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REVIEW

Balancing the risk of stroke and bleeding in atrial fibrillation patients with a history of falls

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ABSTRACT

Introduction: Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and can lead to serious consequences such as ischemic stroke and systemic thromboembolism. The risk of thromboembolism can be reduced by anticoagulation, however many patients with high falls risk do not receive oral anticoagulation.

Areas Covered: In this narrative literature review, performed with searches of the PubMed database, we discuss the factors predisposing AF patients to falls, ways to optimize bleeding risk with individualized assessment, and clarify misconceptions around falls risk and anticoagulation therapy.

Expert Opinion: In general, the advantages of stroke prevention with oral anticoagulation outweigh the risk of bleeding resulting from falls, especially with the increasing use of non-vitamin K oral anticoagulants, which are associated with fewer intracranial hemorrhages and thromboembolic complications than vitamin K anticoagulants. Most studies in this field are observational and randomized controlled studies would be beneficial.

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Anticoagulants; bleeding; atrial fibrillation; fall; safety

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. AF predisposes to thromboembolic complications, such as ischemic stroke, mesenteric ischemia and acute limb ischemia [1,2]. With improvements in preventative medicine, and the aging population, the prevalence of AF is rising. The lifetime risk of AF is approximately 33% [3], with estimates modified by patient-level factors such as age, sex, race and burden of clinical risk factors [3]. Aging is associated with increased AF burden, with a sharp incline after age 65 [4]. Ischemic stroke is most feared complication of AF, and the most common cause of embolism-related death in patients with AF [2]. Oral anticoagulation decreases the risk of stroke, but also increases the risk of bleeding.

Bleeding complications are a common reason for discontinuation of anticoagulation, as are frailty and falls risk [5]. In the ORBIT-AF registry, for example, 17.6% of those with contraindications to anticoagulation had 'frequent falls/frailty' documented as the reason [6]. Hence, many AF patients at high risk of falling do not receive anticoagulation [7,8]. Unfortunately, such patients tend to be older and more susceptible to thrombosis. Additionally, AF is an independent risk factor for frailty-related falls [9].

In this narrative review, we discuss the risk of falling in patients with AF, and the associated risk of major bleeding secondary to falling. We also review the use of oral anticoagulation for stroke prevention in AF patients at risk of falls.

2. Factors associated with falls risk

Falls are one of the features of the frailty syndrome, along with functional decline, delirium, incontinence, and pressure ulcers. Older patients with AF tend to have one or more of these features [10]. Epidemiological studies show that falls are the leading cause of both fatal and non-fatal injuries in older people. A 2016 study showed that almost a third of older adults experienced at least one fall over a 12-month period, of whom 37.5% suffered injury [11]. Another study found that 30% of people older than 65 and 50% of people older than 80 fall at least once a year [12]. Fall-related hospital admissions cause considerable distress to the patient and their loved ones, as well as a significant impact upon healthcare and social services [13]. Hence, it is crucial to assess falls risk and implement preventative measures where possible.

AF is an independent risk factor for falls in the elderly [14,15]. Although logically those with AF may be expected to have more co-morbidities, Hung et al. found AF to be an independent predictor after multivariable adjustment. The reasons behind this may be multifactorial and relate to hemodynamics and cerebral perfusion, however this is beyond the scope of our article. Individuals with AF and other cardiovascular diseases may also be treated with antihypertensives, antiarrhythmics and diuretics; both the comorbidities themselves and the associated medications may further predispose them to falls [16]. In one study of 509 elderly NVAF patients, using ≥10 medications resulted

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Article highlights

- Patients with atrial fibrillation may be at elevated falls risk for multifactorial reasons
- Anticoagulation is often inappropriately withheld in such patients
- Individualised risk assessment to address modifiable risk factors and minimize falls risk is important
- Generally, anticoagulation should be favored even in high-risk patients, as the risk of ischemic stroke outweighs the risk of significant bleeding from a fall
- Prospective studies would be beneficial to further substantiate the observational evidence base

in an almost 5-fold increase in falls or fracture risk compared to those using ≤3 medications [17].

A 2010 meta-analysis of 74 community-based studies found that the strongest predictors of falls risk were a history of prior falls, gait problems, use of walking aids, vertigo, Parkinson's disease, and use of antiepileptics [18]. In those with prior stroke, which is particularly relevant in the context of AF potentially without anticoagulation, a meta-analysis of 21 studies found impaired mobility or balance, sedative or psychotropic medications, difficulty with self-care, depression or cognitive impairment and history of falls to be predictive of falls risk [19]. Fear of falling and female sex may also contribute significantly to falls risk [20]. Leipzig et al. specifically studied the effects of drugs on falls risk [21]. Significant odds ratios were found for diuretics (1.08), class Ia antiarrhythmics (1.59) and Digoxin (1.22).

Physical aspects of frailty, such as muscle atrophy and impaired balance and coordination, significantly increase the risk of falls [22]. In adults with cardiovascular disease – particularly AF – loss of brain volume in the hippocampus, frontal lobes, and parietal lobes due to cerebral hypoperfusion may result in cognitive impairment [23] which also increases the risks of falls [24]. The relationship between AF and falls is summarized in Figure 1.

3. Mitigation of falls risk

Falls screening tools, such as FRAT (Falls Risk Assessment Tool), Morse Falls Scale (MFS) and STRATIFY (St. Thomas Risk Assessment Tool in Falling elderly inpatients) may be utilized to assess the risk of falls [25]. Risk factors include the number of recent falls, number of medications, and use of specific medications such as sedatives, anti-depressants, anti-Parkinsonians, diuretics, anti-hypertensives and hypnotics. Psychological states such as anxiety and depression, reduced cooperation, impaired insight or judgment, reduced mobility and cognitive status are also part of the assessment.

Multifactorial risk assessment and management can be undertaken by healthcare professionals. This includes comprehensive assessment of falls risk factors including prior falls history, muscle weakness, balance, visual impairment, polypharmacy and home hazards [26]. Exercise programs such as FaME, Otago and Tai Chi are known to be effective in improving balance, flexibility and strength as well as reducing number of falls and risk of injury from falls [27–29]. Evaluation of the

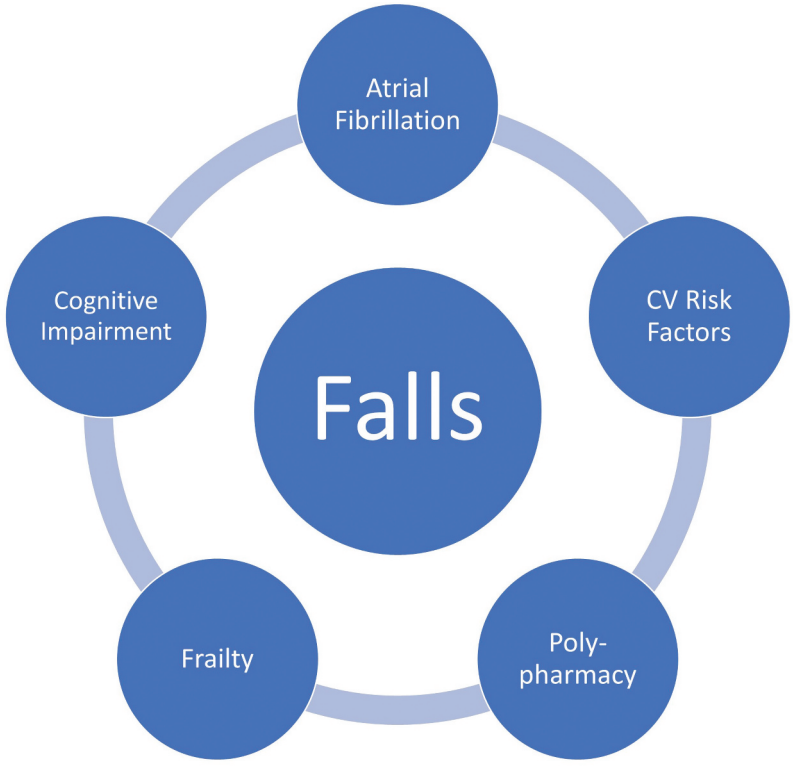

Figure 1. The interrelationship of atrial fibrillation and falls risk.

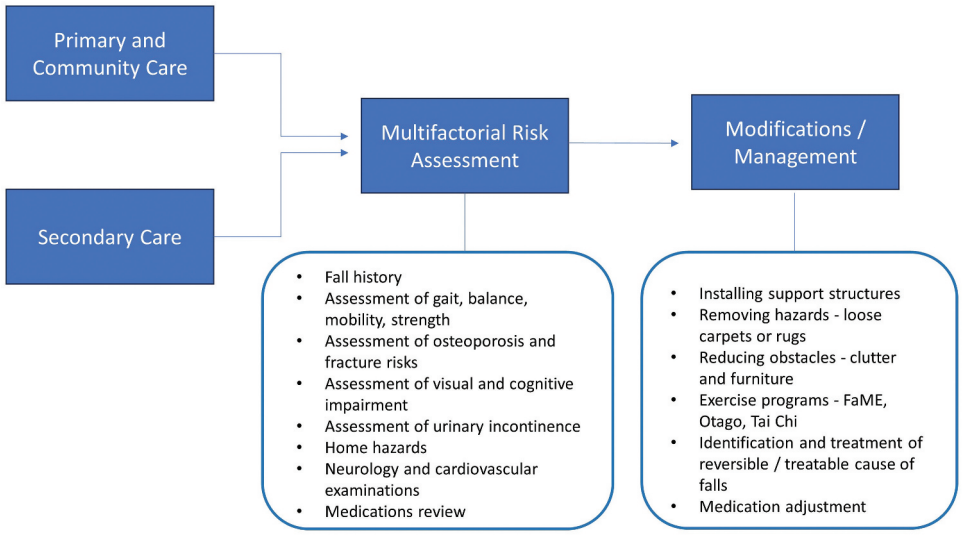

Figure 2. Falls risk assessment and mitigation.
FaME = Falls Management Exercise

home environment allows identification of potential hazards for falls or accidents. Based upon this assessment, modifications such as installing grab rails, and removing hazards such as loose carpets, rugs, obstacles, clutter and furniture can be undertaken to reduce the risks of falls. Patient education, lifestyle modification and psychosocial management are part of integrated care as per international recommendations [30] (Figure 2).

4. Stroke prevention in atrial fibrillation

Prevention of ischemic stroke and systemic thromboembolism is central to the management of AF and forms the 'A' component of the guideline-recommended Atrial fibrillation Better Care (ABC) pathway [31], given the improved clinical outcomes by adherence to such a management pathway [32]. Risk reduction in those with elevated stroke risk scores can be achieved by pharmacotherapy, with vitamin K anticoagulants (VKAs, e.g. warfarin) or non-VKA oral anticoagulants (NOACs). Alternatively, in those with contraindications to oral therapy, percutaneous left atrial appendage occlusion (LAAO) may be an option [33].

Traditionally, VKAs were the mainstay of thromboembolic prevention for AF, and they are known to be more effective than antiplatelets, even in elderly patients. For example, the BAFTA trial randomized 973 patients aged 75 years or over to warfarin or aspirin, whereby annual stroke risk was 1.8% on warfarin versus 3.8% on aspirin (RR 0.48, 95% CI 0.28–0.80, $p = 0.003$). The yearly risk of extracranial hemorrhage was 1.4% with warfarin versus 1.6% with aspirin (RR 0.87, 0.43–1.73) [34]. However, VKAs have a narrow therapeutic range, requiring frequent monitoring and dose adjustments.

NOACs have emerged as a non-inferior alternative to VKAs [35–39] for stroke prevention in AF, supported by randomized trials and real world evidence [40]. Whilst dose adjustment may be required according to age, body weight, renal function and use of interacting medications, the dose usually remains constant thereafter. For these reasons, NOACs are recommended by international guidelines in preference to VKAs for stroke prevention in AF [41].

However, clinicians need to consider the risk of major bleeding – especially intracranial hemorrhage – when prescribing anticoagulation. Is it safe to prescribe OACs for patients at high falls risk? We explore this concept below.

5. Anticoagulation safety in patients at risk of falls (**Table 1**)

The main concern with anticoagulant use is the risk of bleeding, and the assessment and mitigation of bleeding risks has been recently reviewed [42]. AF patients often manifest clinical complexity, which is associated with a high risk of adverse outcomes, under-treatment with anticoagulation and higher rates of discontinuation [42]. In general, the risk of major bleeding with VKAs is low, and a high falls risk has not been significantly associated with increased risk [43]. However, managing VKAs with the inherent requirement for blood tests and dose adjustments may be challenging in elderly, frail patients, particularly in those with cognitive impairment. In this setting, NOACs provide benefit by maintaining a consistent dose and negating the requirement for blood tests.

The safety of NOACs in patients at high risk of falls has been demonstrated in several studies. A pre-specified analysis of ENGAGE AF-TIMI 48, comparing patients with versus without increased falls risk, showed that edoxaban was associated with a lower risk of severe bleeding events and all-cause mortality compared to warfarin [44]. In the ARISTOTLE study, the efficacy and safety of apixaban compared to warfarin was constant in individuals with versus without a history of falls [45–47].

These trial data are supported by real world observational evidence. For example, Miao et al. retrospectively studied over 25,000 high falls risk patients from the MarketScan database and found NOAC use was associated with a 43% reduction in

intracranial hemorrhage, and similar reductions in thromboembolic events, compared to warfarin [48].

A recent systematic review and multilevel meta-analysis by Thibaut et al. demonstrated that NOACs reduced the risk of ischemic stroke or systemic embolism and intracranial hemorrhage compared with VKAs in patients at risk of falls [49]. Another meta-analysis by Gao et al. also showed that NOAC use significantly lowers the chances of hemorrhagic stroke and major hemorrhage in AF patients at risk of falling [50].

It has been estimated that a patient taking rivaroxaban would need to fall at least 45 times per year for discontinuation of anticoagulant therapy to be potentially beneficial; this figure increases to over 450 times per year on the lowest risk NOAC (apixaban) [51]. Given that most high-risk patients fall 2–3 times per year [52,53], it seems clear that the benefit is in favor of NOAC therapy for the vast majority.

A retrospective study evaluated the consequences of falling in patients with AF receiving different anticoagulants and found that type of anticoagulant significantly affected survival after first fall, with worse survival rates in patients inadequately anticoagulated with warfarin compared to best survival in patients on apixaban or dabigatran [54].

Despite these figures, clinicians may overestimate the risk of bleeding in those with prior falls and studies suggest that these patients may have anticoagulation inappropriately withdrawn [5–8]. There are only a few absolute contraindications to OAC which include active serious bleeding, associated comorbidities or recent high-risk bleeding events such as intracranial hemorrhage. In such cases, non-drug options such as LAAO may provide an alternative option to reduce stroke risk [41].

6. Left atrial appendage occlusion in frail patients

It has been shown that LAAO is an alternative option and non-inferior to warfarin in patients with absolute contraindication to anticoagulants [55,56]. However, patients with contraindications to OAC may be older, more frail, and have a higher burden of comorbidities. An observational study conducted by Shubrandu et al. compared the rate of in-hospital major adverse events after LAAO in patients older than 80 years to younger patients [57]. Patients ≥80 years old experienced a higher rate of major adverse events (MAE) compared to those aged <80 years old (6.0% versus 4.6%, $p = 0.01$). While female sex, the presence of heart failure, diabetes, renal disease and anemia were factors associated with in-hospital MAE among both groups, dementia was associated with significant ~ 5-fold increase in MAE in ≥80 years old patients' group [57].

In a recent metanalysis by Han et al. [58] stroke/TIA rates at 1 year follow-up did not differ between elderly and non-elderly group, following successful LAAO. The elderly group experienced more periprocedural mortality (OR 2.62; 95% CI 1.79–3.83, $p < 0.01$; $I^2 = 0\%$), pericardial effusion/tamponade (OR 1.39; 95% CI: 1.06–1.82, $p < 0.01$; $I^2 = 0\%$), major bleeding events (OR 1.32; 95% CI 1.17–1.48, $p < 0.01$; $I^2 = 0\%$), and vascular access complications (OR 1.34; 95% CI 1.16–1.55, $p < 0.01$; $I^2 = 0\%$) than the non-elderly patients [58].

Frailty is also associated with increased risk of prolonged hospital stay, re-admissions and short-term mortality post LAAO [59]. In a retrospective cohort study by Wang et al., patients were classified into low, intermediate and high-risk groups according to Hospital Frailty Risk Score (HFRS): the mortality rate was 16.1% in the low-risk group, 26.7% in the intermediate-risk group, and 41.1% in the high-risk group ($P < .001$) [59]. High frailty risk score was associated with a higher risk of prolonged hospital stay (odds ratio [OR] 8.29; 95% confidence interval [CI] 5.94–11.57), 30-day re-admission (OR 1.80, 95% CI 1.58–2.05), 30-day mortality (OR 5.68, 95% CI 3.40–9.40), and 1-year mortality (OR 2.83, 95% CI 2.39–3.35) [59].

It is well established that the benefits of LAAO take a long time to accrue, due to the overall relatively low rates of both stroke and bleeding events in patients with AF. It is therefore crucial that long-term prognosis is considered when referring a patient for LAAO. If a patient is not expected to live for at least 2–3 years following LAAO, then risks of adverse outcomes from the procedure itself are unlikely to be offset by prognostic gains in stroke and bleeding reduction.

7. The Impact of head trauma on patients taking oral anticoagulants (**Table 2**)

The most feared outcome of a fall while taking anticoagulation is ICH with resultant traumatic brain injury. It is logical, therefore, that healthcare providers may be reluctant to prescribe anticoagulants to those they feel are at higher risk of head trauma through falling. A mixed methods study recently addressed the concerns of prescribers in balancing thromboembolism reduction against bleeding risks in the high-risk patients with AF who have had serious bleeding [63]

Much of the concern about anticoagulation in head injury stems from older studies assessing VKAs such as warfarin. Older age, injury severity and Warfarin use have previously been shown to be independent predictors of morbidity and mortality in people with head injury [64–66]. Fortunately, as discussed below, this situation has much improved with the advent of NOACs [67]

Studies in the emergency department (ED) have shown that patients anticoagulated with NOACs are at low risk for developing intracranial hemorrhage (ICH). One retrospective study found that, of 316 patients suffering traumatic brain injury (TBI) whilst taking a NOAC, only 24 had ICH and only 1 required surgical intervention [68]. Notably in this study, anticoagulation was associated with progression of ICH when ICH was present, so the risk is not entirely negligible. Similarly, a large retrospective study of >69,000 ED patients assessed the risk of delayed ICH (within 90 days of initial presentation). The investigators found that only 1% had delayed ICH – the risk was higher for those on warfarin (OR 1.5; 95% CI 1-1-21) but not for NOACs (OR 0.9; 95% CI 0.6–1.1) [69].

A further meta-analysis looked at delayed ICH across 12 studies and 5,289 patients [70]. Only 69 patients suffered delayed ICH and 86% of these had no clinically significant adverse outcomes. Two NOAC patients vs eight Warfarin patients died from ICH-related complications. This suggests that, when the initial CT scan is normal, the risk of delayed

Table 1. Studies assessing anticoagulation safety in patients at risk of Falls.

Study	Design	Population	Intervention/ Comparison	Key Findings
Steffel et al. [44]	Pre-specified sub-analysis of ENGAGE AF-TIMI 48 RCT	High falls risk patients 310 on high dose edoxaban vs 307 on warfarin	Edoxaban vs Warfarin	Safety was similar to those with low falls risk, with no significant treatment interaction.
Rao et al. [45]	Post-hoc subgroup analysis of ARISTOTLE RCT	Patients with falls within 1 year 386 on apixaban vs 367 on warfarin	Apixaban vs Warfarin	Safety was similar to those with low falls risk, with no significant treatment interaction.
Miao et al. [48]	Retrospective cohort	High falls risk patients 13,027 on NOAC 12,117 on warfarin	NOAC vs Warfarin	NOACs were associated with a 43% reduced hazard of intracranial haemorrhage compared with warfarin.
Fanning et al. [60]	Retrospective cohort	AF patients with dementia 1,013 on NOAC 1,386 on warfarin	NOAC vs Warfarin	NOACs were associated with lower risk of intracranial bleeding (IRR 0.27; p=0.02) but a higher risk of GI bleeding (IRR 2.11, p=0.003) and all-cause mortality (IRR 2.06, p<0.001) compared with warfarin.
Lip et al. [61]	Retrospective cohort	AF patients with frailty 87,332 on NOAC 63,155 on warfarin	NOAC vs Warfarin	Apixaban (HR 0.62, p<0.001) and Dabigatran (HR 0.79, p<0.001) were associated with reduced risk of major bleeding compared with warfarin. Rivaroxaban (HR 1.14, p<0.001) was associated with a higher risk of major bleeding. All three NOACs were associated with lower risk of intracranial bleeding compared with warfarin.
Wilkinson et al. [62]	Retrospective cohort	AF patients with frailty 43,228 patients on OAC • 23.9% on NOAC • 76.1% on VKA	NOAC vs VKA	NOACs and VKAs were associated with no significant increase in the hazard of major bleeding across three categories of frailty.

HR – Hazard Ratio; IRR – Incidence Rate Ratio; NOAC – Non-vitamin-K Oral Anticoagulant; OAC – Oral Anticoagulation; RCT – Randomised controlled trial.

Table 2. Impact of head trauma on patients taking oral Anticoagulants.

Study	Design	Population	Intervention/ Comparison	Key Findings
Fuller et al. [75]	Observational cohort	148 patients with minor head injury taking NOAC	No comparator	Intracranial haemorrhage, death, or requirement for neurosurgery: 3.4% (95% CI 1.4–8.0).
Scotti et al. [67]	Retrospective analysis	1,365 head trauma patients on various combinations of anticoagulants and antiplatelets	NOAC, antiplatelets and VKAs	Antiplatelets and warfarin associated with an increased risk of intracranial haemorrhage in those with traumatic brain injury. NOACs were associated with lower rates of intracranial haemorrhage progression and poor functional outcome at discharge compared with warfarin.
Feeney et al. [74]	Retrospective analysis	162 patients with traumatic intracranial haemorrhage whilst taking anticoagulants. 61 on NOAC 101 on warfarin	NOACs vs warfarin	Compared with warfarin, NOACs were associated with lower mortality (4.9% vs 20.8%; p< 0.008), lower rate of surgery (8.2% vs 26.7%; p= 0.023) and less frequent discharge to nursing facilities (28.8% vs 39.7%; p=0.03).
Santing et al. [68]	Retrospective analysis	316 patients with traumatic brain injury whilst taking NOACs	No comparator	7.6% of patients had intracranial bleeding identified on imaging. Of these patients, haematoma progression occurred in 25%.

NOAC – Non-vitamin-K Oral Anticoagulant.

ICH is very low and the decision to perform subsequent imaging should be guided by clinical signs.

Clinical assessment of patients in the ED is paramount. Studies have found that CT imaging of the brain is likely over-utilized in these patients. In general, CT imaging is recommended in patients who have impaired consciousness and/or focal neurological signs; in those with normal conscious level and no focal neurology, CT scans are almost exclusively negative [71–73]. One study demonstrated that a specific ED trauma pathway for older and/or anticoagulated patients may improve resource utilization in these patients [66].

Even in those patients with established ICH, there is evidence that NOAC therapy carries a lower risk than VKA. In one such study, NOACs were associated with significantly lower mortality (4.9% vs 20.8%; $p < 0.008$), reduced surgical requirement (8.2% vs 26.7%; $p = 0.023$) and lower rates of discharge to nursing care (28.8% vs 39.7%; $p = 0.03$) [74].

In summary, the risk of traumatic ICH in elderly people taking NOAC anticoagulation is low, again supporting the concept that falls risk should not be considered a contraindication to NOAC therapy for stroke prevention in AF.

8. Conclusion

Clinicians may inappropriately avoid anticoagulation in patients at high falls risk, due to the perceived risk of injury, head trauma and major bleeding events. In contrast, the

evidence suggests that, in most cases, the benefits of anticoagulation outweigh these risks.

Most high risk falls patients fall 2–3 times per year, but upwards of 45 falls per year would be required for serious harm to arise from anticoagulation. These patients are also frequently those at highest risk of ischemic stroke and hence stand to gain the most benefit from anticoagulation.

Shared decision making and individualized patient assessment remain crucial, but high falls risk in isolation should not be considered a contraindication to oral anticoagulation in the setting of AF.

9. Expert opinion

Ischaemic stroke is a life-threatening and life-changing condition, which can have substantial effects of quality of life. Despite well-known benefits in atrial fibrillation, anticoagulation is often withheld in those perceived to have a high falls risk. These patients often have multiple co-morbidities, predisposing not just to falls but also to cardioembolic stroke. Hence, these patients may stand to gain the most benefit from anticoagulation.

Of major concern to many clinicians is the risk of intracranial bleeding secondary to head trauma from a fall. The quintessential phrase 'first do no harm' guides us away from recommending medications which could, by their very mechanism, worsen outcomes in such cases. However, it should be recognized that withholding preventative medications may also be harmful, potentially resulting in ischemic stroke.

Importantly, the risk of ischemic stroke is usually higher than the risk of major bleeding on currently available anticoagulants. As described in our review, the evidence suggests that 'high risk' patients fall, on average, 2–3 times per year – but upwards of 45 times is needed for bleeding risk to outweigh stroke reduction. Although anticoagulants worsen bleeding when it occurs, studies suggest that the risk of major bleeding events despite anticoagulation – particularly with modern NOAC therapy – remains low.

Of course, such striking figures apply to populations, not to individuals. This emphasizes the importance of shared, individualized decision making. Patients and their loved ones should be counseled about the risk of both ischemic stroke and bleeding. In general, we suggest that the balance should lean in favor of anticoagulation even in the setting of high falls risk, but again, this decision should involve the patient and their family.

It is also crucial to consider strategies to minimize falls risk. This may be achieved, for example, by comprehensive assessments of living environments, and exercise programmes. Medications predisposing to falls – such as antihypertensives and diuretics – should be reviewed. Similarly, co-prescription of antiplatelets should be reviewed – it is uncommon for both anticoagulants and antiplatelets to be required long term.

In those patients who, after evaluation and discussion, are felt unsuitable for long-term anticoagulation, left atrial appendage occlusion may be an appropriate non-pharmacological method to reduce stroke risk. Long-term prognosis should be carefully considered, as the risks of this procedure must be offset by an expected long-term gain. This may require several years to accrue, and hence is not an appropriate option in those with end-stage frailty with an expected poor prognosis.

The majority of evidence for the safety of anticoagulation in high falls risks patients comes from observational data, including sub-analyses of randomized controlled trials. There are no existing randomized trials comparing high falls risk patients on vs off anticoagulation. Although the observational data are strong, such studies are prone to undetected bias and confounding. Hence, whilst we would still recommend anticoagulation as for the majority of these patients, this should not preclude a high quality, randomized controlled trial to thoroughly assess the risk vs benefit.

Future research may also include novel anticoagulant drugs, such as the Factor XI inhibitors, which are currently undergoing phase III clinical trials. The outcomes for high falls risk patients taking these drugs will be important to inform best practice going forward.

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Author contribution statement

NKZL created the first draft and revisions. PC provided critical review and revisions. GYHL provided critical revisions and senior oversight.

Data availability statement

No new data were generated during the production of this manuscript.

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