Outcomes of complex older patients with acute ischaemic stroke and atrial fibrillation: A comparison study with and without the use of oral anticoagulants for secondary stroke prevention

Chee Sing Hui, MRCP, Tan Kit Mun, FRCP, Ooi Seok Ling, MMed (Internal Medicine), Ting Lee Yee, MRCP

Division of Geriatric Medicine, Department of Medicine, University Malaya Medical Centre, Malaysia

ABSTRACT

Introduction: Direct oral anticoagulants (DOACs) have become the mainstay of stroke prevention in patients with atrial fibrillation (AF). Decision to anticoagulate frail and post-stroke patients with AF may be challenging and complex. This study aimed to compare the outcomes of complex older patients with acute ischaemic stroke and AF who were treated with and without oral anticoagulants for secondary stroke prevention.

Materials and Methods: This is a retrospective observational study of all older persons (≥65 years) admitted to the geriatric medicine ward in our university hospital with acute ischaemic stroke and AF from January 2016 - December 2021. The inclusion criteria in our study were patients discharged alive from hospital post-ischaemic stroke with AF. Exclusion criteria were those who died as inpatient, those undergoing end-of-life care or with very severe frailty which are contraindication to anticoagulation. Comparison was done between patients who were anticoagulated and patients who were eligible for anticoagulation but were not anticoagulated for various reasons.

Results: There were 539 patients with ischaemic stroke, of whom 110 (21%) had AF. Among them, 29 patients were excluded due to death during hospitalization (19), end-of-life (4), and very severe frailty (6). While 65 (80%, mean age 84.1 ± SD 6.3) were discharged on anticoagulation, 16 (20%, mean age 88.3 ± SD 4.3, p=0.388) were discharged without anticoagulation. The median clinical frailty score was six in both groups. Among the anticoagulated, 59 (91%) were commenced on DOACs and six (9%) were on warfarin. The main reasons recorded for not commencing anticoagulants in eligible patients were patient/family did not agree to start (8), high bleeding risk (7), and poor social support (1). Mortality was significantly higher in the non-anticoagulated group (n=10, 63%) compared to the anticoagulated group (n=22, 32%) (p=0.036).

Conclusion: Although frail older persons are perceived to have a poorer benefit/risk ratio when anticoagulated, our study demonstrated lower mortality in post-stroke anticoagulated complex older AF patients compared to those who were not anticoagulated. However, given the small numbers of participants in our study, further studies are required to determine characteristics of patients who may have better outcomes or lower risk of adverse events on anticoagulants. These findings also underscore the pressing need for a standardized, frailty-prescribing and monitoring protocol to maximise benefit and minimise risks of adverse outcomes.

KEYWORDS:
Anticoagulation, stroke, atrial fibrillation, frail, older persons, geriatric

INTRODUCTION

Atrial fibrillation (AF) is a common arrythmia in frail, complex older persons. The prevalence of AF increases with age, affecting up to 4.2% of those aged 60–70 years and 17% of those aged 80 years or older.[1] People with AF have increased risk of stroke.[2] In the Framingham study, the annual risk of stroke in patients with AF was 1.5% in those aged 50–59 years and 23.5% in those aged 80–89 years.[3]

Frailty is a clinically identifiable state of diminished physiological reserve and increased vulnerability to a broad range of adverse health outcomes.[4] For frail older patients, stroke is associated with an increased risk of severe functional decline and loss of health-related quality of life.[5]

Older persons with AF have more favourable outcomes on direct oral anticoagulants (DOACs) than without, and on DOACs than on vitamin K antagonists (VKA).[6-7] The net clinical benefit for DOACs declines with advanced age due to competing risks for bleeding and death but is maintained longer with DOACs than VKA.[8] When given anticoagulation, older age is an accepted risk for haemorrhage and bleeding complications are likely to be higher in people with frailty. In the 2021 European Heart Rhythm Association (EHRA) practical guide on the use of DOACs, the benefit over risk ratio is greater in the fit older person with the ratio reducing with increasing levels of frailty.[9] The EHRA guide suggests that very severe frailty and terminal illness typically indicate a contraindication to anticoagulation.[10] In this EHRA practical guide where the Clinical Frailty Scale (CFS) was used, very severe frailty is defined as completely dependent for personal care and approaching end-of-life and typically they could not recover even from a minor illness.

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Corresponding Author: Tan Kit Mun
Email: tankitmun@um.edu.my

Despite the evident benefits of anticoagulants in preventing stroke, there are many considerations in starting anticoagulation in older frail persons, which include multiple chronic diseases, polypharmacy, drug-drug interactions, pharmacokinetics and pharmacodynamics which can all be affected by ageing.[11] A study by Mant et al. in 2007 in a population of over the age of 75 years clearly supports the use of anticoagulation therapy for people who have AF.[12] However, Perera et al (2009) concluded that frail older inpatients with AF are significantly less likely to receive anticoagulation than those who are non-frail and appear more vulnerable to adverse clinical outcomes, with and without antithrombotic therapy.[13] Nishimura et al. (2023) demonstrated in his study that increasing levels of frailty, the incidence of the composite bleeding outcome increased rapidly: for patients classified as "not frail," the incident rate 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.[14] Meanwhile Nguyen et al.'s study in 2016 found that frailty status had no independent impact on pharmacological treatment of AF, but the rate of major bleeding complications may reflect careful patient selection and management of anticoagulation.[15] Hence the decision of prescribing can be complex and individualised. This study is aimed to determine the characteristics and outcomes of older persons with AF and ischaemic stroke who were anticoagulated compared to those who were eligible for anticoagulation but were not anticoagulated.

MATERIALS AND METHODS

Study Population

This was a retrospective observational study approved by the ethics committee of our university hospital (MEC ID: 201312-0636). All older persons aged 65 years old and above who were admitted to the geriatric medicine ward in our university hospital from January 2016 – December 2021 with an acute ischaemic stroke and a background medical history or new diagnosis of AF were included. Exclusion criteria were those who died as an inpatient, very severe frailty (CFS of 8), and those who were undergoing end-of-life care (CFS of 9) which are contraindications to anticoagulation. The index date is defined as when the patient was first admitted for the acute ischaemic stroke. The follow-up period was defined as the duration from the index date until the death of the patient, or until the end date of the study period (December 31, 2024) which was 3 years after the end of recruitment period.

Patients' characteristics, medications, and outcomes were collected using our university hospital's in-house Electronic Medical Record system. Patient's frailty status was determined according to the Rockwood CFS version 2, based on the functional, and dependency status of the patient before stroke and upon discharge from the stroke admission. Very severe frailty was defined as completely dependent, approaching end-of-life, and could not recover even from a minor illness. End-of-life was defined as progressive life-limiting disease with a prognosis of months or less.[16] The subsequent outcome and complications were based on reports in our electronic medical record, with at least one follow-up visit to our hospital after discharge. The degree of disability or dependence in the daily activities were also recorded using modified Rankin scale (mRS), a standardized and validated measure for assessing the impact of a new stroke.[17]

Statistical Analysis

Results were presented as mean (SD) ± standard deviation, compared using t-tests, and correlation test. Counts and percentages were analysed using c^2 and Fisher's exact test. All tests were two-sided, with the level of significance set at $p<0.05$, performed using SPSS statistic version 23 for Windows©.

Outcome

The primary outcome of interest was the overall mortality. Secondary outcomes were the complications associated with anticoagulation: major bleeding, clinically relevant non-major bleeding (CRNMB), non-clinically consequential minor bleeding and recurrent ischemic stroke. There was also composite secondary outcome of all 3 categories of bleeding combined.

The above classification of severity of bleeding is according to the International Society on Thrombosis and Haemostasis (ISTH)'s definition of bleeding in non-surgical patients. It can be divided into major bleeding, CRNMB, and non–clinically consequential minor bleeding event. Major bleeding is defined as having a fatal bleeding, symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome.[18] A CRNMB is defined as any sign or symptom of haemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding but does prompt a clinical response, which leads to one of the following: a hospital admission, a physician guided medical or surgical treatment for bleeding, prompting a face to face evaluation.[19] A non-clinically consequential minor bleeding event is defined as bleeding that is not actionable. A decrease of haemoglobin of 2g/dL or more is considered major bleeding by ISTH, this is often encountered during assessment after initiation of anticoagulant but there is no obvious source of bleeding identified.

RESULTS

There were 539 patients with stroke who were admitted to the geriatric medicine ward in our university hospital from January 2016 - December 2021 (Figure 1), of whom 110 (20%) had AF (paroxysmal or persistent). Among the 110, 73 were commenced on anticoagulation for secondary stroke prevention, but eight died during the admission, leaving 65 discharged (80%, mean age 84.1 ± SD 6.3). On the other hand, 37 were not prescribed anticoagulation. Among them, 11 died during the admission period, four were undergoing end-of-life care due to stroke, and six had very severe frailty post-stroke. At last, there were 16 who were eligible for anticoagulation but discharged without anticoagulation (20%, mean age 88.3 ± SD 4.3). Those not anticoagulated were significantly older (median: 88 vs 84, p=0.016) and had

Table I: Characteristics of participants with and without anticoagulants

Characteristic	Anticoagulated n =65	Non-anticoagulated n = 16	p-value
Sex			
Male	28 (43%)	5 (31%)	0.388
Female	37 (57%)	11 (69%)	
Median age ± IQR Year	84.0 ± 9	88.5 ± 6	0.016*
Body weight (kg)	57.2 ± 11.1	44.8 ±7.18	0.001*
No. of comorbidities	3.8 ± 1.3	3.7 ± 1.4	0.863
Types of anticoagulation			
Apixaban	38 (58%)		
Dabigatran	20 (31%)		
Rivaroxaban	1 (2%)		
Warfarin	6 (9%)		
Median CFS (pre-stroke)	5 ± 1	5 ± 1	0.829
Median CFS (Post-stroke)	6 ± 1	6 ± 1	0.357
mRS	4.0 ± 0.9	4.2 ± 0.9	0.459
No. of medications	6.6 ± 3.1	4.7 ± 1.7	0.021*
CHA2DS2-VASc Score	5.6 ± 1.6	5.6 ± 1.1	0.954
HAS-BLED Score	2.8 ± 0.9	2.9 ± 0.8	0.909
CKD stage	2.3 ± 0.9	2.0 ± 0.6	0.357

*Statistically significant.
Abbreviation: IQR = Interquartile range. CFS = Clinical Frailty Score. CHA2DS2-VASc = Score for Atrial fibrillation stroke risk. HAS-BLED = Score for Major bleeding risk on anticoagulant. mRS = modified Rankin Scale. CKD = chronic kidney disease.

Table II: Clinical outcomes among patients with and without anticoagulation

Complication	Anticoagulated n = 65	Non-anticoagulated n = 16	p-value
Major bleed	17 (26%)	1 (6%)	0.086
CRNMB	7 (10%)	3 (18%)	0.385
Combined bleed	22 (34%)	3 (19%)	0.242
Recurrent ischemic stroke	10 (15%)	4 (25%)	0.362
Death	22 (32%)	10 (63%)	0.036*
Ischemic Stroke	4	1	0.989
Intracranial bleed	2	0	0.477
GI bleed	2	0	0.477
Sepsis	8	2	0.888
Malignancy	1	0	0.618
Heart failure	2	0	0.474
HHS	0	1	0.043*
Undetermined cause	3	6	

* Statistically significant
Abbreviation: CRNMB = clinically relevant non-major bleeding, Hb = Haemoglobin, GI = Gastrointestinal, HHS = Hyperosmolar hyperglycaemic syndrome.

a lower mean body weight 44.8kg vs 57.2kg (p=0.001) with fewer medications (6.6 vs 4.7, p=0.021). The average length of follow-up was 30 months (±SD 20 months). The median Clinical Frailty Score v2.0 post stroke was six in both groups of those with and without anticoagulation. In the anticoagulated group, 65 (89%) were commenced on DOACS and eight (11%) on warfarin (Table I). The reported anticoagulants used were apixaban (38/65, 58%), dabigatran (20/65, 31%), rivaroxaban (1/65, 2%) and warfarin (6/65, 9%). With the 59 who were discharged with DOACs, 56 (95%) were prescribed with appropriate dose and three were prescribed with off-label inappropriately reduced dose based on the treating physicians' clinical judgement due to bleeding history.

For the 16 patients who were discharged without anticoagulant, the main reason recorded for not commencing on anticoagulant was because family members or patient did not agree to start (8/16, 50%). The reasons for not agreeing to anticoagulation could not be determined from the medical notes. The second reason was perceived high bleeding risk (7/16, 44%), which was evident in patients with high HAS-BLED score (≥3), history of major bleeding with anticoagulation or antiplatelet, and cancer imposing the patient with higher bleeding risks.[20] Only one (1/16, 6%) was not started on anticoagulation due to poor social support.

For the overall mortality, the outcome of death was significantly higher in the non-anticoagulated group (10/16, 63%) compared to the anticoagulated group (22/65, 32%, p=0.036). The occurrence of major bleed (26% vs 6%, p=0.086), CRNMB (10% vs 18%, p=0.385), and combined bleed (34% vs 19%, p=0.242) were similar in the anticoagulated group compared to non-anticoagulated group. There was no non–clinically consequential minor bleeding event reported in our study. Despite given anticoagulation, 10 out of 65 patients (15%) experienced

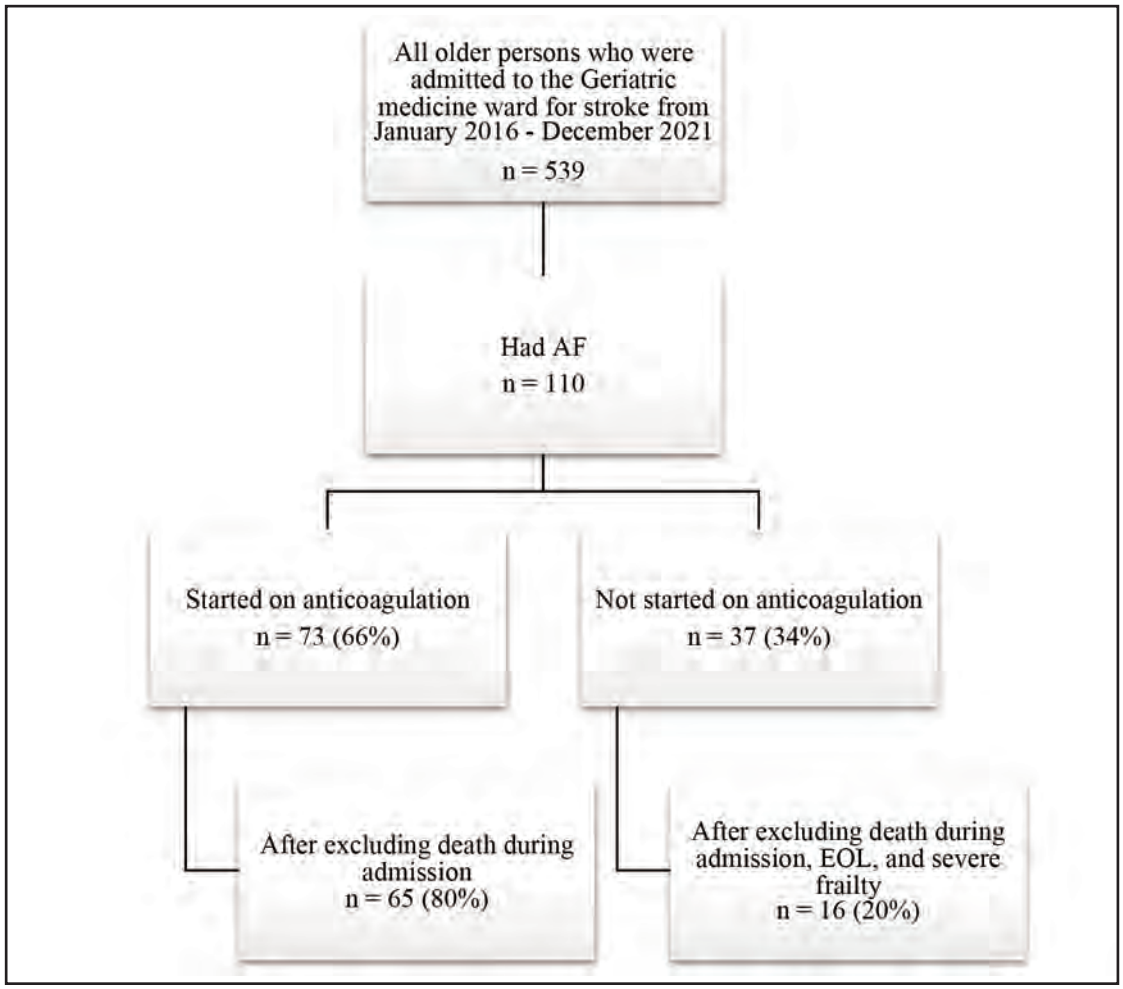

Fig. 1: Flow chart of subjects included in the study following inclusion and exclusion criteria. Abbreviation: AF = Atrial fibrillation, EOL = End of life

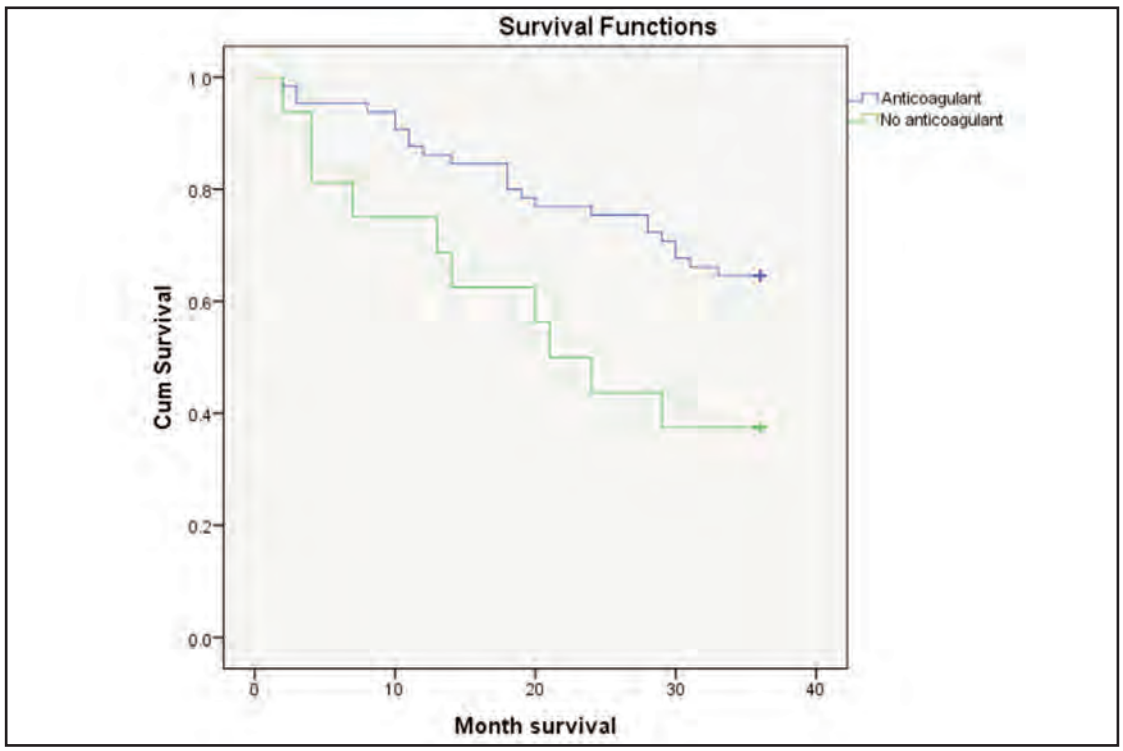

Fig. 2: Kaplan-Meier curve shows the survival between anticoagulant group (blue line) and non-anticoagulant group (Green line). Y-axis represents cumulative survival probabilities, and X-axis shows the number of months of survival

recurrent ischemic stroke, while four out of 16 (25%, p=0.362) had recurrent ischemic stroke in the non-anticoagulated group (Table II).

The causes of death are listed below the row of death. Most died due to sepsis (eight in the anticoagulated group vs two in the non-anticoagulated group). Four anticoagulated patients had deadly recurrent ischemic stroke compared to one in the non-anticoagulated group. There were four deaths due to major bleeding (intracranial bleed and gastrointestinal bleed) in the anticoagulated group, while none in the non-anticoagulated group. There were deaths due to undetermined cause when patients were dead on arrival, or cause of deaths were not clearly be found in the record.

To compare the time to survival rate in anticoagulated and non-anticoagulated participants, the Kaplan–Meier estimator was employed to compute survival curves over three years (36 months) follow-up period (follow-up intervals varied depending on individuals' condition and prognosis, usually on a four to six monthly basis), and differences between anticoagulated and non-anticoagulated groups were assessed using log rank tests (Figure 2). The curve showed significant difference (log-rank: 0.021), showing higher survival rate of 68% in the anticoagulated group compared to 37% in the non-anticoagulated group in the three years period analysed for survival. However, given the extreme imbalance in group sizes and the very small denominator in the untreated arm, this analysis was underpowered, and the survival estimates were unstable and prone to heavy influence by individual outliers. In the anticoagulated group, six (6/22, 27%) were cardiovascular deaths, and 16 (73%) were non-cardiovascular deaths.

DISCUSSION

The management of AF in frail, older patients who have already suffered an ischemic stroke presents a profound clinical dilemma. AF-related strokes tend to be more severe, generally presenting with greater disability and higher mortality compared to non-AF stroke.[21] Patients with AF had poorer survival and more stroke recurrences during one year of follow-up. A study by Lin et al. showed that the AF subjects had lower mean Barthel index scores acutely (29.6 versus 58.6, p<0.01) and at three months p=0.005), six months (p=0.003), and 12 months (p=0.130) after stroke among survivors.[22] A meta-analysis by Huang et al. showed the prevalence of frailty and prefrailty in stroke patients to be 27% (95% CI: 22.9–31.1%, <0.01) and 47.9% (95% CI: 42.5–53.3%, p<0.01) respectively.[23] The increased frailty associated with these strokes leads to higher adverse events including major bleeds, ischemic stroke and death.[24]

Our study directly reflects this vulnerable population and highlights a critical disconnect between perceived clinical risk and actual mortality outcomes. We observed a significantly lower overall mortality rate in frail, post-stroke patients who were discharged on anticoagulation compared to those who were eligible for anticoagulation but not anticoagulated (32% vs. 63%, p=0.036), which was also reflected in the survival curve demonstrating a significant 68% survival rate at three years for the anticoagulated cohort versus only 37% for the non-anticoagulated group (log-rank: 0.021).

More importantly, this substantial survival benefit was achieved despite the anticipated risks of anticoagulation in an older demographic. Physicians frequently harbour deep worries about prescribing anticoagulants to frail patients due to bleeding concerns. Indeed, in our non-anticoagulated cohort, a perceived high bleeding risk was driven by high HAS-BLED scores, previous bleeding history, or concurrent cancer. While our findings did show an upward trend in bleeding complications among anticoagulated patients (such as major bleeding at 26% vs. 6%), these differences did not reach statistical significance, likely limited by our small sample size.

The critical interpretation of these findings is that the survival benefit of anticoagulation in this cohort appears to heavily outweigh the bleeding risks. The fear of iatrogenic harm (bleeding) often overshadows the natural, highly lethal progression of untreated AF. By withholding anticoagulation, we may be inadvertently subjecting these patients to a much higher risk of all-cause mortality.

However, this survival benefit is not absolute and must be contextualized and individualised within the spectrum of frailty. Our study design explicitly excluded patients with very severe frailty (CFS of 8) and those undergoing end-of-life care with a prognosis of less than six months (CFS of 9). In these profoundly frail individuals, the risk-benefit ratio heavily inverses, and anticoagulation is fundamentally contraindicated. This aligns tightly with the 2021 EHRA practical guide on the use of DOACs, which reinforces that while fit and moderately frail older persons benefit greatly, very severe frailty and terminal illness preclude the use of anticoagulation.

The prescription of anticoagulants in frail, older post-stroke patients demand careful consideration and individualized assessment. Our data has suggested that frailty alone should not be a barrier to treatment. Moving forward, clinical practice must shift from avoidance to active management, which includes rigorous surveillance for bleeding complications and comprehensive education for frail patients and their families regarding the true balance of risks and benefits.

STRENGTHS AND LIMITATIONS

The strengths of this study are that it comprised a sample of very old and frail people, where the risk of complications is high. This group have been under-represented in clinical trials and are at a higher risk of both stroke and bleeding complications. We used a validated Rockwood CFS version 2 which is being used worldwide. Although this study did not focus on the types of anticoagulation used and their associated bleeding risks, it aimed to overall compare patients who were anticoagulated against those who were eligible for anticoagulation but were not anticoagulated for the stated reasons.

There are several limitations of this study. First, this was a retrospective study, from which we were unable to detect compliance and adherence to treatment. Our study could have led to bias due to missing data and retrospective interpretation. Furthermore, this study was based on what was recorded in our electronic medical record, hence certain complications might not be captured if patients did not report the complications or sought treatment in other hospitals, especially non–clinically consequential minor bleeding event which tend to be under-reported by patients or their families. HAS-BLED score may underestimate the bleeding risks in frail older persons, as there were many other risk factors of bleeding which may not be captured but may influence the physicians' decision for not prescribing anticoagulation. These risk factors of bleeding include high falls risk, recent anaemia, thrombocytopenia, coagulopathy, malignancy (greatly increases both bleeding and clotting risks), and cerebral amyloid angiopathy. On the other spectrum, the inability to elicit the reasons why or family members refused anticoagulation may pose significant selection bias.

CONCLUSION

Our observational study found lower overall mortality rates in the anticoagulated group of post-stroke patients with atrial fibrillation compared to those who were not anticoagulated. Frail older patients who are anticoagulated require more surveillance in terms of anticoagulation associated bleeding risks and education to increase awareness of bleeding risks among patients.

These findings underscore the pressing need for a standardized, frailty-prescribing and monitoring protocol to maximise benefit and minimise adverse events. A structured guideline would ensure that complex, uncaptured bleeding risks, and strict DOAC pharmacokinetic dosing are formally integrated into clinical decision-making, moving subjective and hesitative local practice toward objective, decisive patient-centred care. Further studies are also required to determine characteristics of patients who may have better outcomes or lower risk of adverse events on anticoagulants.

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CONFLICT OF INTEREST

There is no conflict of interest regarding the publication of this study.

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REFERENCES

1. Wilkinson C, Todd O, Clegg A, Gale CP, Hall M. Management of atrial fibrillation for older people with frailty: a systematic review and meta-analysis. Age Ageing 2019; 48(2): 196-203.
2. Fuster V, Ryden LE, Asinger RW, Cannom DS, Crijns HJ, Frye RL et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences. Circulation 2001; 104: 2118-50.
3. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991; 22(8): 983-8.
4. Kim DH, Rockwood K. Frailty in older adults. N Engl J Med 2024; 8; 391(6): 538-48.
5. Zhou J, Liu F, Zhou M, Long J, Zha F, Chen M et al. Functional status and its related factors among stroke survivors in rehabilitation departments of hospitals in Shenzhen, China: a cross-sectional study. BMC Neurol 2022; 22(1): 173.
6. Bai Y, Guo SD, Deng H, Shantsila A, Fauchier L, Ma CS, et al. Effectiveness and safety of oral anticoagulants in older patients with atrial fibrillation: a systematic review and meta-regression analysis. Age and ageing 2018; 47(1): 9-17.
7. Haas S, Camm AJ, Bassand JP, Angchaisuksiri P, Cools F, Corbalan R, et al. GARFIELD-AF Investigators. Predictors of NOAC versus VKA use for stroke prevention in patients with newly diagnosed atrial fibrillation: results from GARFIELD-AF. Am Heart J 2019; 213: 35-46.
8. Shah SJ, Singer DE, Fang MC, Reynolds K, Go AS, Eckman MH. Net clinical benefit of oral anticoagulation among older adults with atrial fibrillation. Circ Cardiovasc Qual Outcomes 2019; 12(11): e006212.
9. Johnson CE, Lim WK, Workman BS. People aged over 75 in atrial fibrillation on warfarin: the rate of major hemorrhage and stroke in more than 500 patient-years of follow-up. J Am Geriatr Soc 2005; 53(4): 655-9.
10. Steffel J, Collins R, Antz M, Cornu P, Desteghe L, Haeusler KG, et al. European heart rhythm association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Europace 2021; 23(10): 1612-76.
11. Hilmer SN, Gnjidic D, Le Couteur DG. Thinking through the medication list appropriate prescribing and deprescribing in robust and frail older patients. Aust Fam Physician 2012; 41: 924-8.
12. Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, et al; BAFTA investigators; Midland Research Practices Network (MidReC). Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. Lancet 2007 11; 370(9586): 493-503.
13. Perera V, Bajorek BV, Matthews S, Hilmer SN. The impact of frailty on the utilisation of antithrombotic therapy in older patients with atrial fibrillation. Age Ageing 2009; 38(2): 156-62.
14. Nishimura S, Kumamaru H, Shoji S, Nakatani E, Yamamoto H, Ichihara N, et al. Frailty and subsequent adverse outcomes in older patients with atrial fibrillation treated with oral anticoagulants: The Shizuoka study. Res Pract Thromb Haemost 2023; 7(3): 100129.
15. Nguyen TN, Cumming RG, & Hilmer SN. Atrial fibrillation in older inpatients: are there any differences in clinical characteristics and pharmacological treatment between the frail and the non-frail? Internal Medicine Journal 2016; 46(1): 86-95.
16. Hui D, Nooruddin Z, Didwaniya N, Dev R, De La Cruz M, Kim SH, et al. Concepts and definitions for "actively dying," "end of life," "terminally ill," "terminal care," and "transition of care": a systematic review. J Pain Symptom Manage 2014; 47(1): 77-89.
17. Banks JL, Marotta CA. Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis. Stroke 2007; 38(3): 1091-6.
18. Schulman S, Kearon C. "Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients". J Thromb Haemost 2005; 3(4): 692-4.

19. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S & subcommittee on control of anticoagulation. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost JTH 2015; 13(11): 2119-26.
20. Bassand JP, Virdone S, Badoz M, Verheugt FWA, Camm AJ, Cools F, et al. Bleeding and related mortality with NOACs and VKAs in newly diagnosed atrial fibrillation: results from the GARFIELD-AF registry. Blood Adv 2021; 5(4): 1081-91.
21. Henninger N, Goddeau RP Jr, Karmarkar A, Helenius J, McManus DD. Atrial fibrillation is associated with a worse 90-day outcome than other cardioembolic stroke subtypes. Stroke 2016; 47(6): 1486-92.
22. Lin HJ, Wolf PA, Kelly-Hayes M, Beiser AS, Kase CS, Benjamin EJ, et al. Stroke severity in atrial fibrillation. The Framingham Study. Stroke 1996; 27(10): 1760-4.
23. Huang YN, Yan FH, Wang XY, Chen XL, Chong HY, Su WL, et al. Prevalence and risk factors of frailty in stroke patients: a meta-analysis and systematic review. J Nutr Health Aging 2023; 27(2): 96-102.
24. Kim DH, Pawar A, Gagne JJ, Bessette LG, Lee H, Glynn RJ, et al. Frailty and clinical outcomes of direct oral anticoagulants versus warfarin in older adults with atrial fibrillation: a cohort study. Ann Intern Med 2021; 174(9): 1214-23.