Secondary stroke prevention in patients with atrial fibrillation

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Word count:

Title: 64 characters

Abstract: 208 words

Manuscript: 5638

Tables: 4 + 4 panels

Figures: 4

References: 134

Key words: atrial fibrillation, ischaemic stroke, oral anticoagulation, rhythm control, left atrial appendage

Summary:

Atrial fibrillation is one of the most frequent cardiac arrhythmias and a major cause of ischaemic stroke. Secondary prevention aims to reduce the risk of recurrent ischaemic stroke using oral anticoagulants, mainly direct oral anticoagulants. Recent findings indicate the importance of atrial fibrillation burden (device-detected/subclinical - paroxysmal – persistent/permanent) and whether atrial fibrillation was known before stroke onset or diagnosed after stroke for the risk of recurrence.

In this review, we summarize and discuss advances in secondary prevention in patients with ischaemic stroke and atrial fibrillation including the latest results from randomized controlled trials assessing the optimal timing to introduce direct oral anticoagulant therapy after a recent stroke. We further highlight promising developments regarding
early rhythm control, left atrial appendage occlusion and novel factor XI inhibitor oral anticoagulants, which all have the potential to further reduce the risk of stroke.

We highlight an important clinical dilemma of secondary prevention in patients with atrial fibrillation that have breakthrough strokes despite oral anticoagulation therapy. We discuss the heterogeneous spectrum of causes and current approaches as well as future options for secondary prevention in this vulnerable patient group. Finally, we report the latest data from randomized controlled trials on stroke prevention in patients with atrial fibrillation and a history of intracerebral haemorrhage.

Introduction

Atrial fibrillation is characterized by rapid and irregular beating of the atrial chambers of the heart. It is one of the most frequent cardiac arrhythmias, which is consistently associated with an increased risk of ischaemic stroke from cardioembolism[1]. About 20% to 30% of all ischaemic strokes are related to atrial fibrillation[2], which are more disabling than most other ischemic stroke subtypes[3]. Secondary prevention in atrial fibrillation aims to prevent adeverse events from cardioembolism causing systemic embolism or ischemic stroke. In this review, we provide an update on secondary prevention after stroke in patients with atrial fibrillation. We will discuss recent advances in clinical management of secondary prevention after ischemic stroke in patients with atrial fibrillation including timing of initiation of anticoagulant therapy after a recent stroke, new pharmacological treatment options in the field of anticoagulation, the strategy of early rhythm control and currently available mechanical treatment options (e.g. left atrial appendage occlusion or permanent carotid filter). We will highlight two major unmet medical need: the high risk of recurrence in patients with atrial fibrillation who have had a breakthrough ischaemic stroke despite anticoagulant therapy and stroke prevention in patients with atrial fibrillation and a history of intracerebral haemorrhage.

Epidemiology and disease burden

Atrial fibrillation is a global health priority with an estimate of 43.6 million individuals having prevalent atrial fibrillation[7]. The annualized rate of ischaemic stroke in patients with atrial fibrillation depends on the prevalence of concomitant vascular risk factors and comorbidities (i.e. diabetes mellitus, arterial hypertension, congestive heart failure, peripheral artery disease or myocardial infarction) ranging from 0.7% to 14.7% in the lowest and highest risk groups, respectively[8]. The incidence of atrial fibrillation increases with age, so the incidence of atrial fibrillation and related ischaemic strokes is expected to rise further in the next decades[9] The percentage of ischaemic stroke associated with atrial fibrillation is estimated to be about 20-30% based on historical data[10]. It must be mentioned that most studies reported data on ischaemic stroke associated with atrial fibrillation rather than attributable to atrial fibrillation, as the latter is often difficult to prove in the presence of competing risk factors and aetiologies. More recent data from stroke-unit based cohort studies in Switzerland (2014-2019)[2] and Canada (2003-2013)[11] found 21% and 32% of incident cases of ischaemic stroke to be associated with atrial fibrillation. Putting this in a global perspective, at least 2.4 million cases out of the annually 12.2 million cases of ischaemic stroke worldwide[12] are related to atrial fibrillation. For Europe, this would equal to at least 240 000 cases each year of atrial fibrillation-related

ischaemic stroke[13]. The majority of epidemiological data is from Europe and North America and there is unfortunately a significant lack of knowledge outside these regions[14]. Prevalence of atrial fibrillation seems to be lower in Africa, likely related to a younger population[15] and there are marked unexplained inter-regional variations in the occurrence of stroke and mortality in patients with atrial fibrillation with higher rates in South America and Africa[16].

Atrial fibrillation is known before onset of ischaemic stroke in the majority of patients[11]. Among those patients, a significant proportion are on anticoagulant therapy ranging from 16% in the US[17] up to 36% in Denmark[18] and 38% in Switzerland[2]. Up to a quarter of all atrial fibrillation is detected after ischaemic stroke during cardiac diagnostic work-up[19] (please see panel 1 for current recommendations regarding cardiac monitoring). Atrial fibrillation detected after stroke seems to be a distinguished condition, different from atrial fibrillation known before stroke onset[20,21]. Current evidence points towards the possibility that atrial fibrillation detected after stroke may arise from the interplay between cardiac and neurogenic factors, has a lower burden of vascular risk factors and is associated with a lower risk of recurrent ischaemic stroke compared to atrial fibrillation known before stroke[11,22,23]. This is closely related to the topic of stroke-heart interactions and the stroke-heart syndrome. e[24,25].A novel classification for atrial fibrillation detected after stroke has been recently proposed aiming to harmonize future research in the field[21].

Another important aspect is the duration or burden of paroxysmal atrial fibrillation as this seems directly related to the risk of ischemic stroke and systemic embolism. The natural history of paroxysmal atrial fibrillation burden has a lower stroke risk compared to persistent and permanent atrial fibrillation (approximately 2%/year vs. 3%/year)[26] and the stroke rate in patients with device-detected atrial fibrillation (also called “atrial high-rate episode”/AHRE or “subclinical atrial fibrillation”/SCAF, consensus term *device detected”) is even lower (1%/year)[27-29].

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General aspects and guideline recommendations for secondary prevention treatment in patients with atrial fibrillation and ischemic stroke

The primary goal of secondary prevention therapy in patients with atrial fibrillation and ischemic stroke is the prevention of further recurrent strokes by oral anticoagulation therapy as recommended by major guidelines like those of the European Stroke Organisation[39], the American Heart and Stroke Association[40] and the Canadian Best Practice guidelines[41]. Long-term oral anticoagulation is a highly effective treatment to reduce the risk of ischaemic stroke

in patients with atrial fibrillation[4]. Since the early 2010s, direct oral anticoagulants (direct factor Xa-inhibitors: apixaban, edoxaban and rivaroxaban; direct thrombin-inhibitor: dabigatran) have largely replaced vitamin K antagonists (e.g. warfarin, marcoumar, acenocumarol, phenprocoumon) as the mainstay of anticoagulation for ischaemic stroke prevention in patients with non-valvular atrial fibrillation[5 6].

Beyond anticoagulation, European Society of Cardiology[7] guidelines recommend a holistic approach for integrated care in patients with atrial fibrillation, the Atrial fibrillation Better Care (ABC) pathway ('A' Anticoagulation/Avoid stroke; 'B' Better symptom management; 'C' Cardiovascular and Comorbidity optimization), regardless whether they have had a history of ischaemic stroke or not. Further details on this useful pathway can be found in the specific guidelines [37] including recommendations for the treatment of heart failure which is frequent in patients with atrial fibrillation. Patients with rheumatic valve disease-related atrial fibrillation are recommended to use vitamin K antagonists as rivaroxaban was associated with higher rates of outcome events in these patients[38].

Timing of oral anticoagulation therapy: balancing the risk of recurrent stroke and risk of early haemorrhagic transformation

Since the early 2010, direct oral anticoagulants (direct factor Xa inhibitors: apixaban, edoxaban, rivaroxaban; the direct thrombin inhibitor dabigatran) have largely replaced vitamin K antagonists treatment in patients with non-valvular atrial fibrillation[5]. Direct oral anticoagulants were found to be associated with comparable rates of ischaemic stroke but half the risk of symptomatic intracranial haemorrhage as compared to vitamin K antagonists[5]. Subgroup analysis from the pivotal randomized controlled trials in patients with atrial fibrillation comparing direct oral anticoagulants with vitamin K antagonists focussing on patients with a history of ischaemic stroke confirmed their efficacy and safety in this vulnerable subpopulation[42-44]. Further data from prospective observational studies also confirmed the translation of these findings from randomized controlled trials to real-world stroke unit patients [6]. Contemporary guidelines from the European Stroke Organisation now recommend the use of direct oral anticoagulants over vitamin K antagonists for secondary prevention therapy[39].

The pivotal phase-III randomized controlled trials excluded patients with a recent ischaemic stroke[45] due to a feared increased risk of intracranial bleeding complications, leading to substantial uncertainty about the optimal timing to initiate anticoagulant therapy post stroke. Therefore, balancing the risk of recurrent ischaemic stroke against the risk of early haemorrhagic transformation[46] of the infarcted brain tissue has been among the most

challenging clinical scenarios[47]. Early anticoagulation is feared to increase haemorrhagic transformation of the infarcted brain tissue resulting in additional neurological disability and death[46,48]. Early after stroke the blood-brain barrier breaks down and infarcted tissue is prone to haemorrhagic transformation[49,50]. Anticoagulation is feared to increase this risk by promoting extravasation of blood and preventing clotting, but evidence to support this hypothesis is very limited. Historical data suggested that the risk of early recurrent stroke may be as high as 1%/day in the first 10 days after a stroke without anticoagulation[51]. Therefore, the benefits of anticoagulation are potentially high in this early and vulnerable phase as the absolute risk of ischaemic stroke is high. In the absence of randomized controlled trials, emerging observational data provided some guidance, [7,52]. [53] [6,54-58]. summarized in 2019[47]. Taken together, these observational studies suggested that a significant number of early recurrent ischaemic strokes are presumably preventable by early anticoagulation and the observed risk of haemorrhagic transformation seemed considerably lower than that perceived by physicians. Another advantage of early anticoagulation is organisational as starting the treatment in the hospital might lower the chance that anticoagulation is forgotten in the case of late anticoagulation start recommendations made at discharge.

Triggered by this observational data, several investigator-initiated randomized trials have been launched (table 1). Recently, the first two of these trials published results. TIMING (Timing of Oral Anticoagulant Therapy in Acute Ischemic Stroke With Atrial Fibrillation, NCT02961348)[59] was an open-label non-inferiority trial embedded in the Swedish national stroke registry, the Riksstroke. Patients were randomized (1:1) to either early (≤4 days) or late (5-10 days) start of direct oral anticoagulation therapy. The primary outcome was the composite of recurrent ischaemic stroke, symptomatic intracerebral haemorrhage, or all-cause mortality at 90 days. The trial was stopped prematurely due to exhausted funding and lack of recruitment related to COVID-19 and enrolled 888 of 3000 planned patients. The primary endpoint reached the pre-specified 3% non-inferiority margin. Of interest, the rate of ischaemic stroke was 3.11% in patients started early compared to 4.57% in patients started late and there were no patients in either group that had symptomatic intracranial bleeding. The majority of the patients included in this study had a low NIHSS indicating that early initiation of anticoagulants is safe in patients with mild stroke. ELAN (Early versus Late initiation of direct oral Anticoagulants in post-ischaemic stroke patients with atrial fibrillation, NCT03148457)[60,61] was a randomized, open-label trial assigning 2013 participants in a 1:1 ratio to early anticoagulation (within 48 hours after 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). The primary outcome was a composite of recurrent ischaemic stroke, systemic embolism, major extracranial bleeding, symptomatic intracranial haemorrhage, or vascular death within 30 days after randomisation. Secondary outcomes included the components of the composite primary outcome at 30 and 90 days. The median NIHSS on admission was 5 and at randomisation 3, and one fifth of the patients had a major stroke according to the ELAN imaging classification. Furthermore, one fifth of the patients received thrombectomy and one third thrombolysis prior randomisation. Patients with parenchymal haemorrhage type 1 and 2 (but not those with haemorrhagic infarction type 1 and 2), or therapeutic anticoagulation at symptom onset were excluded. A primary-outcome event occurred in 29 participants (2.9%) in the early-treatment group and 41 participants (4.1%) in the later-treatment group (risk difference, -1.18 percentage points; 95% confidence interval [CI], -2.84 to 0.47) by 30 days. Recurrent ischaemic stroke occurred in 14 participants (1.4%) in the early-treatment group and 25 participants (2.5%) in the later-treatment group (odds ratio, 0.57; 95% CI, 0.29 to 1.07) by 30 days and in 18 participants (1.9%) and 30 participants (3.1%), respectively, by 90 days (odds ratio, 0.60; 95% CI, 0.33 to 1.06). Symptomatic intracranial haemorrhage occurred in 2 participants (0.2%) in both groups by 30 days. The trial did not test a hypothesis but provided reasonable estimates about the risks of ischaemic stroke or intracranial haemorrhage occurring after early versus late initiation of anticoagulant therapy after a recent stroke. The major strengths of ELAN was the use of baseline infarct size as a biologically plausible parameter to estimate bleeding risk and a tailored approach according to infarct size categories. The fact that infarct size was estimated by local investigators using a visual analogue scale using heterogeneous imaging modalities provides additional reassurance about the validity and generalizability of the findings of this trial in contrast to any central lab determined infarct size.

OPTIMAS (OPtimal TIMing of Anticoagulation After Acute Ischaemic Stroke, NCT03759938)[62] is a third ongoing large randomized trial, which aims to enrol at least 3478 participants randomized 1:1 to early (within 96 hours) or late (7-14 days) start after a recent stroke. The trial is still recruiting (n=3114 by 2 July 2023). OPTIMAS is designed as a non-inferiority trial, followed by a test for superiority if non-inferiority is established; it will include patients with parenchymal haemorrhage type 1 (but not PH2), and ischaemic stroke occurring under therapeutic oral anticoagulation at symptom onset.

The design of these trials varies but similar outcomes will allow an individual patient data meta-analysis (CollAboration on the optimal Timing of anticoagulation after ischaemic stroke and Atrial fibrillation: prospective individuaL participant data meta-analYsiS (IPDMA) of randomized controlled Trials (CATALYST), which is planned to seek stronger evidence for

noninferiority, safety and superiority, including highlighting important subgroups (i.e., infarct volume, clinical stroke severity, pre-existing haemorrhagic transformation, or cerebral small vessel disease).

Rhythm control therapy

Rhythm control therapy using anti-arrhythmic drugs or ablation has emerged as novel therapeutic option on top of anticoagulation in patients with atrial fibrillation[63].

Although first studies produced neutral outcomes of prior "rhythm versus rate" trials including AFFIRM[64] (Atrial Fibrillation Follow-up Investigation of Rhythm Management; 70% of patients taking warfarin) and AF-CHF[65] (Atrial Fibrillation Follow-up Investigation of Rhythm Management; 88% of patients taking warfarin), a mediator analysis of AFFIRM identified presence of sinus rhythm as a key mediator of better outcomes, while withdrawal of anticoagulation, commonly done at that time in patients undergoing rhythm control therapy, mediated poor outcome[66]. ATHENA trial (A Trial With Dronedarone to Prevent Hospitalization or Death in Patients With Atrial Fibrillation; 60% of patients taking warfarin) provided a first signal that rhythm control therapy using dronedarone, when delivered safely, can improve outcomes in patients with atrial fibrillation[67], including a reduction in ischaemic strokes in post hoc analysis[68]. Conceptually, systematic and early initiation of rhythm control therapy has the potential to deliver safe and effective secondary thromboembolic event prevention as well as control of rhythm[69,70].

In 2020, the early treatment of atrial fibrillation for stroke prevention (EAST – AFNET 4,) trial[71] revitalized rhythm control therapy by showing that systematic, early rhythm control therapy reduced a composite of stroke, cardiovascular death, acute coronary syndrome and hospitalization for heart failure compared to usual care in patients with recently diagnosed AF at risk of stroke (table 2) [72]. Early rhythm control reduced ischaemic strokes [72]. A recent mediator analysis looked at every feature that was different between randomized groups at the one-year visit and analysed its association with events during the remaining follow-up in the trial. The presence of sinus rhythm at 12 months explained 81% of the treatment effect compared to usual care during the remainder of follow-up of 4.1 years. In patients not in sinus rhythm at 12 months, early rhythm control did not reduce future cardiovascular outcomes (HR 0.94, 95% CI 0.65-1.67). Early rhythm control therapy as tested in EAST – AFNET 4 mainly relied on antiarrhythmic drugs, with atrial fibrillation ablation providing an important second line component. Atrial fibrillation ablation restores sinus rhythm more effectively than

antiarrhythmic drugs[73,74] and improves quality of life[75], without a clear signal for improved stroke prevention in completed trials[73,76].

The aforementioned trials where conducted in a general population of patients with atrial fibrillation and were not specific to the setting of secondary prevention after ischaemic stroke. A prespecified subgroup analysis of EAST-AFNET 4 participants with a history of ischaemic stroke found consistent results with the main trial [77]. The effect in the subgroup of patients with a history of ischaemic stroke seemed larger than in the overall cohort. In EAST-AFNET 4, the outcome-reducing effect of early rhythm control therapy was most pronounced in patients with multiple comorbidities[78], a cohort that is not dissimilar to patients with atrial fibrillation and acute stroke.

The RAFAS trial (Risks and Benefits of Early Rhythm Control in Patients With Acute Strokes and Atrial Fibrillation: A Multicenter, Prospective, Randomized Study) was a randomized controlled trial in patients with acute stroke and atrial fibrillation comparing early rhythm control therapy (within 2 months of stroke) to usual care. The trial found lower rates of ischaemic stroke at 12 months in patients with early rhythm control compared to those on usual care. However, there was regarding broad spectrum of approaches for early rhythm control. Anti-arrhythmic drugs where introduced with a mean delay of 9 days after stroke but invasive interventions (i.e. electric cardioversion, ablation) were performed >3 months after stroke.

Anticoagulation only has a weak stroke-preventing effect in patients with device-detected atrial fibrillation, mainly due to an unexpected, low rate of stroke without anticoagulation in these patients[27,28,30]. This questions whether there is a net clinical benefit of anticoagulation in these patients. Two recent randomized controlled trials assessed safety and efficacy of anticoagulation with apixaban or edoxaban in patients with device-detected and short-lasting episodes of atrial fibrillation detected by implantable cardiac devices[27,28]. While one trial using edoxaban (NOAH-AFNET 6)[28] did not found a reduction in ischaemic stroke or systemic embolism compared to placebo, the other trial found a lower risk of stroke or systemic embolism with apixaban over aspirin (ARTESiA)[27]. These diverging findings came to a surprise and might be related to the study setting and trial population. The low stroke rate in patients with device-detected AF without anticoagulation is potentially the most consistent and surprising finding of NOAH-AFNET 6 and ARTESiA. A meta-analysis including both trials found a significant reduction in the risk of ischaemic stroke and systemic embolism with oral anticoagulation with the results from both trials being consistent with each other[30]. All individual trials and the meta-analysis found an increase in the risk of major bleeding with anticoagulation.

More research is needed, but the low rate of stroke may be related to the low arrhythmia burden in patients with device-detected atrial fibrillation, but without ECG-documented atrial fibrillation[79]. This finding supports the notion that a low burden of atrial fibrillation – natural history or achieved through rhythm control – is associated with a low risk of stroke.

Taken together, there is robust data that rhythm control therapy initiated early after diagnosis of atrial fibrillation is safe and effective. Emerging data also suggest that this benefit is observed in patients with a history of ischaemic stroke and might even be larger than in the general population given the higher stroke risk early after a recent ischaemic stroke. Initial data from RAFAS also provide reassuring evidence about safety and efficacy of rhythm control if initiated early after recent ischaemic stroke. The optimal role and timing of early rhythm control after a recent ischaemic stroke remains to be determined.

Non-pharmacological interventions

The occlusion of the left atrial appendage represents a mechanical option for the prevention of stroke in patients with atrial fibrillation. The basic concept of left atrial appendage occlusion is based on the observation that 90% of thrombi with potential to embolise are located in the left appendage, an observation made in a cohort of patients with non-valvular atrial fibrillation undergoing cardioversion[80]. Recent evidence from cardiac CT in acute stroke patients confirmed a high rate of cardiac thrombi located in the left atrial appendage[81].

The occlusion can be achieved by surgical ligation or percutaneous occlusion most often with the two FDA approved devices Amulet (Abbott) and Watchman (Boston Scientific). Left atrial appendage occlusion has been primarily used as alternative treatment in patients with atrial fibrillation unsuitable for oral anticoagulation[7]. However, it has been tested in three randomized controlled trials in patients suitable for oral anticoagulation therapy (compared to vitamin k antagonists[82,83] in two trials and direct oral anticoagulants[84] in one trial) and found to be non-inferior for efficacy[85] and superior for safety compared to vitamin K antagonists and non-inferior compared to direct oral anticoagulants[86]. No dedicated randomized controlled trial has investigated so far whether surgical or percutaneous left atrial appendage occlusion lowers the risk of recurrent stroke in atrial fibrillation patients with prior stroke despite oral anticoagulation. However, in one large multicenter trial, the LAAOS III study (Left Atrial Appendage Occlusion Study)[87] patients with atrial fibrillation and a CHA_2DS_2-VASc score of at least 2 undergoing heart surgery for other indications such as valve replacement and coronary artery bypass grafting were enrolled. A total of 4770 patients were randomly allocated to

undergo or not undergo surgical left atrial appendage occlusion on top of usual care, including oral anticoagulation, during follow-up. The primary outcome was the occurrence of ischaemic stroke or systemic embolism. After a mean of 3.8 years follow up duration, stroke or systemic embolism occurred in 114 patients (4.8%) in the occlusion group and in 168 patients (7.0%) in the non-occlusion group (HR 0.67; 95% CI, 0.53 to 0.85). The difference in stroke and systemic embolism was amplified beyond the perioperative timeframe (HR 0.58; 95% CI, 0.42 to 0.80) and occurred despite 75-80% of patients receiving oral anticoagulation in both treatment groups throughout the study duration. This trial supports the concept that surgical exclusion of the left atrial appendage can provide substantial reduction of stroke and systemic embolism when used in addition to anticoagulation and highlights the promising potential of combining mechanical and anticoagulant therapy as a strategy to optimize stroke prevention in patients with atrial fibrillation who experience stroke despite anticoagulation. However, surgical left atrial appendage occlusion is too invasive for patients without other indication for heart surgery and will not be applicable to the majority of stroke patients. Percutaneous left atrial appendage occlusion is a less invasive alternative to surgical ligation. Whether the results of LAAOS III are applicable to percutaneous left atrial appendage occlusion is unclear. Potential drawbacks of percutaneous left atrial appendage occlusion include direct periprocedural complications, device related thrombus formation (2-5% of patients)[88] and residual leaks following device implantation. Table 2 summarizes findings of completed left atrial appendage occlusion trials. Future studies are needed to explore the potential role of percutaneous left atrial appendage occlusion to reduce the recurrent stroke risk in patients with breakthrough stroke while treated with anticoagulation. Currently ongoing randomized controlled studies focus on the efficacy of percutaneous left atrial appendage occlusion in patients with stroke who have contraindications to oral anticoagulation (including previous intracranial haemorrhage; see the section below for a more detailed discussion of this group) (COMPARE LAAO[89], NCT04676880; STROKE-CLOSE, NCT02830152) or as an alternative to direct oral anticoagulant therapy in a general population (CHAMPION-AF, NCT04394546) or in patients after ablation (OPTION, NCT03795298).

A different approach to protect the brain from central thromboembolism are novel permanent carotid filter devices for percutaneous implantation[90], which have been developed recently. Preclinical data seem promising with continuous improvement of the device and implementation technique[91]. A first clinical study has been performed in patients unsuitable for oral anticoagulation[92]. Based on this data, a large phase-III randomized controlled trial is planned comparing percutaneous permanent carotid filter implantation on top of direct oral

anticoagulants with direct oral anticoagulants alone in a high-risk patient population with atrial fibrillation and stroke (Carotid Implants for PreveNtion of STrokE ReCurrEnce From Large Vessel Occlusion in Atrial Fibrillation Patients Treated With Oral Anticoagulation (INTERCEPT), NCT05723926).

Special considerations for secondary prevention in patients with stroke despite anticoagulation

Although oral anticoagulation is a highly effective treatment significantly reducing the risk of ischaemic stroke in patients with atrial fibrillation by about two-thirds[4], there is a residual risk of ischaemic stroke while on anticoagulation therapy. Among patients enrolled in the pivotal randomized controlled trials, the risk of ischaemic stroke in all participants (~35% with prior history of stroke) was between 1-2% annually depending on the study and treatment[93-96] (figure 1). Evidence from a large, nation-wide stroke-unit based prospective study from Switzerland found that 38% of patients with atrial fibrillation who have an ischaemic stroke are on oral anticoagulation therapy with a vitamin K antagonist or direct oral anticoagulant at the time of stroke onset[2], not including patients where anticoagulation was stopped/paused for >2 days for medical reasons (i.e. peri-interventional, due to bleeding complications). The spectrum of anticoagulants changed over time reflecting the market share of direct oral anticoagulants with the majority of patients now having a stroke despite direct oral anticoagulant therapy. Independent observational studies found consistently high rates of recurrent ischaemic stroke in patients with atrial fibrillation who had at least one index ischaemic stroke despite oral anticoagulant therapy[97-99] (figure 1). Therefore, this patient groups seems particularly vulnerable and in need of better prevention strategies[100,101].

Aetiology of ischaemic stroke despite anticoagulation therapy in patients with atrial fibrillation (excluding those patients in whom anticoagulation was stopped/paused for medical reasons) is heterogeneous and may include causes related to atrial fibrillation (i.e. inadequate intensity of anticoagulation due to under dosing, non-compliance, failure to account for food interaction (particularly for rivaroxaban) or drug-drug interactions, inappropriate perioperative management, and cardioembolism despite anticoagulation) and causes not-related to atrial fibrillation (i.e. stroke caused by competing aetiology like large vessel arteriosclerosis, cerebral small vessel disease, aortic arch disease and occult cancer[102]). Based on expert consensus[103,104], it is currently classified into three categories: non-atrial fibrillation related stroke aetiology (case study in panel 2), medication error (case study in panel 3) and cardioembolism despite anticoagulation (case study in panel 4). A complete etiological work up is therefore

recommended (figure 2) assessing adequate drug dosing and adherence as well as presence of competing stroke aetiologies unrelated to atrial fibrillation (figure 3). In particular, although on-label dose reductions are required in selected patients with atrial fibrillation, the prevalent inappropriate use of off-label lower doses of direct oral anticoagulants is emerging as a significant modifiable risk factor for atrial fibrillation-related stroke in current practice[101].

A survey among vascular neurologist in Germany found that the majority of physicians switch the type of anticoagulation in a patient who had a stroke despite anticoagulant therapy, i.e. change from a vitamin K antagonist to a direct oral anticoagulant or changing between different direct oral anticoagulants[105]. However, there is no evidence to support this strategy[106-108]. Although expert opinion often suggest considering dabigatran 150 mg twice daily in this population due to this regimen being the sole one amongst direct oral anticoagulants to significantly reduce the risk of ischaemic stroke relative to warfarin in the RE-LY trial[109], there is no head-to-head comparison with other direct oral anticoagulants to support this recommendation. In addition, recent observational studies found no association between a change of anticoagulation therapy and decreased risk of recurrent stroke[98,101,106-108]. Additional antiplatelet therapy – also often initiated in this setting on top of anticoagulation treatment - has also been found to result in an increased risk of major haemorrhage and – paradoxically – ischaemic stroke, possibly due to greater interruptions in antithrombotic treatment surrounding bleeding events[101,106,107,110]. Therefore, the optimal treatment of patients with atrial fibrillation having a stroke despite anticoagulant therapy is currently unknown. This unmet medical need triggered substantial efforts to investigate novel treatment approaches aimed to provide better protection for patients with atrial fibrillation and ischaemic stroke despite anticoagulation assessing permanent bilateral carotid filters (INTERCEPT, NCT05723926) or percutaneous left atrial appendage occlusion (ELPASE, NCT05976685, funded by the Swiss National Science Foundation) on top of direct oral anticoagulant therapy (table 3). Patients with breakthrough stroke may also be enrolled in the Fourth Left Atrial Appendage Occlusion trial (LAAOS-4, NCT05963698) among other patients at high risk of stroke despite anticoagulant therapy. These trials are about to start recruitment and results are awaited in the next 4-5 years. In the absence of randomized controlled trial evidence, a personalized approach assessing individual risk profiles and targeting the most likely cause of stroke seems reasonable pending further trial data (figure 4).

Direct factor XI/XIa-inhibitors and ongoing trials

There is an ongoing effort to further improve stroke prevention in patients with atrial fibrillation. A novel generation of oral anticoagulants is currently being investigated in phase 2 and 3 randomized controlled trials. Direct factor XI/XIa-inhibitors target a key factor in the coagulation cascade. Due to the primary role of factor XIa in thrombus amplification but its lesser subsidiary role in haemostasis, it is hypothesized that inhibition of factor XI/XIa can prevent pathologic thrombus formation with minimal associated increase in spontaneous major bleeding events. Promising preclinical data, mendelian randomization analyses and epidemiologic data demonstrating reduced rates of ischaemic stroke and venous thromboembolism with reduced factor XI levels have led to the development of various compounds targeting factor XI/XIa for clinical application. Asundexian[111] and milvexian[112] are two small molecule oral direct inhibitors of factor Xia and Abelacimab is a highly selective, fully human monoclonal antibody targeting factor XI administered once monthly subcutaneously.). Recently, dose finding phase 2b randomized controlled trials testing these medications for prevention of venous thromboembolism in patients undergoing total knee arthroplasty (milvexian[113]), greater safety in patients with atrial fibrillation (asundexian)[114], reduction of major adverse cardiovascular events after acute myocardial infarction (asundexian)[115] and secondary stroke prevention following non-cardioembolic stroke (asundexian[116] and milvexian [117]) have been completed. In the PACIFIC-AF trial 876 patients with atrial fibrillation were enrolled and randomly assigned to apixaban or two different doses of the factor XI-inhibitor asundexian. Ratios of incidence proportions for the primary endpoint of the composite of major or clinically relevant non-major bleeding according to International Society on Thrombosis and Haemostasis criteria were 0·50 (90% CI 0·14–1·68) for asundexian 20 mg 0·16 (0·01–0·99) for asundexian 50 mg, and 0·33 (0·09–0·97) for pooled asundexian arms versus apixaban. The rate of ischaemic events was similar in all three groups, albeit underpowered with very few ischaemic vascular events occurring during study follow-up. Based on these promising safety results, phase 3 stroke prevention in atrial fibrillation trials of both asundexian (OCEANIC-AF, NCT05643573) and milvexian (LIBREXIA-AF, NCT05757869) were lunched but the trial testing asundexian was prematurely stopped after interim analysis found a lack of efficacy. Abelacimab also reported promising results from a phase 2b study with a 67% reduction in the primary endpoint of major or clinically relevant non-major bleeding compared with rivaroxaban and is currently investigated in a study of patients with atrial fibrillation deemed unsuitable for anticoagulation but patients with a recent stroke are excluded from this trial (NCT05712200)

Secondary prevention after intracerebral haemorrhage

Atrial fibrillation is frequent in patients with intracerebral haemorrhage[118], affecting around 25% of patients[119] and probably mainly related to prevalence of overlapping risk factors (e.g. arterial hypertension, age). Anticoagulation therapy is frequently withheld in patients with a history of intracerebral haemorrhage due to the feared possibility that anticoagulation may increase the risk of recurrent intracerebral haemorrhage in this population. In addition, anticoagulation-associated intracerebral haemorrhage are reported to have greater rates of death and disability[120,121]. However, there is growing evidence that patients on oral anticoagulation therapy are bleeding in the brain due to underlying cerebral small vessel disease and anticoagulation is rather a complicating factor than a sufficient or necessary cause of bleeding[122]. Further observational data consistently found that patients with intracerebral haemorrhage in general and especially those with atrial fibrillation are at high risk of ischemic events[123,124]. The frequency of ischemic stroke usually exceeds that of recurrent intracerebral haemorrhage. Further observational data suggest that resumption of anticoagulation might be associated with satisfactory ischaemic stroke prevention without an accompanying increase in intracranial haemorrhage, regardless of the underlying small vessel disease and haematoma location, which are seen as predictors of future risk of recurrent intracerebral haemorrhage[125-127]. These observations have led to several randomized controlled trials investigating stroke prevention strategies in patients with atrial fibrillation and a history of intracerebral haemorrhage (table 4). Three trials have so far been completed but results are preliminary[128,129].. A recent individual patient data meta-analysis of completed early phase trials found that in patients with a history of intracranial haemorrhage, the benefits of oral anticoagulation, i.e. the significant reduction of ischaemic stroke and systemic embolism, is consistent with that established in patients without intracranial hemorrhage[130]. However, the number of patients was insufficient to reliably estimate the risk of bleeding in this vulnerable patient population and large adequately powered trials are needed. Adding to the complexity of this dilemma, the data safety and monitoring board of the largest ongoing trial (ENRICH-AF) recently recommended to stop the enrolment of patients with lobar intracerebral haemorrhage or isolated convexity subarachnoid haemorrhage – both likely caused by bleeding-prone cerebral amyloid angiopathy – due to an excess risk in recurrent haemorrhage with anticoagulation in this subgroup of patients[131]. The results of these trials are eagerly awaited and planned collaborations for IPDMA providing sufficient power for meaningful subgroup analysis are underway (COCROACH)[130].

Conclusions and future directions

Atrial fibrillation is a major cause of ischaemic stroke and associated with significant mortality and morbidity. Based on current evidence, we propose an integrated pathway optimizing diagnostic work-up and treatment (figure 2). Secondary prevention strategies include direct oral anticoagulants and early initiation after a recent stroke appears to be safe and might reduce the risk of early recurrence; further data from ongoing trials (e.g., OPTIMAS) and IPDMA (CATALYST) are needed regarding key subgroups. Rhythm control reduces the risk of ischaemic stroke on top of anticoagulation but the optimal timing and best approach (anti-arrhythmic drugs, electric cardioversion, ablation) needs to be determined. Close collaboration between neurologists and cardiologist seems key to offer this treatment to a broader group of patients. Special consideration is required for patients with atrial fibrillation who have a stroke despite anticoagulant therapy. In those patients, non-atrial fibrillation related causes should be considered along with medication issues (non-adherence, inadequate dosing). Switching anticoagulation seems ineffective based on observational data, and or adding antiplatelet therapy on top of anticoagulation is harmful. Thus, the optimal treatment for this vulnerable group of patients is still unknown. Additional non-pharmacological options include surgical or percutaneous left atrial appendage occlusion and permanent carotid filter. There efficacy and safety in secondary prevention after ischaemic stroke is currently studied in large randomized controlled trials.. Novel pharmacological therapies targeting factor XI/XIa are currently being tested in phase II/III randomized controlled trials and may provide similar efficacy with enhanced safety relative to currently available direct oral anticoagulants. Stroke prevention in patients with atrial fibrillation after intracerebral haemorrhage is currently investigated in several randomized controlled trials involving different strategies (i.e. direct oral anticoagulants and left atrial appendage occlusion).

Search strategy:

We searched the literature using pubmed/medline and relevant clinical trial registries (i.e. clinicaltrials.gov or ISRCTN) for relevant literature or trials in English published between 2013 and June 2023. Based on expert opinion consensus among co-authors of this review, we focused on papers in following fields of particular clinical interest for secondary prevention after stroke in patients with atrial fibrillation: 1) Timing of anticoagulation after recent ischemic stroke, 2) Early rhythm control 3) Left atrial appendage occlusion and other mechanical protection devices, 4) ischemic stroke despite anticoagulation therapy, 5) novel anticoagulation strategies including factor XI inhibitors, 6) stroke prevention in patients with a history of intracerebral haemorrhage and atrial fibrillation. For each section, specific search strategies were used. Literature search was amended by personal notes if applicable and results were selected according to clinical relevance for this review paper.

Acknowledgement:

We thank Anja Giger, Department of Neurosurgery Inselspital Bern Switzerland for creating the medical illustrations in figure 3 and 4.

Contributions:

DJS and VaC designed the review paper with inputs from all co-authors. DJS, ViC, MP, LR, AM, AS, UF, PK and VaC performed the literature research.

DJS wrote the first draft with ViC, LR, MP, AM, PK, UF, DJW and AS writing each one chapter. DJS, ViC and VaC created the figures with help from Anja Giger (medical illustrations). All authors provided critical revisions to the final manuscript.

Potential conflicts of interest (last 3 years):

Dr Seiffge:

- Employed by Insel Gruppe AG (Inselspital University Hospital of Bern, Switzerland)
- Advisory board: Portola/Alexion, Bayer AG Switzerland, Javeline, Bioxodes, VarmX (all fees paid to employer and used for academic research funding)
- Research funding: Bangerter Rhyner Foundation and Swiss National Science Foundation (all paid to employer and used for academic research funding)

Dr. Caso:

- Advisory boards & speaker fees: Boehringer-Ingelheim, Pfizer/BMS, Bayer, Mindmaze, Daiichi Sankyo, Ever-NeuroPharma (All fees paid to employer ARS UMBRIA)

Dr. Räber:

- Employed by Insel Gruppe AG (Inselspital University Hospital of Bern, Switzerland)
- Research grants to institution by Abbott, Biotronik, BostonScientific, Sanofi, Infraredx, Regeneron, Swiss National Science Foundation
- Speaker fees by Abbott, Amgen, Occlutech, Medtronic, Novo Nordisc, Sanofi
- Stocks: Shockwave, Verve Therapeutics

Dr. Fischer:

- research support from the Swiss National Science Foundation and Swiss Heart Foundation
- research grants from Medtronic, Stryker, Penumbra, Rapid Medical, Phenox, Boehringer Ingelheim
- consultancies for Medtronic, Stryker, and CSL Behring (fees paid to institution).
- participation in an advisory board for Alexion/Portola and Boehringer Ingelheim (fees paid to institution).
- member of a clinical event committee (CEC) of the COATING study (Phenox) and member of the data and safety monitoring committee (DSMB) of the TITAN, LATE_MT, RapidPulse and IN EXTREMIS trials.
- Advisory board: Alexion/Portola, Boehringer Ingelheim, Biogen, Acthera
- President of the Swiss Neurological Society

Dr. Werring:

- Honoraria (speaking) from Bayer 2022 (talks or debates on anticoagulants, intracerebral haemorrhage, atrial fibrillation, dementia)
- Consultancy fees from Alnylam (2019), NovoNordisk (2021)

- Chief investigator OPTIMAS trial of early DOAC treatment after ischaemic stroke (BHF funded)

Dr. Shoamanesh:

- Advisory boards: AstraZeneca, Bayer AG, Daiichi Sankyo, Servier Canada,
- Research funding: Canadian Institute of Health Research, Heart and Stroke Foundation of Canada, Marta and Owen Boris Foundation, National Institues of Aging, National Institutes of Health, AstraZeneca, Bayer AG, Daiichi Sankyo, Javelin Medical, Servier Canada, Bristol-Myers Squibb

Dr. Kirchhof:

- PK was partially supported by European Union AFFECT-AF (grant agreement 847770), BigData@Heart (grant agreement EU IMI 116074), and MAESTRIA (grant agreement 965286), British Heart Foundation (PG/20/22/35093; AA/18/2/34218), German Center for Cardiovascular Research supported by the German Ministry of Education and Research (DZHK, grant numbers DZHK FKZ 81X2800182, 81Z0710116, and 81Z0710110), and Leducq Foundation.
- PK receives research support for basic, translational, and clinical research projects from European Union, British Heart Foundation, Leducq Foundation, Medical Research Council (UK), and German Centre for Cardiovascular Research, from several drug and device companies active in atrial fibrillation
- PK is listed as inventor on two issued patents held by University of Hamburg (Atrial Fibrillation Therapy WO 2015140571, Markers for Atrial Fibrillation WO 2016012783).
- Board member European Society of Cardiology
- Speaker of the Board, AFNET
- PK receives research support for basic, translational, and clinical research projects from European Union, British Heart Foundation, Leducq Foundation, Medical Research Council (UK), and German Center for Cardiovascular Research, from several drug and device companies active in atrial fibrillation, and has received honoraria from several such companies in the past, but not in the last three years.
- PK receives research support for basic, translational, and clinical research projects from European Union, British Heart Foundation, Leducq Foundation, Medical Research Council (UK), and German Center for Cardiovascular Research, from several drug and

device companies active in atrial fibrillation, and has received honoraria from several such companies in the past, but not in the last three years.

Dr. Paciaroni received honoraria as a member of the speaker bureau of Sanofi-Aventis, BMS, Daiiki Sankyo, and Pfizer.

Tables:

Panels:

Panel 1: Detection of atrial fibrillation in patients with ischaemic stroke . Current recommendations from the European Stroke Organisation (2023)[132] recommend at least 48 hours of monitoring. While the effectiveness of prolonged cardiac monitoring using implantable loop recorder (ILP) or continuous portable ECG monitoring is unclear, it increases the chance to detect subclinical atrial fibrillation and many guideline recommend ILP[132] or >2 weeks of portable ECT monitoring in patients with embolic stroke of unknown source[41]. The blood biomarker Midregional pro-atrial natriuretic peptide (MR-proANP) may help to guide the decision which patient should undergo prolonged monitoring[134].

Panel 2: Case study: Competing non-AF related aetiology in a patient with atrial fibrillation and ischaemic stroke despite anticoagulation in a patient with atrial fibrillation

A 68-year-old female patient known for paroxysmal atrial fibrillation was admitted to the hospital with two episodes of transient left hand weakness and numbness. MRI revealed several small cortical DWI-lesions in the right side territory of the middle cerebral artery and a high-grade stenosis of the ipsilateral internal carotid artery. The patient was on oral anticoagulation therapy with apixaban 5mg BID with the last intake 8 hours before admission and the calibrated anti-Xa activity was 140ng/ml. Carotid ultrasound and MR plaque imaging revealed a vulnerable plaque with intra-plaque haemorrhage. The ipsilateral high-grade carotid artery stenosis was deemed the most likely cause and the patient received carotid artery stenting 4 days after admission.

Panel 3: Case study: Medication error in a patient with atrial fibrillation and ischaemic stroke despite anticoagulation

A 83-year-old male patient known for persistent atrial fibrillation was admitted to hospital for acute right side hemianopsia. MRI revealed occlusion of the left posterior cerebral artery P2 segment and corresponding lesion on DWI and FLAIR. The patient was on oral anticoagulation with apixaban 5mg twice daily without any interruption for medical reasons. The patient confirmed that he regularly takes all pills from the blister, including this morning, 6 hours

before admission. Calibrated anti-Xa activity was not detectable (<30ng/ml). Advanced history revealed that his wife was preparing medication blisters for the patient and no apixaban tablet was found in the blister prepared for the upcoming days. His wife was recently diagnosed with dementia. Patient was discharged on unchanged apixaban therapy and arrangements were made that medication blisters are now prepared be the local pharmacy.

Panel 4: Case study: Cardioembolism despite sufficient anticoagulation in a patient with atrial fibrillation

A 73-year-old male patient known for persistent atrial fibrillation was admitted to the hospital with acute right side hemiparesis and aphasia. MRI revealed occlusion of the left middle cerebral artery M2 segment. The patient was on oral anticoagulant therapy with rivaroxaban 20mg per day and last intake 12 hours before admission. Admission calibrated anti-Xa activity was 90ng/ml. The patient received intravenous thrombolysis and mechanical thrombectomy experiencing major improvements. Additional clinical exams did not provide any evidence for competing non-AF stroke aetiology. Patient was continued on rivaroxaban. After interdisciplinary discussion involving Neurology and Cardiology, the patient was offered percutaneous left atrial appendage occlusion on an individual case decision on top of oral anticoagulation with rivaroxaban. The invervention was performed 4 weeks after stroke onset, the patient continued rivaroxaban treatment (with additional short-term clopidogrel 75mg for 6 weeks).

Figures :

Figure 1: Annualized rates of ischaemic stroke in randomized controlled trials comparing vitamin K antagonists (blue bars) with different direct oral anticoagulants (red bars) and in studies of patients with breakthrough strokes despite anticoagulant therapy

Figure 2: Clinical pathway for secondary prevention in patients with atrial fibrillation and ischaemic stroke.

Disclaimer: Level of evidence for some recommendations in this figure is low.

Figure 3: Aetiology of stroke despite anticoagulation and frequent non-AF stroke aetiologies (based on Polymeris et al.[107])

Figure 4:

Ischaemic stroke despite anticoagulant therapy in patients with atrial fibrillation: frequent causes and potential secondary prevention strategies

Disclaimer: Level of evidence for some recommendations in this figure is low.

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