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Stroke Risk Stratification and Oral Anticoagulation in Atrial Fibrillation Patients Aged 65–74 Years

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Abstract **Review Article**

This article investigates stroke prevention strategies in low-risk atrial fibrillation (AF) patients aged 65-74, a demographic with increased AF prevalence and stroke risk. While current guidelines advocate oral anticoagulation (OAC) for CHA2DS2-VA scores ≥2, guidance for those with a score of 1 (or CHA2DS2-VASc 2 with female sex) is less clear. We highlight the continuous rise in risk with advancing age and the influence of co-factors like chronic kidney disease, obesity, and smoking. Furthermore, we explore the benefits of anticoagulation, particularly direct oral anticoagulants (DOACs), which offer a more favourable safety profile compared to Vitamin K Antagonists in this age group. Until comprehensive clinical trial data are available for the CHA2DS2-VA 1 cohort, clinical decision-making must employ dynamic and nuanced risk stratification accounting for additional risk factors, AF burden and biomarker assessment to ensure OAC therapy is administered to achieve net clinical benefit.

Keywords: Atrial Fibrillation (AF), Stroke Prevention, Oral Anticoagulation (OAC), CHA2DS2-VA score, Direct Oral Anticoagulants (DOACs), Risk Stratification.

INTRODUCTION

Atrial fibrillation (AF) represents the most common sustained cardiac arrhythmia globally, with its prevalence strongly correlated with advancing age (Go *et al.*, 2001). Older age, particularly reaching 75 years or more, is a well-established independent risk factor for thromboembolic stroke in AF patients (Lip *et al.*, 2015). The clinical significance of this risk is underscored by data indicating that up to one-quarter of all strokes may be attributable to AF in individuals in their ninth decade of life (Wolf, Abbott and Kannel, 1991).

The necessity for clear thromboprophylaxis guidelines is further amplified by regional variances, such as those collected in the Middle East. In our region, studies demonstrate that older patients (aged >70 years) hospitalised with AF exhibit a higher burden of stroke and excess mortality. A likely factor contributing to this unfavourable prognosis is the lower reported utilisation of oral anticoagulation (OAC) therapy (Salam *et al.*, 2012), with only half of patients in one registry study adherent to guideline therapy for secondary prevention (Miyazawa *et al.*, 2019).

It is widely recognised that individuals with a CHA_2DS_2-VA score (non-gendered) of 2 or higher should be considered for oral anticoagulation (OAC) due to a higher net clinical benefit from anticoagulation (Van *et al.*, 2024), a recommendation that already includes those aged ≥75 as an isolated risk factor.

However, the guidance for lower-risk individuals with CHA_2DS_2-VA score of 1 or CHA_2DS_2-VASc of 2 with female sex remains less definitive. This score is recognised as an indicator of increased stroke risk and should be taken into account when considering OAC therapy, but its application is not established. In this paper, we explore the evidence for the 65-74-year age group, highlighting the specific risks associated with AF, as well as the potential benefits of anticoagulation therapy.

METHODS

A comprehensive, non-systematic literature review was undertaken to identify and evaluate existing publications relevant to AF, stroke risk stratification, and the net clinical benefit of OAC therapy. The primary focus was on the intermediate-risk cohort, specifically patients aged 65–74 years.

Reported Risk Variability:

In general, a CHA_2DS_2-VASc (gendered) risk score of 0 is associated with a low annual stroke rate, even accounting for variation across studies. However, for those with a score of CHA_2DS_2-VASc 1, stroke rates can range from 0.2% to 6.64% annually (Abraham *et al.*, 2013 and Siu *et al.*, 2014), with 3 out of 17 studies identified exceeding a 2% annual stroke rate in one analysis (Chao *et al.*, 2016, Olesen *et al.*, 2011 and Siu *et al.*, 2014). Therefore, the absolute net benefit is difficult to derive. While genuine differences in risk rates may exist between different patient cohorts (e.g. between European and Far-East Asian populations) and within similar patient cohorts (e.g., demographics, genetic factors, co-morbidities), this implies that a portion of this variability could be attributable to methodological inconsistencies across studies (Quinn *et al.*, 2017). This includes heterogeneity in methodologies relating to time in therapeutic range for Vitamin K Antagonists (VKAs) and assessment AF burden in individuals. Additionally, although Western body guidance has moved away from gendered scoring, there remains some evidence that female gender consistently interacts with AF and ischaemic stroke risk (Basem *et al.*, 2025).

Risk Stratification by Age and Additional Related Factors:

In general, it can be assumed in this age bracket is that stroke risk is not fixed but increases continuously across the 65–74 age range. This is supported by one cohort study where stroke incidence increased gradually from 66 years (0.7%; 95% CI, 0.5%-0.9%) to 74 years (1.7%; 95% CI, 1.3%-2.1%) with no significant difference between men and women (Husam Abdel-Qadir *et al.*, 2021) (Figure 1). Additionally, a recent study examining a European cohort found a 2-fold risk of stroke in AF patients aged >70 (Morseth *et al.*, 2021), continuing to imply a trend towards a higher risk score at the upper end of our age bracket. This increasing realisation has led some authors to suggest lowering the age threshold for risk stratification and intervention (Kim *et al.*, 2018).

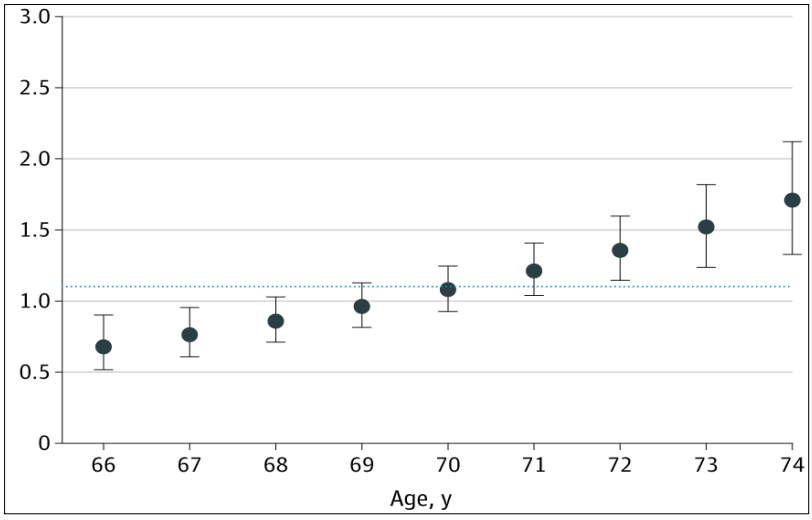

Figure 1: Cumulative Stroke Incidence (%) in patients aged 66 to 74 years (taken from Husam Abdel-Qadir *et al.*, 2021)

Advancing age must then be coupled with additional known risk factors for stroke in AF patients, including chronic kidney disease (CKD), which increases the stroke risk by up to two-fold (Ocak *et al.*, 2022) and is more prevalent in the elderly (Salam *et al.*, 2012). Additionally, left atrial enlargement (Maurizio Paciaroni *et al.*, 2015) and certain biomarkers, including interlukin-6, troponin and naturieutic peptides (Singleton *et al.*, 2021 and Hijazi *et al.*, 2017) also confer increased risk, with ongoing studies evaluating biomarker-led stroke prevention. More relevant to the Middle-East, Obesity and smoking status are also established risk factors for AF and subsequent stroke (Bassand *et al.*, 2018 and Seiffge *et al.*, 2020).

Benefits of anticoagulation:

Bleeding risk is known to correlate with the CHA2DS2-VASc score (Jarrah *et al.*, 2022), and therefore those scoring 1 point are also likely to confer a lower bleeding risk. On the other hand, although it has been well-established that OAC therapy with VKAs can reduce the risk of stroke by up to 64% in non-valvular AF (Hart, Pearce and Aguilar, 2007), the net clinical benefit is not certain, with some studies suggesting no net clinical benefit in low-risk groups (Friberg, Skeppholm and Terént, 2015 and Singer, 2009) and others showing some benefit (Fauchier *et al.*, 2016).

With the advent of newer direct OACs (DOACs), which have shown efficacy at least non-inferior to VKAs, there is the added advantage of a 50% reduction in intracranial bleeding risk (Carnicelli *et al.*, 2022). Additionally, DOACs have demonstrated a more favourable profile than warfarin for both stroke/systemic embolism risk and major bleeding risk, particularly in the 65-75 age group (Carnicelli *et al.*, 2022). As a result, the

net clinical benefit of DOACs is likely to surpass that of VKAs, making them a more favourable choice for patients in this age group, further reinforced by a recent meta-analysis showing that DOAC profile is overwhelmingly more favourable than VKA, maximising the probability of a positive net clinical benefit in the lower risk groups (Fong *et al.*, 2023).

CONCLUSION

The management of AF patients aged 65–74 years, who generally present with CHA_2DS_2-VA score of 1, requires an elevated degree of clinical nuance and a departure from strictly categorical score reliance. There is a clear need to standardise methodologies for analysing patient cohorts and interrogating population databases to improve risk stratification in lower-risk groups with AF. Until further evidence is available from clinical trials, the net clinical benefit of OAC for individuals aged 65-74 must be considered with dynamic risk assessment, not discounting sex and accounting for other risk modifiers, including but not limited to CKD, obesity, smoking status and biomarkers. Further research on biomarker-led stroke prevention is therefore welcome and may help to further risk-stratify this age group and improve clinical decision-making on OAC. The evidence presented here supports the idea that older patients within the 65-74 age range are more likely to have a higher stroke risk, with a continuously increasing risk with advancing age, thus potentially benefiting more from DOACs in non-valvular AF, which appear to be the more favourable option for net clinical benefit than VKAs.

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