INTERNATIONAL JOURNAL OF
INTEGRATIVE AND
MODERN MEDICINE

Prevention of Secondary Stroke in Individuals with Atrial Fibrillation: Interventions and Studies

Shodiyev Mirshodbek Marufovich
Bukhara State Medical Institute, Assistant of the Department of Internal Medicine in Family Medicine. Bukhara, Republic of Uzbekistan

Annotation: Atrial fibrillation, a prevalent cardiac arrhythmia, significantly contributes to ischemic stroke risk. Recent research highlights the importance of atrial fibrillation burden and its association with stroke recurrence. Secondary prevention aims to reduce this risk in atrial fibrillation stroke patients. Early initiation of direct oral anticoagulant medication (within 48-5 days for severe strokes) may lower early recurrence risk. Other promising strategies include early rhythm control, left atrial appendage closure, and new factor XI inhibitor oral anticoagulants. Despite the availability of oral anticoagulants, there's an unmet medical need for secondary preventive techniques in atrial fibrillation stroke patients. Current research explores novel strategies, suggesting diverse factors influencing stroke prevention. Recent randomized controlled trials indicate oral anticoagulation lowers the risk of ischemic stroke in patients with atrial fibrillation and a history of intracerebral hemorrhage, but further evidence is required to assess safety.

Keywords: Atrial fibrillation, Cardioembolism, Oral anticoagulation, Secondary prevention, Intracerebral haemorrhage.

Introduction:

Atrial fibrillation, a prevalent cardiac arrhythmia, causes rapid and irregular heartbeats. It's associated with a higher risk of ischemic stroke due to cardioembolism. About 20–30% of ischemic strokes are caused by atrial fibrillation, which are more severe than other stroke subtypes. This review updates data from observational studies and trials on preventing subsequent strokes in patients with atrial fibrillation. It discusses the latest developments in clinical management, such as anticoagulant therapy, new pharmacological options, early rhythm control, and non-pharmacological treatments. It also addresses unmet medical needs, like stroke prevention in patients with atrial fibrillation and a history of intracerebral hemorrhage, and the high risk of recurrence in patients with atrial fibrillation who've experienced an ischemic stroke despite anticoagulant therapy.

Epidemiology:

Atrial fibrillation affects around 44 million people globally, according to epidemiology.Four The prevalence of concomitant vascular risk factors and comorbidities (such as diabetes, arterial hypertension, congestive heart failure, peripheral artery disease, or myocardial infarction) determines the annualized rate of ischemic stroke in patients with atrial fibrillation. According to the CHA2DS2-VASc score, the highest risk group has a rate of 14·7%, while the lowest risk group has a rate of 0·7%.Five Since the prevalence of atrial fibrillation rises with age, it is anticipated that the incidence of ischemic strokes linked to atrial fibrillation would also grow over the next decades.Six Based on past statistics, it is anticipated that between 20 and 30 percent of instances of ischemic stroke are linked to atrial fibrillation. However, because attributability is sometimes challenging to establish in the context of conflicting risk factors and causes, the majority of research presented data on ischemic stroke associated with atrial fibrillation rather than attributable to atrial fibrillation. According to data from stroke-unit based cohort studies conducted in Switzerland (2014–19)2 and Canada (2003–13)8, atrial fibrillation was linked to around 21% and 32%, respectively, of incident instances of ischemic stroke. Therefore, atrial fibrillation may be linked to at least 2·4 million of the 12·2 million ischemic stroke cases that occur each year worldwide. The incidence would be at least 240 000 cases annually in

Europe.10. Unfortunately, there is a significant shortage of knowledge outside of Europe and North America, where the majority of epidemiological data are found. Africa appears to have a lower prevalence of atrial fibrillation, most likely due to its youthful population.12 In individuals with atrial fibrillation, there are geographical differences in the incidence of stroke and the death rate associated with it.

Detection and types of atrial fibrillation.

In most individuals, atrial fibrillation is identified prior to an ischemic stroke. A significant percentage of the individuals are on anticoagulant medication. However, during a cardiac diagnostic work-up following an ischemic stroke, up to 25% of all instances of atrial fibrillation are discovered. Current guidelines for cardiac monitoring following an ischemic stroke are shown in Panel 1. It appears that atrial fibrillation identified during a stroke or a brief ischemic event is a separate condition from that known before to a stroke.Compared to patients with atrial fibrillation identified prior to stroke, those with atrial fibrillation discovered after stroke may have a lower burden of vascular risk factors, be at risk for recurrent ischemic stroke, and be the result of the interaction between cardiac and neurogenic factors. The issue of stroke–heart interactions and the stroke–heart syndrome are strongly connected to the distinction between atrial fibrillation that is known to occur before to a stroke (i.e., because of conventional risk factors) and atrial fibrillation that is discovered after a stroke (i.e., partially owing to neurogenic causes).For atrial fibrillation found following a stroke, a unique categorization has been suggested.The risk of ischemic stroke and systemic embolism may be correlated with the load or length of paroxysmal atrial fibrillation, or the proportion of time that individuals with this illness are truly experiencing atrial fibrillation. People with paroxysmal atrial fibrillation have a lower risk of stroke than those with persistent or permanent atrial fibrillation (roughly 2% annually versus 3% annually), and patients with device-detected atrial fibrillation (also known as an atrial high-rate episode or subclinical atrial fibrillation) have an even lower stroke rate (1% annually).

Pharmacological prevention.

As advised by guidelines like those of the American Heart and Stroke Association, the European Stroke Organization, and the Canadian Best Practice, the primary objective of secondary prevention in patients with atrial fibrillation following an ischemic stroke is to prevent recurrent strokes through the use of oral anticoagulation therapy.For both primary and secondary prophylaxis, long-term oral anticoagulation is quite effective in lowering the risk of ischemic stroke in individuals with atrial fibrillation.Since the early 2010s, vitamin K antagonists (such as warfarin, marcoumar, acenocumarol, or phenprocoumon) have mostly been supplanted by direct oral anticoagulants (the direct factor Xa inhibitors apixaban, edoxaban, and rivaroxaban, as well as the direct thrombin-inhibitor dabigatran) as the primary anticoagulation treatment for preventing ischemic stroke in patients with non-valvular atrial fibrillation. Regardless of whether a patient has a history of ischemic stroke or not, the European Society of Cardiology guidelines suggest a comprehensive approach for integrated care in patients with atrial fibrillation, known as the atrial fibrillation better care pathway (abbreviated ABC pathway: anticoagulation or avoid stroke, better symptom management, and cardiovascular and comorbidity optimization). The therapy of heart failure, which is frequent in individuals with atrial fibrillation, is also recommended in these guidelines. Recent results from a randomized controlled study suggest that vitamin K antagonists should be recommended for individuals with atrial fibrillation caused by rheumatic valve disease since rivaroxaban was linked to increased rates of cardiovascular outcome events and mortality in these patients.

Timing of oral anticoagulation

Their safety and effectiveness in this susceptible subgroup were validated by subgroup analyses from pivotal randomized controlled trials that compared direct oral anticoagulants with vitamin K antagonists in patients with a history of atrial fibrillation and ischemic stroke. There is much debate regarding the best time to start anticoagulant medication following a stroke because individuals who had a recent ischemic stroke40 were not included in the key phase 3 studies due to a feared elevated risk of intracranial bleeding problems. Thus, a difficult clinical situation is weighing the danger of

early hemorrhagic transformation of the infarcted brain tissue against the risk of recurrent ischemic stroke.Early anticoagulation may worsen the infarcted brain tissue's hemorrhagic change, leading to further neurological impairment and perhaps death. The blood–brain barrier may deteriorate in the early stages of a stroke, making infarcted tissue vulnerable to hemorrhagic transformation. Although there is no data to support this theory, anticoagulation may raise the risk of hemorrhagic transformation by encouraging blood extravasation and inhibiting clotting. According to historical statistics, the risk of an early recurrence stroke in the first 10 days following a stroke might reach 1% daily in the absence of anticoagulation. Because there is a substantial absolute risk of ischemic stroke at this early stage, anticoagulation may have significant advantages. The timing of anticoagulation has been the subject of several investigator-initiated experiments (table 1). We've finished two of these trials. TIMING (NCT02961348) was an open-label non-inferiority study integrated in the Swedish national stroke registry, the Riksstroke. Patients were randomly randomized (1:1) to either early (≤4 days) or late (5–10 days) commencement of direct oral anticoagulation. The composite of all-cause death at 90 days, symptomatic intracerebral hemorrhage, or recurrent ischemic stroke was the main outcome. Only 888 of the 3000 targeted participants were enrolled in the experiment when it was abruptly terminated due to lack of recruitment during the COVID-19 epidemic and depleted funds. The predetermined 3% non-inferiority margin was attained by the main endpoint. Interestingly, individuals who began anticoagulation early experienced a 3·11% chance of ischemic stroke, whereas those who started late experienced a 4·57% chance Neither group's patients experienced any signs of intracranial hemorrhage. Early anticoagulant start is safe for individuals with mild stroke, as evidenced by the low National Institutes of Health Stroke Scale (NIHSS) scores of the majority of the study participants. A 1:1 ratio of 2013 participants were assigned to either early anticoagulation (within 48 hours of a minor or moderate stroke or on day 6 or 7 after a major stroke) or later anticoagulation (day 3 or 4 after a minor stroke, day 6 or 7 after a moderate stroke, or day 12, 13, or 14 after a major stroke) in the open-label randomised trial ELAN (NCT03148457). Within 30 days following randomization, the main outcome was a composite of recurrent ischemic stroke, systemic embolism, significant extracranial hemorrhage, symptomatic intracranial hemorrhage, or vascular death. Recurrent ischaemic stroke occurred in 14 participants (1·4%, of 1006) in the early- treatment group and 25 participants (2·5%, of 1007) in the later-treatment group (odds ratio [OR] 0·57, 95% CI 0·29 to 1·07) by 30 days, and in 18 participants (1·9%, of 1006) and 30 participants (3·1%, of 1007), respectively, (OR 0·60, 95% CI 0·33 to 1·06) by 90 days. By 30 days, four trial subjects (two in each therapy group [0·2%]) experienced symptomatic cerebral hemorrhage. The trial gave plausible estimates of the risks of ischemic stroke or cerebral hemorrhage following early vs late commencement of anticoagulant medication in patients following a recent stroke, but it did not test any hypotheses. ELAN's primary advantages were its customized method based on infarct size categories and its use of baseline infarct size as a physiologically realistic metric to evaluate bleeding risk. The findings' validity and generalizability are further supported by the fact that local scientists used a visual analogue scale to quantify infarct size while utilizing a variety of imaging modalities. OPTIMAS is a third big randomized experiment (NCT03759938). Enrolment finished on Feb 1, 2024. Following a recent stroke, 3648 patients were randomized 1:1 to begin anticoagulant medication early (within 96 hours) or late (7–14 days). OPTIMAS was created as a non-inferiority trial with a superiority test if non-inferiority is shown. Patients with ischemic stroke or parenchymal hemorrhage type 1 (but not type 2) who were taking oral anticoagulation prior to the beginning of stroke symptoms are included in the study. By the end of 2024, OPTIMAS findings are anticipated. Although the design of these trials differs, similar results will enable a meta-analysis of individual patient data (The CollAboration on the optimal Timing of Anticoagulation after Ischemic Stroke and Atrial Fibrillation: prospective Individual Participant Data Meta-analysis [IPDMA] of Randomized Controlled Trials [CATALYST]). This meta-analysis will be used to find stronger evidence for superiority, safety, and non-inferiority, including the examination of anticoagulation in pertinent subgroups (e.g., according to cerebral small vessel disease, pre-existing hemorrhagic transformation, infarct volume, or clinical stroke severity).

Secondary prevention in patients with stroke despite anticoagulation. Despite the fact that oral anticoagulation is a very successful treatment that lowers the risk of ischemic stroke in patients with

atrial fibrillation by around two-thirds, there is still a chance of ischemic stroke while using anticoagulant medication. In the major randomised controlled trials, the risk of ischemic stroke in all patients (about 35% with history of stroke) was between 1–2% yearly, depending on the study and therapy.38% of atrial fibrillation patients who experience an ischemic stroke are receiving oral anticoagulation medication with a vitamin K antagonist or direct oral anticoagulant at the time of stroke start, according to a large, countrywide, prospective research from Switzerland that was based on stroke units. Despite using oral anticoagulants, individuals with atrial fibrillation who experienced at least one index ischemic stroke had a continuously high rate of recurrent ischemic stroke, according to independent observational studies. As a result, these patients appear to be more at risk and require improved preventative measures. Additionally, there was no correlation between a change in anticoagulant treatment and a lower risk of recurrent stroke in observational studies. It has also been shown that additional antiplatelet therapy, which is frequently started in addition to anticoagulation treatment, increases the risk of significant bleeding and, ironically, ischemic stroke. This might be because antithrombotic treatment is interrupted for longer following bleeding episodes.As a result, it is still uncertain how best to manage atrial fibrillation patients who have a stroke in spite of anticoagulant medication. In addition to direct oral anticoagulant therapy, this unmet medical need led to significant efforts to explore novel treatment approaches, such as evaluating permanent bilateral carotid filters (INTERCEPT) or percutaneous left atrial appendage occlusion (ELPASE, NCT05976685, funded by the Swiss National Science Foundation). Along with other patients at high risk of stroke despite anticoagulant medication, stroke patients will also be included in the Fourth Left Atrial Appendage Occlusion trial (LAAOS-4, NCT05963698).

Secondary prevention after intracerebral haemorrhage. About 25% of patients with intracerebral hemorrhage experience atrial fibrillation, which is likely primarily caused by the presence of overlapping risk factors (such as arterial hypertension and advanced age). Because anticoagulation may raise the risk of recurrent intracerebral hemorrhage, anticoagulation medication is often stopped in individuals with a history of intracerebral hemorrhage. Additionally, compared to intracerebral hemorrhage unrelated to oral anticoagulation medication, anticoagulation-associated hemorrhage may be linked to a higher risk of mortality and disability.However, mounting data indicates that anticoagulation seems to be a contributing component rather than a sufficient or required cause of bleeding in patients receiving oral anticoagulation medication who have brain hemorrhage from underlying cerebral small artery disease. The risk of ischemic events is elevated in patients with intracerebral hemorrhage, particularly those with atrial fibrillation, according to further observational evidence.Ischemic stroke often occurs more frequently in these individuals than repeated intracerebral hemorrhage. Additional observational evidence also indicates that, independent of the location of the hemorrhage and the underlying small vessel disease, which are thought to be predictors of future risk of recurrent intracerebral hemorrhage, resuming anticoagulation may be linked to ischemic stroke prevention without increasing the risk of intracranial hemorrhage.Due to these findings, a number of randomized controlled studies have been conducted to examine stroke prevention techniques in individuals who have experienced an intracerebral hemorrhage in the past and have atrial fibrillation.

Conclusions and future directions.

Atrial fibrillation is a major cause of ischemic stroke and is associated with significant mortality and morbidity. Recent trials and individual patient data meta-analyses are needed to better understand certain patients with specific characteristics. Direct oral anticoagulants are a primary secondary prevention strategy, but their early initiation after a stroke may lower the risk of recurrence. Rhythm management also lowers the risk of ischemic stroke, but the ideal time and method (e.g., ablation, electric cardioversion, or anti-arrhythmic medications) must be identified. Close cooperation between cardiologists and neurologists is essential to provide this treatment to a larger patient population. Patients with atrial fibrillation who have a stroke despite anticoagulant medication require special attention. Medication problems (non-adherence or insufficient dose) and non-atrial fibrillation-related factors should be considered. Switching anticoagulation appears ineffective and may be hazardous, so the best course of action for this susceptible patient population is unclear. Non-pharmacological

treatments include permanent carotid filters and surgical or percutaneous left atrial appendage closure, which are being evaluated for their safety and effectiveness. Novel pharmacological treatments that target factor XI and XIa are being evaluated in phase 2 and phase 3 studies and may offer comparable effectiveness with improved safety. Several trials are also being conducted to prevent stroke in individuals with atrial fibrillation following intracerebral hemorrhage.

References

1. Wolf PA, Dawber TR, Thomas HE Jr, Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. Neurology 1978; 28: 973–77.
2. Meinel TR, Branca M, De Marchis GM, et al. Prior anticoagulationin patients with ischemic stroke and atrial fibrillation. Ann Neurol 2021; 89: 42–53.
3. Adams HP Jr, Davis PH, Leira EC, et al. Baseline NIH Stroke Scale score strongly predicts outcome after stroke: a report of the trial of Org 10172 in acute stroke treatment (TOAST). Neurology 1999; 53: 126–31.
4. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J 2021; 42: 373–498.
5. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor- based approach: the euro heart survey on atrial fibrillation. Chest 2010; 137: 263–72.
6. Béjot Y, Ben Salem D, Osseby GV, et al. Epidemiology of ischemic stroke from atrial fibrillation in Dijon, France, from 1985 to 2006. Neurology 2009; 72: 346–53.
7. Grau AJ, Weimar C, Buggle F, et al. Risk factors, outcome, and treatment in subtypes of ischemic stroke: the German stroke data bank. Stroke 2001; 32: 2559–66.
8. Sposato LA, Cerasuolo JO, Cipriano LE, et al. Atrial fibrillation detected after stroke is related to a low risk of ischemic stroke recurrence. Neurology 2018; 90: e 924–31.
9. Feigin VL, Stark BA, Johnson CO, et al. Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Neurol 2021; 20: 795–820.
10. Wafa HA, Wolfe CDA, Emmett E, Roth GA, Johnson CO, Wang Y. Burden of stroke in Europe: thirty-year projections of incidence, prevalence, deaths, and disability-adjusted life years. Stroke 2020; 51: 2418–27.
11. Lip GYH, Brechin CM, Lane DA. The global burden of atrial fibrillation and stroke: a systematic review of the epidemiology of atrial fibrillation in regions outside North America and Europe. Chest 2012; 142: 1489–98.
12. Pitman BM, Chew SH, Wong CX, et al. Prevalence and risk factors for atrial fibrillation in a semi-rural sub-Saharan African population: the heart oF Ethiopia: focus on atrial fibrillation (TEFF-AF) study. Heart Rhythm O2 2022; 3: 839–46.
13. Healey JS, Oldgren J, Ezekowitz M, et al. Occurrence of death and stroke in patients in 47 countries 1 year after presenting with atrial fibrillation: a cohort study. Lancet 2016; 388: 1161–69.
14. Xian Y, O'Brien EC, Liang L, et al. Association of preceding antithrombotic treatment with acute ischemic stroke severity and in-hospital outcomes among patients with atrial fibrillation. JAMA 2017; 317: 1057–67.

15. Gundlund A, Xian Y, Peterson ED, et al. Prestroke and poststroke antithrombotic therapy in patients with atrial fibrillation: results from a nationwide cohort. JAMA Netw Open 2018; 1: e180171.

16. Rubiera M, Aires A, Antonenko K, et al. European Stroke Organisation (ESO) guideline on screening for subclinical atrial fibrillation after stroke or transient ischaemic attack of undetermined origin. Eur Stroke J 2022; 7: VI.

17. Gladstone DJ, Lindsay MP, Douketis J, et al. Canadian stroke best practice recommendations: secondary prevention of stroke update 2020. Can J Neurol Sci 2022; 49: 315–37.

18. Schweizer J, Arnold M, König IR, et al. Measurement of midregional pro-atrial natriuretic peptide to discover atrial fibrillation in patients with ischemic stroke. J Am Coll Cardiol 2022; 79: 1369–81.