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Frailty and anticoagulation in patients with atrial fibrillation

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Крехкост и антикоагулация при пациенти с предсърдно мъждене

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Abstract:

Frailty and atrial fibrillation (AF) frequently coexist in older adults and collectively contribute to a substantial increase in thromboembolic events, bleeding complications, hospitalization, and mortality. Frailty is characterized by diminished physiological reserve, multisystem dysregulation, and increased vulnerability to external stressors, thereby complicating therapeutic decision-making regarding oral anticoagulant (OAC) therapy. Although frail patients carry a disproportionately high risk of ischemic stroke, they are often undertreated because of concerns related to falls, cognitive impairment, polypharmacy, and bleeding risk – a phenomenon commonly referred to as the “risk-treatment paradox.” This review summarizes the current evidence regarding the pathophysiological interplay between frailty, AF, and thrombosis, as well as contemporary approaches to optimizing OAC therapy through multidisciplinary models of care.

Key words: frailty, atrial fibrillation, direct oral anticoagulants, geriatric cardiology, bleeding risk

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Резюме:

Здравната крехкост и предсърдното мъждене (ПМ) често съществуват едновременно при възрастни хора и заедно допринасят за значително увеличение на тромбоемболичните събития, хеморагичните усложнения, хоспитализациите и смъртността. Здравната крехкост се характеризира с намален физиологичен резерв, мултисистемна дисрегулация и повишена уязвимост към външни стресови фактори, като по този начин усложнява вземането на терапевтични решения относно терапията с перорални антикоагуланти (ОАК). Въпреки че здравно крехките пациенти носят непропорционално висок риск от исхемичен инсулт, те често не получават адекватно лечение поради опасения, свързани с падания, когнитивни нарушения, полипрагмазия и риск от кървене, феномен, обикновено наричан „парадоксът на риска и лечението“. Този обзор обобщава настоящите доказателства относно патофизиологичната връзка между крехкостта, ПМ и тромбозата и подходите за оптимизиране на терапията с ОАК посредством мултидисциплинарни модели на грижа.

Ключови думи: крехкост, предсърдно мъждене, директни орални антикоагуланти, гериатрична кардиология, риск от кървене

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Introduction

The global demographic transition toward an aging population has led to a steadily increasing prevalence of both atrial fibrillation (AF) and frailty, two conditions that frequently coexist in contemporary clinical practice. Frailty is defined as a multidimensional geriatric condition characterized by diminished physiological reserve and increased vulnerability to stressors, resulting from cumulative declines across multiple physiological systems [1]. In patients with AF, frailty is not only a marker of advanced age, but an independent predictor of adverse clinical outcomes, including stroke, major bleeding, and all-cause mortality [2].

Despite the well-established efficacy of oral anticoagulants (OACs) in reducing thromboembolic risk,

a substantial proportion of older frail adults remain undertreated, a phenomenon commonly referred to as the "risk-treatment paradox" [3]. Clinicians frequently withhold OAC therapy because of concerns regarding polypharmacy, cognitive impairment, and a perceived high risk of falls that can lead to traumatic intracranial hemorrhage. However, emerging evidence suggests that the absolute clinical benefit of anticoagulant therapy, particularly with direct oral anticoagulants (DOACs), may be greater in frail individuals than in nonfrail patients [4].

This review aims to provide an evidence-based overview of the complex therapeutic challenges associated with anticoagulant therapy in frail patients with AF, with particular emphasis on individualized risk stratification, bleeding prevention strategies, and contemporary multidisciplinary management approaches.

Pathophysiological basis linking frailty, atrial fibrillation, and thrombosis

Frailty may be conceptualized as a complex prothrombotic phenotype. Central to this condition is the presence of chronic low-grade systemic inflammation, commonly referred to as "inflammaging," characterized by elevated levels of proinflammatory cytokines, particularly interleukin-6, tumor necrosis factor-alpha, and C-reactive protein [5]. This inflammatory milieu contributes to endothelial dysfunction, a key component of Virchow's triad.

Sedentary behavior associated with sarcopenia and frailty, together with reduced mobility, further exacerbates venous stasis and increases the risk of venous thromboembolism. Addressing this issue highlights the significant social burden of age-related muscle loss and emphasizes the prevention and therapeutic potential of advanced physical and magnetic field modalities in treating sarcopenia [58]. Frail individuals also exhibit structural remodeling of the left atrium characterized by increased fibrosis and electromechanical dissociation, thereby creating a favorable substrate for both AF development and thrombus formation [6].

AF itself is a well-established risk factor not only for cognitive impairment, one of the major dimensions of frailty, but also for vascular dementia and Alzheimer's disease, likely mediated through cerebral microembolization and chronic cerebral hypoperfusion [35, 36].

Frailty assessment tools

In contemporary clinical cardiology, objective quantification of frailty is essential for personalizing anticoagulant therapy, as it enables clinicians to assess prognosis and estimate the risk of adverse health outcomes. The primary objective is to facilitate targeted interventions aimed at mitigating risk and optimizing individualized therapeutic strategies, particularly when aggressive or physiologically stressful treatments such as OAC therapy are considered.

Currently, no universal screening tool exists for the identification of frailty or the prediction of poor clinical outcomes. Numerous assessment models have been developed, some tailored to specific diseases or emergency-care settings. The management of these vulnerable patients often requires targeted multidisciplinary protocols, particularly during the acute phase and within intensive care units [57]. Certain instruments focus predominantly on physical frailty, whereas others incorporate cognitive impairment, depression, and psychosocial dimensions. As detailed in Table 1, various validated instruments are utilized for screening and assessing frailty in clinical practice. Each tool relies on distinct methodologies, ranging from objective physical performance tests (e.g., Timed Up and Go) to comprehensive multi-domain deficit accumulation indices (e.g., Frailty Index) and self-reported questionnaires (e.g., PRISMA-7). These instruments serve to identify frailty levels, risk stratify elderly patients, and guide personalized care plans.

Table 1. Frailty Assessment Instruments

Instrument	Components	Frailty Classification
Fried Phenotype [7]	Evaluates five physical domains: unintentional weight loss (≥ 4.5 kg within the previous year), self-reported exhaustion, low physical activity, weakness (reduced grip strength), and slow gait speed	Frailty: ≥-3 points; Prefrail: 1-2 points; Robust: 0 points
Timed Up and Go Test [46]	Assesses physical frailty by measuring the time required to rise from a chair, walk 3 meters, turn around, return, and sit down	> -10 seconds indicates increased fall risk and need for further assessment
Frailty Index [8]	Assesses multiple accumulated health deficits across physical, psychological, and social domains	Frailty: >0.25
Clinical Frailty Scale [9]	Visual 9-level scale with written descriptions and representative images for each level	Frailty: ≥-5
Edmonton Frail Scale [47]	Eleven-item scale assessing cognition, general health, functional independence, social support, medication use, nutrition, mood, continence, and functional performance	0-5: no frailty; 6-7: vulnerable; 8-9: mildly frail; 10-11: moderately frail;12–17: severely frail
PRISMA-7 [48]	Seven-item yes/no questionnaire	≥ 3 positive responses indicate frailty

The Fried Frailty Phenotype defines frailty as a distinct biological syndrome characterized by five physical characteristics: unintentional weight loss, self-reported exhaustion, low physical activity, slow gait speed, and reduced grip strength measured using a dynamometer [7]. Although highly effective in identifying physical frailty, this model is relatively time-consuming and insufficiently captures the cognitive and psychosocial dimensions that are particularly relevant in older patients with AF.

The Rockwood model, also known as the Frailty Index, conceptualizes frailty as the cumulative burden of age-related health deficits, including comorbidities, laboratory abnormalities, and disabilities [8]. This approach often provides a more nuanced prognostic assessment in patients with complex cardiovascular profiles. However, it requires extensive clinical data and is, therefore, less practical for routine use.

The Clinical Frailty Scale (CFS) is a visual 9-point scale that evaluates the patient's global functional status approximately two weeks before the acute clinical event, thereby minimizing the confounding effects of acute illness. Owing to its rapid applicability, practicality, and strong prognostic value, the CFS has become one of the most widely used frailty assessment tools in emergency medicine and cardiovascular care [9].

Integration of these assessment tools into anticoagulation decision-making enables clinicians to move beyond subjective "eyeball" assessments, which have consistently been shown to overestimate treatment-related risks while underestimating the therapeutic benefits of anticoagulation in older adults [8, 9].

Nevertheless, comprehensive geriatric assessment remains time-consuming, and its effectiveness is significantly limited in the absence of integrated interdisciplinary care pathways and dedicated frailty-focused programs. In this context, clinical research in Bulgaria underscores the critical role of specialized geriatric rehabilitation and structured long-term care programs in mitigating functional decline within hospital settings [56].

Evidence supporting anticoagulant therapy in frail patients

In major randomized clinical trials (RCTs), including RE-LY, ROCKET-AF, ARISTOTLE, and ENGAGE AF-TIMI 48, frailty was analyzed retrospectively through subgroup analyses focusing on age, renal dysfunction, and body weight, all of which represent major components of the frailty phenotype [10, 11].

In ARISTOTLE, a dedicated subanalysis focusing on older adults aged ≥75 years demonstrated that apixaban was superior to warfarin in reducing stroke and systemic embolism, while simultaneously conferring a significantly lower risk of major bleeding, irrespective of age or clinical complexity. Notably, the absolute reduction in major bleeding was even more pronounced among older participants [10].

ROCKET-AF and RE-LY further confirmed that DOACs remain effective in these high-risk populations [11]. However, in RE-LY, the 150 mg dose of dabigatran demonstrated a trend toward increased gastrointestinal bleeding in patients older than 75 years, leading to recommendations favoring dose reduction to 110 mg in this specific subgroup in order to optimize the balance between efficacy and safety [11].

When age was analyzed as a continuous variable, advancing age exerted a greater influence on major bleeding risk than on thromboembolic risk in patients with AF. Nevertheless, because rates of bleeding and mortality increase substantially with age, treatment with edoxaban provided an even greater absolute reduction in safety events compared with warfarin among older adults [50].

Likewise, a subanalysis from the PREFER in AF registry demonstrated that stroke risk increases with advancing age more prominently than bleeding risk and that the absolute benefit of OAC therapy is greatest in very elderly patients, in whom it substantially outweighs bleeding risk, resulting in the highest net clinical benefit [51].

DOACs also appear to represent a reasonable therapeutic option for frail, vitamin K antagonist (VKA)-experienced older adults, according to findings from the COMBINE-AF substudy. Frail patients who switched from VKAs to DOACs experienced significant reductions in stroke or systemic embolism, fatal bleeding, intracranial hemorrhage, and all-cause mortality. Although gastrointestinal bleeding was more frequent with DOAC therapy, rates of major bleeding and the primary net clinical outcome remained comparable [52].

Data from the global ETNA-AF registry and the ARISTOPHANES study further indicate that among patients with multiple comorbidities and markers of frailty, DOACs maintain a superior safety profile compared with warfarin, particularly with regard to intracranial and life-threatening bleeding [14]. Moreover, in patients with AF and chronic kidney disease (CKD), VKA therapy has been associated with accelerated decline in estimated glomerular filtration rate (eGFR), a phenomenon potentially explained by the so-called "VKA-related renal calcification hypothesis" [55].

Despite the established benefits of DOACs in older frail populations, large prospective registries

such as GARFIELD-AF and ORBIT-AF demonstrate that frail patients in routine clinical practice are substantially more likely to receive inappropriate dose reductions or to be denied anticoagulation altogether, despite having higher CHA_2DS_2-VASc scores [13].

In the ESC-EHRA EORP-AF General Long-Term Registry, thromboembolic risk and bleeding risk were independently associated with increasing frailty severity. Frail patients were also less likely to receive OAC therapy or rhythm-control strategies [53]. Although the overall net clinical benefit remained in favor of DOAC therapy, it progressively diminished with advancing age and increasing frailty burden [53, 54].

Given the reduced overall benefit of anticoagulation in patients with advanced frailty, decisions regarding initiation and optimal dosing of OAC therapy frequently remain controversial and cautious. Concerns regarding bleeding risk often overshadow the perceived thromboembolic risk, resulting in suboptimal stroke prevention. Importantly, inappropriate dose reduction does not substantially reduce the risk of major bleeding, but significantly increases the risk of ischemic stroke and systemic embolism [12, 13].

Strategies to reduce hemorrhagic risk in frail patients with AF

A common misconception in geriatric cardiology is that high fall risk constitutes a contraindication to anticoagulation. However, clinical evidence suggests that a patient would need to fall approximately 295 times annually for the bleeding risk to outweigh the stroke-prevention benefit of warfarin, and this threshold is likely even higher for DOACs because of their superior intracranial bleeding safety profile [15]. Consequently, frailty management should focus primarily on fall-prevention strategies rather than withholding evidence-based stroke prevention therapy (Table 2) [17].

Modifiable fall risk factors extend beyond environmental hazards such as loose carpets or stairs and include gait and balance disorders, cognitive impairment, depression, polypharmacy and psychotropic medications, visual impairment, reduced contrast sensitivity, orthostatic hypotension, bradyarrhythmias, and urinary incontinence [49].

Although DOACs demonstrate fewer drug-drug interactions compared with VKAs, clinicians should remain vigilant regarding concomitant administration of P-glycoprotein (P-gp) and CYP3A4 inhibitors, including amiodarone, diltiazem, and certain antifungal agents. Furthermore, simultaneous use of antiplatelet agents or non-steroidal anti-inflammatory drugs substantially increases bleeding risk, thereby necessitating a strict deprescribing strategy whenever feasible [16].

Table 2. Practical approach to anticoagulation in frail patients at high risk of falls

Strategy	Actionable Steps
Environmental Modification	Assess home safety, including lighting, loose rugs, stairs, and handrails, to reduce environmental fall hazards [15, 17].
Medication Review	Deprescribe sedative-hypnotics, antihypertensive agents associated with orthostatic hypotension, and unnecessary nonsteroidal anti-inflammatory drugs (NSAIDs) [16].
DOAC Selection	Prefer direct oral anticoagulants with the lowest risk of intracranial hemorrhage, particularly apixaban or edoxaban [14].
Physical Rehabilitation	Implement resistance and balance training programs (e.g., Tai Chi or supervised physiotherapy) to counteract sarcopenia and improve postural stability [15, 17].

Chronic kidney disease (CKD) frequently exacerbates the “malnutrition-inflammation-cachexia” axis, further complicating anticoagulant safety profiles [19]. Although all DOACs appear safer than warfarin in patients with mild-to-moderate CKD, apixaban and edoxaban exhibit particularly favorable safety profiles in patients with creatinine clearance (CrCl) between 30 and 50 mL/min [20].

Patients with low body weight (≤ 60 kg) derive substantial benefit from dose-adjusted regimens, which preserve efficacy while minimizing the risk of spontaneous bleeding [22]. The complex interplay among CKD, low body weight, and advanced age necessitates a vigilant, evidence-based approach to dose selection in order to avoid the pitfalls of inappropriate underdosing (Table 3) [23-25].

Cognitive impairment is a major determinant of poor treatment adherence. In patients with dementia or significant cognitive dysfunction, simplified dosing regimens, such as once-daily DOAC administration when appropriate, together with active caregiver involvement, are essential for maintaining net clinical benefit [17]. In patients with mild-to-moderate dementia, DOACs are generally preferred over VKAs because of their predictable pharmacokinetic profile and the absence of routine INR monitoring requirements [37].

In advanced dementia stages, particularly in patients with Clinical Frailty Scale scores of 8–9, therapeutic priorities increasingly shift toward palliation and quality-of-life considerations. In such cases, anticoagulant therapy should be carefully individualized according to overall prognosis, life expectancy, and patient-centered goals of care [38, 39].

Table 3. Mandated criteria for DOAC dose reduction in atrial fibrillation

Drug	Standard Dose	Reduced Dose	Specific Criteria for Dose Reduction [Ref]
Apixaban	5 mg BID	2.5 mg BID	Presence of ≥ 2 of the following: age ≥80 years, body weight ≤60 kg, serum creatinine ≥ 133 μmol/L [10, 12]
Dabigatran	150 mg BID	110 mg BID	Age ≥ 80 years, concomitant verapamil use, or high bleeding risk [11]
Rivaroxaban	20 mg QD	15 mg QD	Creatinine clearance (CrCl) 15-49 mL/min (renal criterion only) [12]
Edoxaban	60 mg QD	30 mg QD	Body weight ≤ 60 kg, CrCl 15-50 mL/min, or concomitant use of a potent P-gp inhibitor [14]

Integrated care models and multidisciplinary management

Implementation of the "ABC pathway" (Atrial Fibrillation Better Care), which incorporates optimization of comorbidity management together with consideration of cognitive and functional status, has been associated with significant improvements in clinical outcomes among frail patients with AF [40].

Effective communication with caregivers is equally important, particularly in the setting of cognitive impairment or fluctuating functional capacity [43]. A structured therapeutic decision-making approach is illustrated in the algorithm presented in Figure 1 [55].

Future perspectives

Contemporary DOACs inhibit factor Xa or thrombin (factor IIa), both of which play essential roles not only in pathological thrombosis, but also in physiological hemostasis [26, 27]. Factor XI inhibitors, including asundexian and milvexian, offer the potential to dissociate these two processes, thereby enabling anticoagulation with substantially reduced bleeding liability [28].

For frail patients, in whom fear of bleeding remains one of the principal barriers to anticoagulant therapy, these agents may represent a transformative therapeutic advance [29-31]. Clinical trials within the PACIFIC-AF program have already demonstrated that factor XI inhibition is associated with significantly lower bleeding rates compared with standard DOAC therapy [32, 33].

The overarching therapeutic objective remains optimization of net clinical benefit through an integrated, multidimensional, and patient-centered model of care.

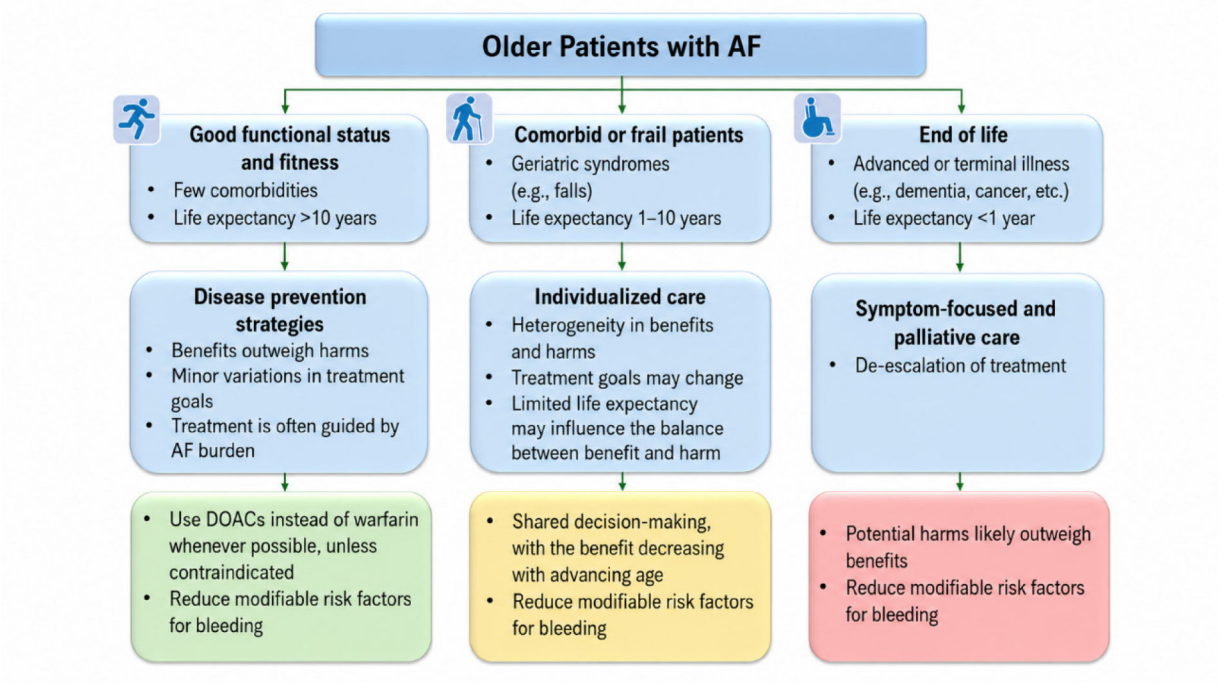

Fig. 1. Decision-making algorithm and therapeutic approaches for older patients with atrial fibrillation based on functional status, comorbidity, and life expectancy

Conclusion

The use of oral anticoagulants in frail patients represents one of the most significant challenges in contemporary geriatric cardiology. Frailty may be viewed as a complex prothrombotic phenotype requiring aggressive, yet cautious pharmacological intervention.

Although frail individuals carry the greatest burden of thromboembolic risk, they are simultaneously the most vulnerable to the "risk-treatment paradox," whereby evidence-based stroke prevention therapy is frequently withheld because of exaggerated concerns regarding bleeding and traumatic injury.

Evidence derived from pivotal randomized clinical trials and large real-world registries consistently demonstrates that DOACs provide superior safety and efficacy profiles compared with VKAs in this population. Integration of validated frailty assessment tools into routine clinical practice is essential for transitioning from subjective clinical intuition toward objective, evidence-based therapeutic decision-making.

Ultimately, frailty should not be viewed as a contraindication to anticoagulation, but rather as a clinical condition requiring individualized, multidimensional, and carefully integrated therapeutic strategies. Through optimization of comorbidity management, reduction of inappropriate polypharmacy, and strict adherence to evidence-based dosing criteria, clinicians may maximize net clinical benefit and improve quality of life in this growing and vulnerable patient population.

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