger than 75 years, dabigatran 110 mg twice daily reduced the risk of major bleeding compared with warfarin (1.89% vs 3.04%; $p < 0.001$), whereas in those aged 75 years or older, the bleeding risk was similar (4.43% vs 4.37%; $p = 0.89$; p for interaction < 0.001). For the 150 mg dose, patients under 75 experienced a lower risk of major bleeding than with warfarin (2.12% vs 3.04%; $p < 0.001$), while those aged 75 and older showed

a trend toward a higher risk (5.10% vs 4.37%; $p = 0.07$; p for interaction < 0.001). The RE-LY trial demonstrates that dabigatran offers an effective and, in many cases, safer alternative to warfarin for long-term anticoagulation, though outcomes are influenced by patient age and dosage. These findings highlight the importance of individualized anticoagulant therapy, where both efficacy and patient characteristics—particularly age—must guide dose selection to optimize safety and therapeutic benefit.

In the Rivaroxaban OnceDaily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF trial), rivaroxaban was compared to warfarin in preventing stroke and systemic embolism in individual with AF.³¹ Rivaroxaban is an oral, direct Factor Xa inhibitor that targets free and clot-bound Factor Xa and Factor Xa in the prothrombinase complex, with maximum plasma concentrations being reached 2 to 4 hours after tablet intake. Elimination of rivaroxaban occurs with a terminal half-life of 5 to 9 hours in young subjects and 11 to 13 hours in elderly individuals.³² This drug is predominantly metabolized by the liver and is less dependent on renal excretion. Moreover, since rivaroxaban has various elimination pathways, it has no clinically relevant interactions with most used medications.

A prespecified secondary analysis of the ROCKET AF trial was able to compare outcomes of rivaroxaban versus warfarin in older and younger individuals with AF.³³ Of the 14,264 individuals enrolled in the main study, 44% (6,229) were aged ≥ 75 years old and suffered atrial fibrillation with ≥ 2 stroke risk factors. Individuals were randomized in a double-blind fashion to treatment with either a fixed dose of rivaroxaban (20 mg once daily or 15 mg daily for patients with moderate kidney injury [creatinine clearance 30–49 mL/min]) or adjusted-dose warfarin (target INR = 2.0 to 3.0). Individuals with severe kidney injury (creatinine clearance < 30 mL/min) were not included in the study. The primary end point was stroke and systemic embolism. The principal safety end point was a composite of major and nonmajor clinically relevant bleeding events.

Median age was 79 years for elderly group compared with 66 years for younger patients, with a mean CHADS2 score of 3.7 for elderly and 3.3 for younger, and a median follow-up of 696 and 721 days, respectively. During 10 866 patient-years of exposure, older individuals suffered a higher rate of stroke and systemic embolism compared to younger (2.57 vs 2.05 per 100 patient-year, $p = 0.0068$). For older patients, primary event rates were neutral among patients treated with rivaroxaban and with warfarin (HR = 0.80; 95% CI, 0.63 to 1.02) with similar treatment effect for younger subjects (HR = 0.95; 95% CI, 0.76 to 1.19). No significant interaction of treatment efficacy with age for the primary end point was found ($p = 0.31$). Bleeding events were higher among older patients than in younger (4.63 vs 2.67 per 100 patient-year, $p < 0.0001$), but there were no significant differences, in rates of major bleeding among individuals on rivaroxaban compared with those on warfarin in both age group and the relative risk of bleeding was comparable among older and younger individuals. Of note, older subjects on rivaroxaban suffered a higher rate of the combined end-point of major or clinically relevant nonmajor bleeding compared to those on warfarin, mainly due to a significant higher rate of nonmajor gastrointestinal bleeding. Hemorrhagic stroke rates were similar in both age groups and consistent with the overall trial results, where rivaroxaban significantly reduced the risk of intracranial hemorrhage and fatal bleeding compared to warfarin. No significant interaction between patient age and the relative safety of rivaroxaban compared with warfarin was found (interaction $p = 0.27$).

Therefore, according to the evidence coming from this study, rivaroxaban demonstrated a similar protection from embolic/ischemic events comparable to warfarin in elderly population, with no significant increase in major hemorrhagic complications, with a lower risk of intracranial hemorrhage at the expense of a higher rate of

gastrointestinal bleeding, supporting the possibility of rivaroxaban use as an alternative for a proper anticoagulation in the elderly.

The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial compared apixaban with warfarin for in 18,201 patients with AF and at least 1 additional risk factor for stroke cardiac failure, hypertension, age 75 years or older, diabetes, previous stroke or TIA).³⁴ The apixaban dose was 5 mg twice daily, or 2.5 mg twice daily for patients with 2 or more of the following factors: age ≥ 80 years, bodyweight ≤ 60 kg, serum creatinine ≥ 133 mmol/L (≥ 1.5 mg/dL). The study demonstrated that apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality.³⁵

Three years later, Halvorsen S and coll. published a subanalysis of the trial according to the patient age. Of the 18,201 patients enrolled in the ARISTOTLE trial, 5,471 (30%) were < 65 lt; 65 years of age, 7,052 (39%) were 65 to < 75 years of age, and 5,678 (31%) were ≥ 75 years of age, with 2,436 patients were ≥ 80 years of age (13% of the total population).³⁶ Patients over 75 years of age were more frequently female and presented with a higher number of comorbidities, along with a greater history of prior stroke, prior bleeding, and renal insufficiency and showed higher risk of all cardiovascular events during the trial irrespective of study drug assignment. This subanalysis demonstrated how the benefits of apixaban versus warfarin were consistent regardless of age for all endpoints of the study: the superiority of apixaban to warfarin in reducing stroke or systemic embolism was consistent across age groups and no differences have been found in the reduction of all-cause mortality in relation to age. Apixaban reduced the rate of major and fatal bleeding and fatal hemorrhagic stroke compared with warfarin across age groups and is associated with a lower rate of ICH in patients 65 to 74 years (HR 0.35, 95% CI 0.20 to 0.60), as well as in patients ≥ 75 years of age (HR 0.34, CI 0.20 to 0.57). In patients < 65 years of age, the number of ICHs were very low in both groups. Treatment with apixaban reduced the risk of net clinical events compared with warfarin in a consistent way across age groups (interaction with continuous age, $p = 0.18$). These results were consistent in patients ≥ 80 years of age: stroke or systemic embolism was reduced from 1.9% per year with warfarin to 1.53% per year with apixaban (HR 0.81) major bleeding from 5.41% per year with warfarin to 3.55% per year with apixaban (HR 0.66) and ICH from 1.32% per year with warfarin to 0.47% per year with apixaban (HR 0.36). Similar results, also have been found in patients ≥ 75 years of age treated with reduced apixaban dose and across the range of estimated glomerular filtration rate also in the elderly.

The results of this subgroup analysis should be emphasized for 2 fundamental reasons. First, they confirm that the safety and efficacy of apixaban compared to warfarin remain unchanged in elderly patients. More importantly, given that subjects over 75 years of age are at the highest risk for both ischemic and hemorrhagic events, the benefit of apixaban is enhanced in this subgroup. A further key strength of the study resides in the fact that the results are confirmed irrespective of renal glomerular filtration rate levels. Renal dysfunction is known to be a particularly common comorbidity in the elderly, and therefore, the possibility to use the reduced dose of apixaban represents a highly appealing therapeutic option.

Similarly to ROCKET-AF trial, the The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48), compared the role of edoxaban (both 60 mg and 30 mg doses) versus warfarin in 21,105 individuals with moderate to high-risk atrial fibrillation.³⁷ Edoxaban is a highly specific, direct inhibitor of factor Xa, absorbed rapidly, with no significant effect of food on its pharmacokinetics or pharmacodynamics.³⁸ Once absorbed, edoxaban is present mostly in the parent drug form; however, there are several metabolites, and those with the highest concentration are formed via hydrolysis, whereas some minor metabolites are produced through cytochrome P450 3A

enzymes.³⁹ The drug has a relatively low protein binding (40% to 59%) and its half-life ranges from 5.8 to 10.7 hours. Renal elimination occurs at a rate higher than glomerular filtration, suggesting an active secretion into the kidney.⁴⁰ Approximately 60% of edoxaban can be found in the feces and 40% in the urine.³⁸ Edoxaban is a substrate of the transporter P-glycoprotein and coadministration with P-glycoprotein substrate/inhibitors (i.e., verapamil, quinidine, or dronedarone) has been shown to increase total exposure of edoxaban by approximately 50%, whereas modest/minimal effects were observed with other P-glycoprotein substrates like amiodarone, atorvastatin, and digoxin.⁴¹

A prespecified analysis from the ENGAGE AF-TIMI 48 trial evaluated clinical outcomes with edoxaban versus warfarin according to age.⁴² The 21,105 participants of the study were stratified into 3 prespecified age groups: < 65 ($n = 5,497$), 65 to 74 ($n = 7,134$), and ≥ 75 ($n = 8,474$) years. Patients were randomized in a 1:1:1 ratio to receive a higher-dose of edoxaban (60 mg once daily), a lower-dose (30 mg once daily) or to warfarin at a target INR of 2.0 to 3.0. The dose of edoxaban was reduced by 50% if any of these characteristics were present (either at the time of randomization or during the study): calculated creatinine clearance of ≤ 50 mL/min using the Cockcroft-Gault formula, bodyweight ≤ 60 kg, or the concomitant use of potent P-glycoprotein inhibitors. Patients with severe renal insufficiency (creatinine clearance < 30 mL/min) were not included in the study. The primary efficacy endpoint was the composite of stroke or systemic embolic events. The principal safety end point was major bleeding as defined by the International Society on Thrombosis and Hemostasis.

Median age of the trial population was 72 years (interquartile range, 64 to 78), and 8,474 (40.2%) were ≥ 75 years. The elderly was more likely to be female, with lower renal function and body weight, meeting more frequently the criteria for edoxaban dose reduction at baseline. In the warfarin group rates of stroke or systemic embolic event (1.1%, 1.8%, and 2.3%) and major bleeding events (1.8%, 3.3%, and 4.8%) resulted increased across age groups ($p < 0.001$ for both), but with no interactions between age group and randomized treatment in the primary efficacy and safety outcomes. In the elderly group (≥ 75 years), the primary endpoint was similar among edoxaban versus warfarin (HR 0.83 [0.66 to 1.04]), while major bleeding was significantly reduced with edoxaban (HR 0.83 [0.70 to 0.99]), with a lower rate of intracranial hemorrhage for edoxaban versus warfarin, but at the expense of major GI bleeding events with high-dose edoxaban. Of note, the efficacy of edoxaban compared with warfarin in preventing stroke or systemic embolism was preserved also with the lower dosage, while there was a significant interaction demonstrating an even greater reduction in major bleeding events among elderly who received a dose reduction of edoxaban as compared to similar patients in the warfarin group (p interaction < 0.01). Indeed, in the subgroup of patients > 80 years, edoxaban 30 mg once daily showed similar ischemic/embolic protection compared to warfarin, with the advantage of a higher reduction in major bleeding events.

All these findings support a favorable risk/benefit ratio for the use of edoxaban compared to warfarin in older individuals, suggesting its role for anticoagulation in the elderly due to an advantageous safety profile.

The ANAFIE (All Nippon AF In the Elderly) registry was established to clarify the anticoagulant therapy and clinical outcomes of elderly patients with nonvalvular AF in real-world clinical practice in Japan.⁴³ Based on the results of ELDERCARE-AF, the investigators divided the patients in the ANAFIE registry into a high bleeding risk group (age: ≥ 80 years; CHADS2 score: ≥ 2 ; and presence of ≥ 1 bleeding risk factor: creatinine clearance of 15 to 30 mL/minute, prior bleeding at critical sites, body weight of ≤ 45 kg, or continuous antiplatelet use) and reference group. Focusing on the high-risk bleeding group, they investigated the therapeutic efficacy and safety of anticoagulant therapy. In the high-risk ($n = 7,104$) and reference

($n = 25,171$) group patients, 89.0% and 93.4%, respectively, used OAC agents. Of these, respectively, 30.1% and 24.2% used warfarin, and 58.9% and 69.1% used DOAC. Compared with the reference group, the high-risk group had higher incidences of stroke/systemic embolism, major bleedings and all-cause death. In the high-risk group, DOAC agent use vs nonuse of OAC agents was associated with reduced incidences of stroke/systemic embolism (HR: 0.53; 95% CI: 0.36 to 0.79) and all-cause death (HR: 0.65; 95% CI: 0.52 to 0.81) but not with major bleeding (HR: 1.09; 95% CI: 0.63 to 1.89). DOAC agents were superior to warfarin in effectiveness and safety. Taken together, the results of the present registry suggest that DOACs should be recommended as anticoagulants for nonvalvular AF according to the current guidelines, even in very elderly patients with high bleeding risk.

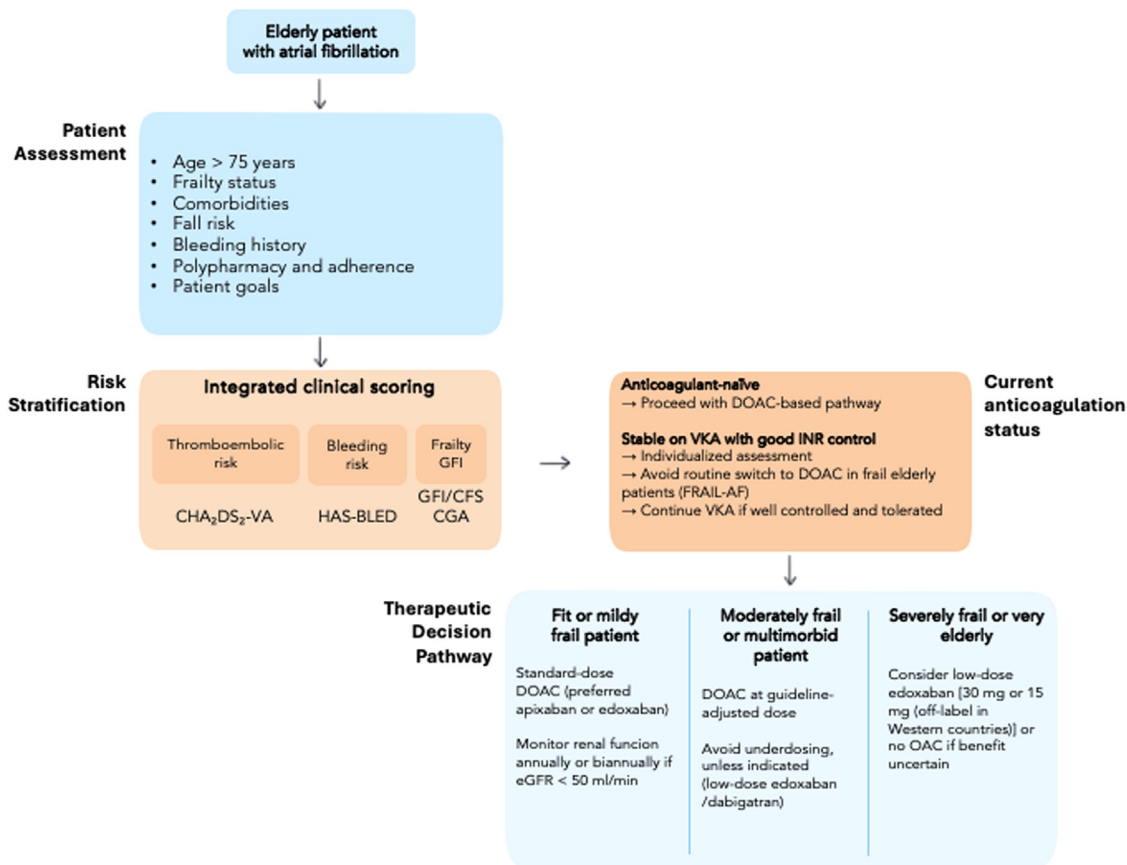
The EORP-AF Long-Term General Registry found that higher frailty burden, was associated with lower likelihood of anticoagulant prescription, even when scores indicated high stroke risk.⁴⁴ Among 10,177 patients, Frail patients with AF were less likely to be treated with OACs (odds ratio 0.70, 95% confidence interval 0.55 to 0.89), especially with nonvitamin K antagonist OACs and managed with a rhythm control strategy, compared with robust patients. Frailty was assessed according to a 40-items physician-reported frailty classification. This discrepancy reflects clinicians' concern over bleeding risks, polypharmacy, renal impairment, and poor adherence, particularly in the context of limited social support or cognitive decline. However, the study showed clinical benefit of OAC in patients with high frailty, but not in very high/extremely frail ones.

Similarly, observational data, including the recent REPOSI registry,⁴⁵ highlight that DOAC use in the elderly and frail is associated with a net clinical benefit, even in those with renal dysfunction, if appropriately dose adjusted.

Current Guidelines and Clinical Practice (Figure 2)

Management of AF in the elderly and frail population presents a nuanced challenge due to the delicate balance between thromboembolic risk reduction and bleeding complications. Both the 2024 European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) guidelines and the 2023 American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) guidelines underscore the primacy of stroke prevention using oral anticoagulants in patients at high thromboembolic risk, including older adults.¹ The ESC/EACTS guidelines recommend anticoagulation in patients with a CHA₂DS₂-VA score of ≥ 2 (class I, Level C) or ≥ 1 (class IIa, level C), irrespective of gender. On the other hand, the 2023 AHA/ACC/HRS guidelines state that patients with AF at an intermediate annual risk of thromboembolic events, such as those with a CHA₂DS₂-VASc score of 1 in men or 2 in women, who remain uncertain about the net clinical benefit of anticoagulation, may benefit from consideration of additional risk modifiers, including advancing age, to guide shared decision-making.⁴⁶ DOACs are recommended over VKAs for nonvalvular AF, given their more predictable pharmacokinetics, absence of routine coagulation monitoring, and superior safety profile, particularly concerning intracranial hemorrhage.⁴⁷

Despite these recommendations, anticoagulation remains underutilized in the elderly, often due to the complexity of balancing stroke prevention against bleeding risk in individuals with multimorbidity and increased fall risk. Elderly patients with AF often present with multiple comorbidities, including frailty, cognitive impairment, and polypharmacy, which complicate anticoagulation management. Current guidelines highlight a significant gap in evidence regarding



the use of DOACs in this population, particularly in those with recent bleeding, a history of intracranial hemorrhage, advanced renal or hepatic impairment, active cancer, or severe obesity. While DOACs are generally favored over VKAs, routine switching (from VKAs to DOACs) in elderly patients has been associated with an increased risk of bleeding, though the reasons for this remain poorly understood.⁴⁸ However, while anticoagulant therapy may elevate the risk of fall-related intracranial hemorrhage, the absolute incidence of such events is low relative to the significantly higher risk of ischemic stroke and venous thromboembolism in untreated.⁴⁹ Despite this, fall risk is frequently cited by clinicians as a reason to avoid prescribing anticoagulants, potentially resulting in undertreatment and increased thromboembolic events. This therapeutic inertia is exacerbated by the lack of validated tools that integrate frailty metrics with standard thromboembolic and bleeding risk scores. Thus, a comprehensive assessment and management of modifiable risk factors for falls, frailty and bleeding can improve the safety profile of anticoagulation in at-risk populations. On the other hand, in everyday clinical practice there can be risk of underdosing of DOACs in older adults affecting approximately 20–40% of those prescribed DOACs for AF. In real-world clinical settings, it's common to see nonstandard dose reductions in individuals who have a history of falls, are at risk of falling, or are considered frail and particularly vulnerable to bleeding. However, using lower doses outside of guideline recommendations has been linked to increased risks of thromboembolic events and mortality.

Nonetheless, lower dose anticoagulant therapy can be beneficial in this setting in some cases. As previously reported, dabigatran given at a dose of 110 mg is associated with similar rates of stroke and systemic embolism as those treated with VKAs, but with lower rates of major hemorrhage.³⁰ In addition, low-dose edoxaban (15 mg/day) as shown in the ELDERCARE trial significantly reduces the risk of stroke and systemic embolism in elderly unsuitable for standard-dose DOAC therapy, with no significant increase in major bleeding.^{29–50} However, close renal monitoring and dose adjustments in accordance with eGFR thresholds are critical to maintaining therapeutic efficacy and minimizing hemorrhagic complications.⁵¹

An important but often overlooked consideration in clinical practice is patient preference and quality of life. Older patients may prioritize independence and cognitive clarity over theoretical reductions in stroke or bleeding risk, highlighting the value of shared decision-making.⁵² Medication adherence is also improved with once-daily DOACs. On the other hand, the availability of reversal agents, such as andexanet alfa for factor Xa inhibitors and idarucizumab for dabigatran, has further enhanced the safety net for clinicians managing high-risk bleeding scenarios.

Additionally, guideline-endorsed bleeding risk tools such as HAS-BLED, while useful, has moderate predictive abilities and may overestimate bleeding in the elderly if not contextualized within broader clinical judgment.⁵³ Indeed, these tools should not be used in isolation to withhold anticoagulation but rather to guide modifiable risk factor management. Newer predictive models incorporating frailty markers and geriatric syndromes are in development to more accurately stratify risk in this population.

On the other hand, adherence and persistence with therapy are also critical and tend to be higher with DOACs than VKAs due to simpler regimens and improved tolerability. Indeed, elderly patients prefer once-daily DOACs and express greater satisfaction when anticoagulation management does not require frequent laboratory visits—an important consideration for those with mobility issues or limited access to transportation.

However, clinical approach is shifting toward a more integrated model of care. Multidisciplinary AF clinics and geriatric cardiology programs are being increasingly adopted to help clinicians address the multifactorial challenges presented by elderly AF patients. These models emphasize comprehensive assessment including frailty

scoring, cognitive screening, fall history, and polypharmacy review to guide evidence-based yet individualized anticoagulation strategies.⁵⁴

An alternative stroke-prevention strategy for patients with atrial fibrillation who have absolute or relative contraindications to long-term oral anticoagulation therapy is offered by percutaneous Left Atrial Appendage Closure (LAAC): several trials have demonstrated high procedural success rates and favorable safety profiles (2024 ESC/EACTS guidelines class IIb, level C).¹ Following implantation, however, individualized antithrombotic regimens with a lower thrombotic burden are often adopted in older and frailer patients to minimize the risk of recurrent bleeding.

AF Patients Undergoing Percutaneous Coronary Intervention (PCI): Implications for Triple Antithrombotic Therapy in the Elderly

In elderly and frail patients with AF undergoing PCI, the coexistence of an indication for long-term oral anticoagulation and the need for antiplatelet therapy creates a particularly high-risk clinical scenario. Triple antithrombotic therapy (TAT) based on combination between oral anticoagulant plus dual antiplatelet therapy (DAPT) substantially increases bleeding risk, which is further amplified by advanced age and frailty.⁵⁵ Notably, both advanced age and chronic oral anticoagulation are independent determinants of hemorrhagic complications after PCI and should be systematically incorporated into bleeding risk stratification and therapeutic decision-making (e.g. PRECISE-HBR score).^{56,57} In this context, contemporary strategies favor minimizing the duration of triple therapy, early transition to dual therapy (oral anticoagulant plus single antiplatelet agent), and careful selection and dose adjustment of direct oral anticoagulants to balance ischemic and bleeding risks.

The combined use of antiplatelet agents with oral anticoagulants—either DOACs or VKAs—has been evaluated in many large, randomized trials and subsequent meta-analyses. These studies consistently demonstrated a lower risk of bleeding, particularly ICH, with DOAC-based regimens compared with VKAs.^{58–61}

Despite this evidence, real-world registry data reveal a persistent gap between evidence and practice. TAT continues to be prescribed for extended durations, thereby exposing patients to an increased risk of bleeding. This discrepancy is especially concerning in older individuals, who inherently carry a higher hemorrhagic risk than younger patients.⁶²

A recent post hoc age-specific analysis of the PERSEO registry evaluated clinical characteristics, treatment strategies, and outcomes in patients aged ≥80 years compared with those <80 years undergoing PCI with a concomitant indication for anticoagulation.⁶³ Although elderly patients had a higher baseline bleeding risk and guideline recommendations favor fewer intensive regimens, more than 75% of patients aged ≥80 years were treated with TAT. DOACs were the most prescribed anticoagulants; however, the 1-year bleeding rate (BARC 2 to 5) reached 21% in this older cohort. Moreover, the incidence of net adverse clinical events (NACE) was significantly higher in elderly patients, driven by increased rates of major adverse cardiac and cerebral events (MACCE) as well as major and clinically relevant bleeding compared with younger individuals.

AQUATIC was a randomized, double-blind, placebo-controlled and multicenter trial designed to evaluate the impact of long-term aspirin therapy versus placebo in patients with chronic coronary syndrome (CCS) who had undergone coronary stenting and had a prior indication for long-term oral anticoagulation.⁶⁴ The study population was characterized by advanced age (median 72 years) and a high burden of comorbidities.

The primary efficacy endpoint—a composite of cardiovascular death, myocardial infarction, stroke, systemic embolism, coronary revascularization, and acute limb ischemia—occurred significantly

more frequently in the aspirin group than in the placebo group (16.9% vs 12.1%; adjusted HR 1.53, 95% CI 1.07 to 2.18; $p = 0.019$). In addition, major bleeding events were more than 3 times as common among patients receiving aspirin compared with placebo (10.2% vs 3.4%; HR 3.35, 95% CI 1.87 to 6.00; $p < 0.0001$).

Based on these findings, and following the recommendation of the independent Data Safety Monitoring Board, the trial was terminated early after a median follow-up of 2.2 years because of an excess of all-cause mortality observed in the aspirin group.

Similar results were obtained from EPIC—CAD trial: for participants aged 75 and older, switching to edoxaban alone provided a significant reduction in bleeding-related outcomes compared to dual therapy (edoxaban plus an antiplatelet agent) while preserving comparable ischemic benefits.⁶⁵ Overall net adverse events were significantly lower in the edoxaban monotherapy arm (6.8% vs 16.2%), largely driven by a sharp drop in bleeding events, even though further studies involving non-Asian cohorts may be needed.

Two ongoing randomized clinical trials, WOEST-3 (What is the optimal antithrombotic strategy in patients with atrial fibrillation undergoing PCI?—NCT 04436978)⁶⁶ and MATRIX-2 (NCT05955365), are currently evaluating novel antithrombotic strategies designed to further reduce bleeding risk without compromising ischemic protection. The results of these studies may be particularly relevant for optimizing management in the elderly population.

Authors' Opinion and Perspectives

Beyond guideline recommendations and trials data, the choice of a specific DOAC in elderly and frail patients with nonvalvular atrial fibrillation should be driven by an individualized assessment integrating clinical, functional, and pharmacokinetic considerations. In this context, apixaban and edoxaban appear to offer the most favorable balance between efficacy and safety, particularly in patients at high bleeding risk, owing to their consistent reduction in intracranial hemorrhage and overall major bleeding compared with vitamin K antagonists. Apixaban benefits from robust evidence across age groups and renal function, while edoxaban—especially at reduced doses—has demonstrated preserved efficacy with enhanced safety in very elderly populations, as highlighted by the ENGAGE AF—TIMI 48 and ELDER-CARE-AF trials. Conversely, rivaroxaban and dabigatran remain valid options in selected patients but may be associated with higher rates of gastrointestinal bleeding in the oldest and frailest individuals, warranting careful patient selection and gastroprotective strategies.

Dose adjustment is a key component of DOAC therapy in elderly and frail patients and should be guided by approved labeling criteria, including age, body weight, renal function, and relevant drug–drug interactions. When appropriately applied, reduced-dose regimens appear to maintain efficacy while lowering bleeding risk. In contrast, empirical or off-label dose reductions, frequently driven by perceived bleeding risk, have been associated with worse thromboembolic outcomes and should be discouraged. Very-low-dose strategies, such as edoxaban 15 mg daily, may be considered in carefully selected patients deemed unsuitable for standard dosing, although their applicability beyond specific populations remains uncertain.

Overall, anticoagulation decisions in elderly and frail patients should be individualized and not based on age alone, incorporating frailty, comorbidities, renal function, and patient preferences. When correctly selected and dose-adjusted, DOACs—particularly apixaban and edoxaban—may offer a favorable balance between stroke prevention and bleeding risk in this vulnerable population.

Future Directions and Innovations

The future of anticoagulation therapy in elderly and frail patients with AF is poised for significant transformation, driven by a

convergence of pharmacologic innovation, precision medicine, and care model restructuring. Central to this evolution is the emergence of novel anticoagulant classes, particularly factor XI inhibitors, which may offer comparable thromboembolic protection with a lower bleeding liability. Agents such as asundexian, milvexian and abelacimab target factor XIa, a component of intrinsic coagulation pathway more implicated in thrombosis than in hemostasis, offering a mechanism that preserves clotting function where needed while reducing pathological thrombogenesis.⁶⁷ Preliminary trials, such as AZALEA-TIMI trial, suggest these agents are especially promising in high-risk populations, including the elderly, where major bleeding risk has historically limited anticoagulation use.⁶⁸

However, caution remains warranted when interpreting these early findings. The recently published OCEANIC-AF trial was terminated prematurely after asundexian was associated with a higher incidence of stroke or systemic embolism compared with apixaban, despite a lower rate of major bleeding. These results underscore that, although factor XI inhibitors may offer a favorable safety profile, their efficacy in preventing thromboembolic events in patients with atrial fibrillation has not yet been conclusively established. Therefore, future trials will elucidate their role in the elderly population.

Indeed, another phase 3 clinical trial, OCEANIC-AFINA (2023-505421-13), a randomized, multicenter, double-blind, placebo-controlled study is designed to assess how effective and safe oral asundexian is in preventing strokes among patients aged 65 and older who have AF and are at high risk of stroke or systemic embolism but are deemed unsuitable for OAC. In addition, the LIBREXIA-AF trial (NCT05757869), a randomized, multicenter, double-blind study, aims to compare the safety and effectiveness of oral milvexian (100 mg twice daily) against apixaban (either 5 mg or 2.5 mg twice daily) in adults with AF. On behalf of abelacimab efficacy, the LILAC-TIMI 76 trial (NCT05712200) is designed to evaluate the effect of abelacimab 150 mg monthly subcutaneous administration relative to placebo on the rate of ischemic stroke or systemic embolism in patients >65 years old with AF who have been deemed to be unsuitable for oral anticoagulation therapy.

Additionally, innovations in risk stratification tools are being developed to enhance decision-making. While current guideline-endorsed scores are helpful, they lack granularity in frail older adults. New algorithms incorporating frailty indices, functional status, and biomarkers such as NT-proBNP, cystatin C, and high-sensitivity troponin may soon allow for more nuanced clinical judgment.^{69,70} Concurrently, integration of the Comprehensive Geriatric Assessment (CGA) into routine AF care is gaining support. CGAs may allow for structured evaluation of mobility, cognition, nutrition, and social support factors that significantly influence anticoagulation safety and adherence in the elderly.⁷¹

Digital health technologies also represent a rapidly advancing frontier. Remote monitoring tools and mobile health platforms can track adherence, flag early signs of complications, and enable virtual follow-ups, thus addressing barriers such as poor access, mobility limitations, and caregiver dependency.^{72–74} Wearable sensors may further provide real-time fall risk assessment and vital signs monitoring, allowing clinicians to adjust anticoagulation dynamically. These tools may empower patients and caregivers, fostering engagement and adherence, 2 critical determinants of therapeutic success in this demographic.

With the growing adoption of cardiac implantable electronic devices (CIEDs) in recent years, the detection of asymptomatic atrial arrhythmias—such as atrial high-rate episodes (AHREs) and device-detected subclinical atrial fibrillation (SCAF)—has become increasingly common in clinical practice.⁷⁵ AHREs have important potential clinical implications, as they are considered precursors of AF. Although the associated thromboembolic risk is lower than clinical AF, both AHREs and device-detected SCAF have been linked to

thromboembolic events, especially in elderly patients.⁷⁶ The association between stroke and AHREs, as well as the potential role of anticoagulant therapy in this context, remains uncertain, even though its routine use is not recommended, and it should be individualized based on patient-specific factors (e.g. AHREs burden, defined by the longest episode or cumulative daily duration of SCAF, and clinical risk of stroke).⁷⁷

Multidisciplinary anticoagulation clinics, incorporating cardiologists, geriatricians, pharmacists, and nurse practitioners, should be included in everyday clinical practice to coordinate complex care, optimize polypharmacy, and tailor regimens to individual patient needs while ensuring close monitoring and timely interventions.

Finally, the design of future clinical trials must be adapted to reflect real-world complexity. Historically, patients over age 85, those with dementia, frailty, or high comorbidity burdens have been generally excluded from pivotal anticoagulation trials. This has contributed to therapeutic hesitancy and a lack of robust evidence to guide care in the most vulnerable populations. The inclusion of these groups in ongoing studies, particularly those regarding factor XI inhibitors and personalized care models may represent a critical step forward in addressing this gap.

Limitations

This review should be interpreted with several limitations. First, it was conducted as a narrative review rather than a systematic review; therefore, no predefined inclusion or exclusion criteria were applied, and no formal assessment of study quality or risk of bias was performed. Consequently, the selection of studies was based on clinical relevance and the authors' judgment, introducing an inherent risk of selection bias. Second, much of the evidence regarding anticoagulation in elderly and frail patients derives from subgroup analyses of randomized trials and observational registries rather than studies specifically designed for this population. As a result, heterogeneity in patient characteristics, frailty definitions, outcome measures, and treatment strategies may limit the generalizability of the findings. To improve transparency, [Supplementary Table S1](#) summarizes the principal studies discussed in this review and the rationale for their inclusion. Finally, the rapidly evolving nature of the field, including the emergence of factor XI inhibitors and novel care models, means that some conclusions may require updating as new evidence becomes available. Accordingly, the findings of this review should be viewed as a qualitative synthesis intended to support clinical decision-making rather than as a definitive evidence-based recommendation.

An additional challenge is the lack of standardization in frailty and comorbidity assessment across studies. Most currently available frailty instruments have been developed and validated primarily in older populations and their prognostic performance in younger patients with atrial fibrillation remains incompletely characterized. Similarly, comorbidity scores are frequently used in observational studies but were not specifically designed to guide anticoagulation decisions in patients with AF.

Conclusions

Anticoagulation in elderly and frail patients with atrial fibrillation remains a complex clinical challenge requiring individualized management. Current evidence supports DOACs as the preferred therapy, given their favorable efficacy and reduced risk of intracranial bleeding compared with VKAs. Among DOACs, apixaban and edoxaban show the best balance between safety and effectiveness when appropriately dose adjusted.

Therapeutic decisions should incorporate frailty, comorbidities, renal function, and patient preference rather than relying solely on traditional risk scores. Trials such as FRAIL-AF and ELDERCARE-AF

emphasize that while routine switching from VKAs may not benefit all patients, low-dose regimens can provide safe and effective protection in the very old.

Looking ahead, the advent of novel factor XI inhibitors, which may decouple thrombosis prevention from bleeding risk, represents a promising frontier that could redefine anticoagulation paradigms in this demographic. Furthermore, the adoption of digital health tools to support adherence and monitor adverse events may help translate evidence into safer, more patient-centered care.

Ultimately, a personalized, multidisciplinary approach remains the cornerstone of optimizing anticoagulation in this growing, vulnerable and complex population.

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.

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Lorenzo Scalia: Writing – review & editing, Writing – original draft, Resources, Data curation, Conceptualization. **Laura Gatto:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Federica Agnello:** Writing – original draft, Formal analysis. **Dario Calderone:** Writing – original draft, Methodology. **Mihail Celeski:** Writing – original draft, Validation. **Antonio Popolo Rubbio:** Supervision, Methodology. **Francesco Prati:** Validation, Supervision. **Luca Testa:** Validation, Supervision. **Davide Capodanno:** Visualization, Validation, Supervision. **Marco Barbanti:** Supervision, Methodology, Formal analysis.

Supplementary materials

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.amjcard.2026.07.006>.

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