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EDITORIAL COMMENT

The Intersectionality of Frailty and Anticoagulation for Atrial Fibrillation*

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As the population ages and longevity increases, the prevalence of nonvalvular atrial fibrillation (AF) is concomitantly increasing.[1] In the ATRIA (AnTicoagulation and Risk Factors in Atrial Fibrillation) Registry in a U.S. health maintenance organization, 70% of patients with AF were at least 65 years of age, and 45% were ≥75 years of age. In this study, it was estimated that the number of U.S. adults with AF would increase to 5.6 million by the year 2050, with more than half of all affected individuals being older than age 80 years.[2]

At older age, patients with AF have a higher risk of both stroke and bleeding, thus presenting a challenge for decision-making regarding anticoagulation. Recorded stroke rates in patients older than 75 years ranged from 6.9% to 8.9%, and gastrointestinal bleeding rates ranged from 5.4% to 6.6% over a 5-year period. In most studies, advanced age and female sex were associated with less anticoagulant treatment. The most common reason for nonprescription of anticoagulation treatment was frequent falls/frailty; with underutilization and inappropriate dosing more common in older age patients. The risk of falls should rarely be a contraindication to anticoagulation. Older patients with a tendency to fall were reported to have 1.81 falls annually. The risk of subdural hematoma has to be >535 fold, so one would have to fall 295 (535/1.81) times a year to outweigh the benefits of anticoagulation with warfarin in one report.[3] Participants with a history of falls in the ARISTOTLE trial or with a risk of falls in the ENGAGE AF-TIMI 48 trial did not demonstrate a significant interaction between a history of falls or risk of falls on either the efficacy or safety of anticoagulation; this was despite the fact that those with a risk of falls were older and had more comorbidity.[4]

The $CHAD_2S_2$-VASC score identifies the stroke risk, whereas the HAS-BLED score identifies bleeding risk. The American AF guidelines[5] do not recommend a specific bleeding risk score, whereas the European AF guidelines recommend using the HAS-BLED bleeding risk score.[6] Importantly, frailty is not a component of either the stroke risk or bleeding risk scores. For patients with nonvalvular AF, global studies have shown a decreased use of warfarin and increased use of novel oral anticoagulants over time to improve the efficacy, safety profile, and convenience, especially in patients at older age.[6,7]

Frailty is defined as a clinically recognizable state of increased vulnerability resulting from aging-associated decline in reserve and function across multiple physiologic systems, such that the ability to cope with everyday or acute stressors is compromised. Scientific criteria that indicate compromised energetic function provide an operational definition: low grip strength, low energy or exhaustion, slow walking speed, low level of physical activity, and/or unintentional weight loss.[8]

Important to emphasize is that there is no gold standard for diagnosing frailty, with multiple instruments developed in recent years.[8] Relevant is that old age per se does not define frailty.

In the Cardiovascular Health Study of community-dwelling older adults, frailty prevalence increased from 2.9% in the 65 to 74 years of age group to 25% in the 80+ years of age group and was greater in women than men. In a study of nonagenarians in the United

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States, the prevalence of frailty was 24% for those aged 90 to 94 years, and 39.5% for those 95 years and older. The effect of frailty is not straightforward, with multiple frailty scores reflecting in part that frailty is a syndrome not manifest as a single phototype.[9]

Regarding the intersectionality of frailty and oral anticoagulation for AF, the paper by Denas et al,[10] in this issue of *JACC: Advances* provides many insights. This prospective multicenter cohort study enrolled consecutive very elderly(age ≥80 years) patients starting recommended doses of edoxaban, with patients characterized as nonfrail, prefrail, or frail using the SHARE-FI (SHARE Frailty Instrument) score. The primary outcome was the composite incidence of stroke/systemic embolism, major bleeding, clinically relevant nonvascular bleeding, and death over the 2 years of follow-up. The strengths of the study included the enrollment of consecutive very elderly patients, a significant number of elderly women (often underrepresented in clinical trials), and a standardized and reproducible frailty score rather than a phenotype; the primary composite outcome was not related to frailty status. On multivariate analysis, only anemia was associated with an increase in thromboembolic events, bleeding complications, and mortality. The authors concluded that anticoagulation with recommended doses of edoxaban was feasible in elderly patients with AF proven as frail, and acknowledged that anticoagulation was underused because of fear of adverse events. This study highlights that frailty is not a contraindication to offset the benefit of anticoagulation.[5]

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