

## COMMENTARY

# Anticoagulants in frail elderly patients with atrial fibrillation: a delicate balance

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Handling Editor: Dr Kristen Sanfilippo

The relationship between frailty, aging, and anticoagulant prescription for stroke prevention in atrial fibrillation (AF) is a topic of ongoing clinical interest as well as research. We know, for instance, that elderly patients with AF and multimorbidity have a high thromboembolic risk necessitating anticoagulants. Yet, when anticoagulated, they also possess a very high risk of bleeding due to an accumulation of bleeding risk factors, notably including aging. For example, in a study by Kooistra et al. [1], already nearly 10 years ago, the incidence rate (IR) of major or clinically relevant nonmajor bleeding while on a vitamin K antagonist (VKA) increased from 14.8 events per 100 person-years in patients with AF aged 70 to 79 years to 18.1 events per 100 person-years in patients with AF aged >90 years (hazard ratio, 1.26; 95% CI, 1.05-1.50). Interestingly, in that study, the thromboembolic IR was lower, yet this also increased with increasing age: from 0.8 events per 100 person-years in the age group 70 to 79 years to 1.8 events per 100 person-years in those aged >90 years [1]. In a more recent study by Patti et al. [2], including also patients on direct oral anticoagulant (DOAC) therapy, similar results were found: the IR of major bleeding increased from 1.9 events per 100 person-years in those aged <75 years to 4.0 per 100 person-years in those aged >85 years ( $P = .003$ ), with a nearly similar increase in the thromboembolic risk, ie, from 1.8 events per 100 person-years in those aged <75 years to 4.8 per 100 person-years in those aged above 85 years ( $P < .001$ ) [2].

Moreover, apart from aging, frailty by itself also complicates clinical decision making regarding optimal anticoagulant management. Dynamic changes over time in both bleeding and thromboembolic risk—caused by altering pharmacokinetics, drug-drug interactions, increased susceptibility to falls (leading to traumatic bleeds), cognitive impairment (potentially impacting treatment adherence), and finally a

decreased renal function—may impact anticoagulation safety [3]. Thus, this requires continuous monitoring and balancing of these risks in frail patients with AF, yet at the context of a paucity of evidence. Specific recommendations for these populations are lacking as frail individuals are often excluded from trial participation, and even if evidence is available, the complexity and heterogeneity of the frailty syndrome often hampers direct transferability of inferences to the individual patient seen during our consultations. Further research on this topic is thus highly welcomed.

In this edition of *Research and Practice in Thrombosis and Haemostasis*, Nishimura et al. [4] describe the results of their study on the association between frailty and bleeding and ischemic stroke/transient ischemic attack (TIA) in patients with AF at the time of anticoagulant initiation. Patients aged  $\geq 65$  years with nonvalvular AF who initiated anticoagulants were selected from an administrative claims database in Japan between 2012 and 2018. Frailty was assessed using the electronic frailty index, which is a validated tool for identifying frail individuals from routine healthcare databases [5]. In total, 12,585 patients were included in the analysis. During a median follow-up of 31 months, the overall IR of the composite of major and nonmajor bleeding (all bleeding events registered in an inpatient or outpatient setting) was 15.5 per 100 person-years, the overall IR of major bleeding was 1.2 per 100 patient-years, and the overall IR of ischemic stroke/TIA was 1.5 per 100 patient-years. With increasing levels of frailty, the incidence of the composite bleeding outcome increased rapidly: for patients classified as “not frail,” the IR of bleeding was 11.2 per 100 person-years, while this nearly doubled to 21.0 per 100 person-years for patients with severe frailty, mainly driven by an increase in nonmajor bleeding events. Interestingly, the incidence of ischemic stroke/TIA in these anticoagulated patients remained

remarkably stable with increasing levels of frailty: for patients classified as “not frail,” the IR of ischemic stroke/TIA was 1.5 per 100 person-years, and this increased only slightly to 1.7 per 100 person-years for patients with severe frailty.

An important observation of this study is that it confirms that in anticoagulated patients with AF, frailty greatly impacts bleeding risk. Yet, at the same time, the impact of frailty on thromboembolic risk is almost negligible as the residual risk of ischemic stroke/TIA remained low even in those with severe frailty. This study serves as a further exemplification of the importance of monitoring (notably) bleeding risk in frail patients with AF using anticoagulants. Importantly, it should not serve as an argument not to prescribe anticoagulants in frail patients with AF: although bleeding events can be very burdensome for patients, the benefit of anticoagulants (ie, the prevention of debilitating ischemic stroke) still outweighs the harm caused by bleeding in most patients [3]. The results of this study do, however, emphasize that these frail patients with AF on anticoagulants should be closely monitored, eg, to evaluate whether the dosing of anticoagulants is still appropriate to prevent overdosing and underdosing. In addition, we believe that more research is needed on the impact of reducing so-called modifiable risk factors for bleeding, for instance, blood pressure management or stopping (or reconsider) of concurrent medication that may increase bleeding risk (eg, nonsteroidal anti-inflammatory drugs). Managing modifiable risk factors for bleeding is part of the current guidelines, for instance, from the European Society of Cardiology, yet these recommendations are mainly based upon consensus and observational studies with little or no supporting trial evidence [3].

Finally, we believe that clinical trials, specifically targeting anticoagulation to this vulnerable and frail population, are needed to provide insight into both their bleeding and thromboembolic risk. Unfortunately, frail individuals were underrepresented in the landmark DOAC trials. Subsequently, evidence on comparative efficacy and safety of DOAC therapy vs VKA therapy in frail patients with AF mainly comes from observational, postmarketing studies, yet these studies obviously are affected by confounding bias [6–8]. Clinical trials in frail individuals can be performed, however, and one example of such a trial specifically enrolling frail, elderly patients with AF that is currently ongoing is the FRAIL-AF trial exploring whether it is safe to switch frail patients with AF from VKA to DOAC [9]. Additionally, research on factor XIa inhibition—an anticoagulant strategy that affects hemostasis less and, therefore, may lead to less bleeding—may be particularly interesting for frail patients with AF. Ongoing phase 3 clinical trials on factor XIa inhibition should thus strive to target and enroll a large proportion of frail patients with AF as well or at the very least not deny trial participation so that subgroup or interaction analyses can be performed.

To conclude, the study by Nishimura et al. [4] once again demonstrates the association between frailty and bleeding in frail elderly patients with AF. This emphasizes the need for monitoring bleeding

risk in clinical practice and exploring more optimal anticoagulant strategies for these vulnerable patients in research.

## FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

## AUTHOR CONTRIBUTIONS

Both authors were involved in the conception of the article, drafting and revising of the article, and approving the final version of the article.

## RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

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