**EDITORIAL**

**Frailty and cognitive impairment are not reasons to withhold anticoagulation in people with atrial fibrillation, but screening could guide management**

Stephanie L. Harrison, PhD1, Asangaedem Akpan, MPH FRCP 2,3, Gregory Y.H. Lip, MD1,4

1Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom

2Institute of Life Course and Medical Sciences & Liverpool University Hospital NHS FT, Liverpool, United Kingdom

3Institute of Health, University of Cumbria, Carlisle, United Kingdom

4Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

Correspondence:

Prof Gregory Y. H. Lip Liverpool Centre for Cardiovascular Science, University of Liverpool, William Henry Duncan Building, Liverpool, L7 8TX United Kingdom [gregory.lip@liverpool.ac.uk](mailto:gregory.lip@liverpool.ac.uk)

Word count: 1620; References: 20

Oral anticoagulants (OACs) reduce the risk of stroke for people with atrial fibrillation (AF), and OACs are recommended in evidence-based guidelines for most people with AF.1 The net clinical benefit of OACs compared with no treatment or aspirin is clear for most people with AF , apart from those at lowest stroke risk.2 The common risk factors for incident AF are also risk factors for stroke and bleeding in AF.3

There are well validated risk scores to assess stroke and bleeding risks in AF, and an independent Patient-Centered Outcomes Research Institute (PCORI) systematic review and evidence appraisal found that of commonly used AF risk scores, the CHADS2, CHA2DS2-VASc and HAS-BLED scores were the best validated scores for use in clinical practice.4 However, stroke risk in people with AF is increased by ageing and incident risk factors, so should be regularly repeated, given that risk is dynamic and not a static ‘one-off’ assessment.5 Similarly, bleeding risk is dynamic and should be determined for all people with AF before (and after) commencing OAC treatment.6 Indeed regular reassessment using the HAS-BLED score is associated with mitigation of modifiable bleeding risk factors, reduced bleeding risk and an increase in OAC use.7 Importantly, a high bleeding risk score should not be used as the sole reason to not initiate anticoagulation. Instead people should be appropriately treated with OAC, monitored and also re-assessed to determine any changes in risks over time. There is no exception in current guidelines for initiating anticoagulation for AF in people with frailty or cognitive impairment.

The risk of stroke without treatment is often of greater consequence than bleeding risk by prescribing OACs for people with AF, including older people, people with cognitive impairment and/or those with a history of falls or frailty. Thus, people with AF, frailty and/or cognitive impairment should be appropriately assessed for stroke and bleeding risk and treated and monitored accordingly. Consideration should be given as to whether a caregiver is available to assist with anticoagulant adherence for people with cognitive impairment and dementia.1 However, there are issues in the current evidence base as people with cognitive impairment or dementia often being excluded from research studies and clinical trials.8

In this issue of the *Journal of the American Geriatrics Society*, Mailhot and colleagues determine the independent and concurrent prevalence of cognitive impairment and frailty in a cohort of over 1200 people aged 65 and over with non-valvular AF in the United States.9 All participants had a CHA2DS2-VASc score ≥2 and had no contraindications to the use of OACs. The Fried Frailty Scale was used to assess frailty and the Montreal Cognitive Assessment (MoCA) was used to assess cognitive impairment, with a defined cut-point of 23 to categorise cognitive impairment with the MoCA. The Anti-Clot Treatment Scale (ACTS) was used to assess patient satisfaction of OACs. The authors reported that almost one half of the study participants had frailty, cognitive impairment or both; approximately 5% had frailty only, 34% cognitive impairment only and 9% had both frailty and cognitive impairment. The majority of participants (85%) were receiving OACs, and frailty or cognitive impairment did not associate with OAC prescribing. This finding indicates that prescribers for the participants of this study were mostly following current guidelines and not withholding oral anticoagulation due to frailty status or cognitive impairment. For the remaining 15%, the reasons for why OACs are not prescribed or whether the participants have ever received OACs are not reported. The analysis of ACTS scores in the study showed people with cognitive impairment, but not frailty or both cognitive impairment and frailty, reported low perceived benefit of OACs compared to people with no impairment, but treatment burden did not significantly differ between the groups. This was partially explained by adjusting for other factors known to associate with treatment adherence such as social support and levels of education, but remained statistically significant after adjustments (Odds Ratio for low benefit of OACs for people with cognitive impairment and frailty vs. people with no impairment: 1.87; 95% confidence intervals: 1.08, 3.27). Consideration of patient satisfaction is important because lower treatment satisfaction may impact adherence and ultimately increase stroke risk for the patients.10

The study by Mailhot et al., provides insights to associations between cognitive impairment, frailty status and prescribing and perceived benefit or OACs.9 The study does not indicate the length of time participants had been prescribed OACs or stratify results of perceived treatment burden and benefit by type of OAC prescribed, such as a comparison of vitamin-K antagonists (VKAs) vs. non-VKA OACs (NOACs). Previous studies have shown differences in satisfaction comparing AF patients prescribed NOACs compared to VKAs, but have not further considered how cognitive impairment or frailty may impact findings.10-12

The Systematic Assessment of Geriatric Elements in Atrial Fibrillation (SAGE-AF) cohort which was utilised in the study by Mailhot and colleagues included a relatively high proportion of people with cognitive impairment, but one of the main limitations of the study, as appropriately noted by the authors, is the exclusion of people with diagnosed dementia.9 A previous meta-analysis of 21 studies has shown people with dementia had 52% lower odds of receiving OACs compared to people without dementia.13 Although this may be a difficult area to study in this population, the exclusion of people with dementia is repeatedly seen across studies of the older population without adequate justification. The reasons for exclusion of people with dementia from studies are infrequently reported or noted as a limitation.13 Similarly, a study which examined treatment satisfaction for people with AF receiving OACs excluded people with a cognitive disorder for reasons of feasibility (ability to respond orally to the questionnaires).11 Treatment adherence and satisfaction for people with AF and dementia remains unknown.

Depression, older age, lower education, race/ethnicities other than non-Hispanic white, and higher bleeding and stroke risk scores were associated with frailty and cognitive impairment for people with AF.9 However, the cross-sectional analysis is limited in the conclusions which can be drawn without repeated measures. Determining people with AF at high-risk of frailty and cognitive impairment could be useful for targeted screening. Screening for frailty and cognitive impairment for people with AF could assist clinicians to make well-informed decisions about treatment and frequency of monitoring and re-assessment. To provide optimal care for people with AF, knowing the presence of cognitive impairment could be important to effectively communicate with patients, for patient-centred decision making and to identify the need for family members or other caregivers to be present to help with treatment adherence and discussion of the risks and benefits of treatment. For people with AF and frailty, appropriate supportive strategies should be considered such as multidisciplinary team assessment, home and community-based rehabilitation and recognition of deterioration.14

Determining frailty and cognitive status should not be used as reasons to withhold anticoagulation. It is critical the patients and/or their family members or caregivers where appropriate are fully informed of the benefits of taking the OACs to improve long-term treatment adherence and reduce risk of incident stroke. There is no evidence that people with AF and dementia have a markedly higher risk of intracerebral haemorrhage in the presence of anticoagulation, but evidence from randomised controlled trials is lacking and may not be feasible. Therefore, anticoagulation should be offered but adherence may need to be assured by a family member or other appropriate caregiver. The NOACs may be preferable to adjusted dose VKA treatment as they may be easier to manage, as they can be administered in fixed doses. However, trial evidence comparing NOACs to VKAs is not available specifically for people with cognitive impairment and dementia. Screening for cognitive impairment should be considered, perhaps in addition to the calculation of the SAMe-TT2R2 score to predict which people on oral anticoagulation with VKAs will reach an adequate TTR to guide whether NOACs or VKAs are more appropriate.15, 16

For all people with AF, the Atrial Fibrillation Better Care (ABC) pathway can be applied as a simple approach to holistic AF care, including those with cognitive impairment or dementia. The ABC pathway is an integrated management pathway for people with AF comprising of: ‘A’ Avoid stroke with Anticoagulants; ‘B’ Better symptom management with appropriate rate or rhythm control; and ‘C’ Cardiovascular and co-morbidity risk management, including appropriate lifestyle recommendations.17 The ABC pathway has been shown to associate with fewer major adverse events in critically complex patients with AF including those with multiple comorbidities, use of polypharmacy, and prior hospitalisation.18 Figure 1 suggests how screening for frailty and cognitive impairment could be integrated within the ABC pathway, to streamline the patient care pathway.

To make the future research findings easier to adopt in clinical practice globally, the use of the Rockwood clinical frailty scale would be a useful addition in categorising frailty status as well as the degree of frailty.19 While treatment satisfaction is important, it is also critical to determine what matters most to older people especially those with frailty, as balancing the benefits of treatment and overall quality of life including polypharmacy-related complications have a bearing on adherence to recommended treatment.20 Using activities of daily living for older people is a much more useful and helpful outcome measure that should be incorporated in future studies. Understanding how social and health inequalities and being in a long-term care setting impacts these findings in future studies would also add knowledge and improve the care we give to these sub-populations as their understanding and challenges are unique.

In conclusion, frailty and cognitive impairment screening could be considered alongside the ABC pathway to help guide optimal care and management of AF. Further research may be needed to determine the feasibility of integration of such screening for people with AF and which measures are most appropriate as well as the points raised above.

**Acknowledgments**

**Conflicts of Interest**

SLH: received funding from Bristol Myers Squibb (BMS), outside of the submitted work. GYHL: consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon and Daiichi-Sankyo and speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are directly received to Gregory Lip personally. AA: No conflicts declared.

**Author Contributions**

SLH drafted the manuscript, and AA and GYHL critically revised the manuscript.

**Sponsor’s role**

No funding was received for this work.

**References**

[1] Lip GYH, Banerjee A, Boriani G*, et al.* Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report. *Chest*. 2018;**154**: 1121-1201.

[2] Lip GY, Skjøth F, Nielsen PB, Larsen TB. Non-valvular atrial fibrillation patients with none or one additional risk factor of the CHA2DS2-VASc score. A comprehensive net clinical benefit analysis for warfarin, aspirin, or no therapy. *Thrombosis and haemostasis*. 2015;**114**: 826-834.

[3] Aronson D, Shalev V, Katz R, Chodick G, Mutlak D. Risk Score for Prediction of 10-Year Atrial Fibrillation: A Community-Based Study. *Thrombosis and haemostasis*. 2018;**118**: 1556-1563.

[4] Borre ED, Goode A, Raitz G*, et al.* Predicting Thromboembolic and Bleeding Event Risk in Patients with Non-Valvular Atrial Fibrillation: A Systematic Review. *Thrombosis and haemostasis*. 2018;**118**: 2171-2187.

[5] Fauchier L, Bodin A, Bisson A*, et al.* Incident Comorbidities, Aging and the Risk of Stroke in 608,108 Patients with Atrial Fibrillation: A Nationwide Analysis. *Journal of clinical medicine*. 2020;**9**.

[6] Chao TF, Lip GYH, Lin YJ*, et al.* Incident Risk Factors and Major Bleeding in Patients with Atrial Fibrillation Treated with Oral Anticoagulants: A Comparison of Baseline, Follow-up and Delta HAS-BLED Scores with an Approach Focused on Modifiable Bleeding Risk Factors. *Thrombosis and haemostasis*. 2018;**118**: 768-777.

[7] Guo Y, Lane DA, Chen Y, Lip GYH, m AFAIITi. Regular Bleeding Risk Assessment Associated with Reduction in Bleeding Outcomes: The mAFA-II Randomized Trial. *The American journal of medicine*. 2020.

[8] Taylor JS, DeMers SM, Vig EK, Borson S. The disappearing subject: exclusion of people with cognitive impairment and dementia from geriatrics research. *Journal of the American Geriatrics Society*. 2012;**60**: 413-419.

[9] Mailhot T, McManus DD, ME W*, et al.* Frailty, Cognitive Impairment and Anticoagulation Among Older Adults with Non-Valvular Atrial Fibrillation. *Journal of the American Geriatrics Society*. 2020.

[10] Okumura Y, Yokoyama K, Matsumoto N*, et al.* Patient Satisfaction with Direct Oral Anticoagulants and Warfarin. *International heart journal*. 2018;**59**: 1266-1274.

[11] Benzimra M, Bonnamour B, Duracinsky M*, et al.* Real-life experience of quality of life, treatment satisfaction, and adherence in patients receiving oral anticoagulants for atrial fibrillation. *Patient preference and adherence*. 2018;**12**: 79-87.

[12] Geng YP, Lan DH, Liu N*, et al.* Patient-Reported Treatment Satisfaction with Dabigatran versus Warfarin in Patients with Non-Valvular Atrial Fibrillation in China. *Thrombosis and haemostasis*. 2018;**118**: 1815-1822.

[13] Fanning L, Ryan-Atwood TE, Bell JS*, et al.* Prevalence, Safety, and Effectiveness of Oral Anticoagulant Use in People with and without Dementia or Cognitive Impairment: A Systematic Review and Meta-Analysis. *Journal of Alzheimer's disease : JAD*. 2018;**65**: 489-517.

[14] NHS England. NHS RightCare: Frailty Toolkit. 2019.

[15] Pastori D, Miyazawa K, Lip GYH. Dementia and Atrial Fibrillation: A Dangerous Combination for Ischemic Stroke and Mortality. *Journal of Alzheimer's Disease*. 2018;**61**: 1129-1132.

[16] Escobar C, Borras X, Bover Freire R*, et al.* A Delphi consensus on the management of oral anticoagulation in patients with non-valvular atrial fibrillation in Spain: ACOPREFERENCE study. *PloS one*. 2020;**15**: e0231565.

[17] Lip GYH. The ABC pathway: an integrated approach to improve AF management. *Nature reviews Cardiology*. 2017;**14**: 627-628.

[18] Proietti M, Romiti Giulio F, Olshansky B, Lane Deirdre A, Lip Gregory YH. Comprehensive Management With the ABC (Atrial Fibrillation Better Care) Pathway in Clinically Complex Patients With Atrial Fibrillation: A Post Hoc Ancillary Analysis From the AFFIRM Trial. *Journal of the American Heart Association*. 2020;**9**: e014932.

[19] Rockwood K, Song X, MacKnight C*, et al.* A global clinical measure of fitness and frailty in elderly people. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*. 2005;**173**: 489-495.

[20] Akpan A, Roberts C, Bandeen-Roche K*, et al.* Standard set of health outcome measures for older persons. *BMC geriatrics*. 2018;**18**: 36.

**Figure legend**

**Figure 1. Modified Atrial Fibrillation Better Care (ABC) pathway to include screening for frailty and cognitive impairment.**

Low stroke risk defined as CHA2DS2-VASc score of 0 in men or 1 in women, with event rates of <1% per year. OAC: oral anticoagulant, VKA: vitamin-K antagonist, NOAC: non-VKA antagonist, TTR: time in therapeutic range.