Frailty and multi-morbidities should not govern oral anticoagulation therapy prescribing for patients with atrial fibrillation

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The risk of stroke in atrial fibrillation (AF) is associated with well-known comorbidities, the more common of which have been used to formulate risk-stratification schemata such as the CHA_2DS_2VASc score.[1] The availability of the NOACs has revolutionized thromboprophylaxis for stroke prevention in the elderly by providing a better, safer, more convenient alternative to warfarin that has led to lower discontinuation rates, better therapy adherence and more effective oral anticoagulation (OAC).[2] The NOACs are particularly invaluable for frail, elderly patients with multiple comorbidities who can struggle to comply with warfarin therapy which, on top of its other limitations, requires a degree of physical and cognitive function.

In an ideal world, all elderly AF patients eligible for OAC should be offered treatment, yet anticoagulation is underprescribed. Safety concerns appear to predominate although anticoagulation discontinuation and avoidance leads to poorer outcomes.[3] Thus, older, frail, cognitively-impaired patients, often with multiple comorbidities, remain at risk for serious adverse events without effective OAC.[4] Even though data from randomized controlled trials (RCTs) focusing on OAC have been reassuring, few 'trial subjects' represent this very high-risk population. Hence, observational studies, to collect 'real-world' data have been undertaken[5] but, even then, information is lacking on factors such as frailty and multi-morbidities, the very elements that influence difficult treatment decisions. Consequently, there is an overwhelming need for studies exploring such factors in relation to OAC.

In this issue of the journal, Alexander et al[6] describe the association between multi-morbidities and clinical outcomes in relation to the safety and efficacy of apixaban versus warfarin in a post-hoc ancillary analysis to the ARISTOTLE trial. This analysis was performed on AF patients aged ≥55 years; 96% of the trial population (n = 16,800) was categorized into 3 groups—no multi-morbidity (0-2 comorbidities), moderate multi-morbidity (3-5 comorbidities) and high multi-morbidity (≥6 comorbidities). It turns out multi-morbidity was present in 64% of AF patients, with 51% (n = 8491) belonging to the moderate multi-morbidity group and 13% (n = 2222) in the high multi-morbidity group. Compared to those without comorbidities, the latter group was older, with higher CHA_2DS_2-VASc scores, taking twice as many medications and at 3-fold increased risk of dying. They were also more likely to have falls, cognitive issues be underweight and, thus, be more vulnerable clinically.

Not surprisingly, risk of stroke and major bleeding increased with the number of multi-morbidities, but no significant differences were noted in the risk of intracranial hemorrhage (ICH). There were also no significant interactions between multi-morbidity and OAC, indicating similar treatment effects of apixaban regardless of the number of comorbidities. Interestingly, a trend towards less ICH was observed with apixaban in the high multi-morbidity group versus no multi-morbidity group. No plausible explanation was provided for this.

What are the implications? The authors estimated that the risk of major bleeding rises by about 15% for every 1 co-morbidity increase, suggesting a linear relationship and that every co-morbidity, regardless of type, contributes equally. In the UK Biobank cohort study, which assessed multi-morbidities in AF and the effects of survival, the presence of a single cardio-metabolic condition was associated with an 83% greater risk of mortality whereas non–cardio-metabolic conditions raised the risk by 45%.[7] The effect size on mortality with certain conditions, such as chronic lung disease and

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osteoporosis, were similar to cardio-metabolic co-morbidities such as heart failure, indicating that the strength of association varied depending on comorbidity type. Further studies may be needed to determine if there are similar associations between the type of comorbidity and risk of bleeding.

Notable aspects of this ARISTOTLE analysis include its large size, its focus on multi-morbidities in relation to OAC, its assessment of outcomes based on the randomized use of apixaban and warfarin and its consistency with the original trial for safety and efficacy outcomes. While constraints of a post-hoc analysis such as underpowering and the possibility of a coincidental association exist, this work has provided insight into this complex group of patients in whom it would have been challenging to conduct a RCT.

Limitations exist, however. Comorbidities were subject to those reported on case report forms. Lack of weighted classification presumes that they all contribute equally in terms of the potential risk they pose. Patients may have accumulated incident comorbidities during the study that could have been missed. This latter point is highly relevant since risk is a dynamic rather than 'static' process.[8-10] Hazard ratios for stroke, death and major bleeds were not significant for the high multi-morbidity group, even though event rates were superior with apixaban compared to warfarin. This may have been due to the small population size of this group compared to the others and further studies with considerable numbers may be needed to observe outcomes of statistical significance. Lastly, the distribution of patients on the lower dose of apixaban, across the three categories was not alluded to.

The study considers frailty, a syndrome prevalent in AF and a major influence on OAC treatment decisions.[11,12] A cumulative deficits approach characterized frailty by number of individual deficits (ie, the more individuals have wrong with them, the more likely they are to be frail) indicating a relationship of multi-morbidities to frailty in this AF population. This would mean that higher multi-morbidity patients were more frail. Using this approach, the results from the study suggest that apixaban's superiority to warfarin would be apparent in those who are frail. However, the number of comorbidities may not be an accurate representation of frailty as, once again, it does not take into account the severity of the comorbidity. An individual with a single comorbidity such as a debilitating stroke may be more frail than another with multiple comorbidities which have a lesser impact on the functional independence. Factors, such as functional status, nutrition and strength are not considered, in contrast to the phenotypic model. Nonetheless, studies comparing the two approaches for identification of frailty show overlap between the phenotype and cumulative deficit models with notable statistical convergence.[13-15]

This does not obviate the need for studies assessing the direct impact of frailty on outcomes with OAC, as challenging as they may be to perform. One study in which comprehensive geriatric assessments were performed on AF patients showed that the frailty status was positively associated with both CHA_2DS_2-VASc ($P < .001$) and HAS-BLED ($P = 0.01$) scores indicating that frail patients are likely to achieve more benefit from OAC when risk of stroke is greater (despite risk of bleeding).[16]

The debate of whom to anticoagulate and not to anticoagulate remains. These results from Alexander et al[6] do not put the matter to rest. Indeed, the analysis of the ARISTOTLE trial only includes patients who were randomized that may be a select group of the healthiest patients even if they are frail and have multi-morbidities. Nonetheless, these results help clear misconceptions, aid decision-making regarding OAC and add validity to the use of OAC in elderly and frail patients with multi-morbidities, as they can be extended safely into clinical practice. Perhaps, a pooled analysis of similar trials with other NOACs may add strength to these findings. In the absence of contradictory evidence, the key message stands: OAC prescription should not be deterred by presence of multi-morbidities or frailty.

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