Secondary stroke prevention in people with atrial fibrillation: treatments and trials

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Atrial fibrillation is one of the most common cardiac arrhythmias and is a major cause of ischaemic stroke. Recent findings indicate the importance of atrial fibrillation burden (device-detected, subclinical, or paroxysmal and persistent or permanent) and whether atrial fibrillation was known before stroke onset or diagnosed after stroke for the risk of recurrence. Secondary prevention in patients with atrial fibrillation and stroke aims to reduce the risk of recurrent ischaemic stroke. Findings from randomised controlled trials assessing the optimal timing to introduce direct oral anticoagulant therapy after a stroke show that early start (ie, within 48 h for minor to moderate strokes and within 4–5 days for large strokes) seems safe and could reduce the risk of early recurrence. Other promising developments regarding early rhythm control, left atrial appendage occlusion, and novel factor XI inhibitor oral anticoagulants suggest that these therapies have the potential to further reduce the risk of stroke. Secondary prevention strategies in patients with atrial fibrillation who have a stroke despite oral anticoagulation therapy is an unmet medical need. Research advances suggest a heterogeneous spectrum of causes, and ongoing trials are investigating new approaches for secondary prevention in this vulnerable patient group. In patients with atrial fibrillation and a history of intracerebral haemorrhage, the latest data from randomised controlled trials on stroke prevention shows that oral anticoagulation reduces the risk of ischaemic stroke but more data are needed to define the safety profile.

Introduction

Atrial fibrillation, one of the most common cardiac arrhythmias, is characterised by rapid and irregular beating of the atrial chambers of the heart, and is consistently associated with an increased risk of ischaemic stroke from cardioembolism.[1] About 20–30% of all ischaemic strokes are related to atrial fibrillation,[2] and these events are more disabling than most other ischemic stroke subtypes.[3] In this Review, we provide an update on evidence from trials and observational studies on secondary stroke prevention in people with atrial fibrillation. We discuss the latest advances in clinical management of secondary prevention in these patients, including timing of initiation of anticoagulant therapy, new pharmacological options for anticoagulation, the strategy of early rhythm control, and non-pharmacological treatment options (eg, left atrial appendage occlusion or permanent carotid filter). We also cover new evidence on two major unmet medical needs: the high risk of recurrence in patients with atrial fibrillation who have had an ischaemic stroke despite having received anticoagulant therapy and stroke prevention in patients with atrial fibrillation and a history of intracerebral haemorrhage.

Epidemiology

About 44 million individuals have atrial fibrillation worldwide.[4] The annualised rate of ischaemic stroke in patients with atrial fibrillation depends on the prevalence of concomitant vascular risk factors and comorbidities (ie, diabetes, arterial hypertension, congestive heart failure, peripheral artery disease, or myocardial infarction) ranging from 0·7% in the lowest risk group to 14·7% in the highest risk group, as defined by the CHA_2DS_2-VASc score.[5] The incidence of atrial fibrillation increases with age, so the incidence of atrial fibrillation-related ischaemic strokes is expected to rise further in the next decades.[6] The proportion of cases of ischaemic stroke associated with atrial fibrillation is estimated to be about 20–30%, based on historical data.[7] However, most studies reported data on ischaemic stroke associated with atrial fibrillation, rather than attributable to atrial fibrillation, as the attributability is often difficult to prove in the presence of competing risk factors and causes. Data from stroke-unit based cohort studies in Canada (2003–13)[8] and in Switzerland (2014–19)[2] found that about 21% and 32%, respectively, of incident cases of ischaemic stroke were associated with atrial fibrillation. Hence, out of the annual 12·2 million cases of ischaemic stroke worldwide,[9] at least 2·4 million cases might be related to atrial fibrillation. In Europe, the incidence would equal at least 240 000 cases each year.[10] The majority of epidemiological data are from Europe and North America and there is, unfortunately, a substantial lack of knowledge outside these regions.[11] Prevalence of atrial fibrillation seems to be lower in Africa, probably because of its younger population.[12] Inter-regional variations in the incidence of stroke and in its associated mortality in patients with atrial fibrillation exist, with higher prevalence in Africa and South America compared with North America and Europe.[13]

Detection and types of atrial fibrillation

Atrial fibrillation is known before an ischaemic stroke in the majority of patients.[8] Among those patients, a substantial proportion are on anticoagulant therapy, ranging from 16% in the USA[14] up to 36% in Denmark[15]

and 38% in Switzerland.[2] However, up to a quarter of all cases of atrial fibrillation are detected after an ischaemic stroke, during cardiac diagnostic work-up. Panel 1 presents current recommendations regarding cardiac monitoring after ischaemic stroke.[19] Atrial fibrillation detected after stroke or a transient ischaemic attack seems to be a distinct condition, different from that known before a stroke.[20,21] Atrial fibrillation detected after stroke might arise from the interplay between cardiac and neurogenic factors, might have a lower burden of vascular risk factors, and might be associated with a lower risk of recurrent ischaemic stroke compared with patients with atrial fibrillation known before stroke.[8,22,23] This difference between atrial fibrillation known before stroke (ie, due to traditional risk factors) and atrial fibrillation detected after stroke (in part likely to be caused by neurogenic factors) is closely related to the topic of stroke–heart interactions and the stroke–heart syndrome.[24,25] A novel classification for atrial fibrillation detected after stroke has been proposed.[21]

The duration or burden (ie, the percentage of time people with this condition are actually in atrial fibrillation) of paroxysmal atrial fibrillation might be related to the risk of ischemic stroke and systemic embolism. The risk of stroke is lower in people with paroxysmal atrial fibrillation than in those with persistent or permanent atrial fibrillation (approximately 2% per year *vs* 3% per year)[26] and the stroke rate in patients with device-detected atrial fibrillation (also called an atrial high-rate episode or subclinical atrial fibrillation; is even lower (1% per year).[27–29]

Panel 1: **Detection of atrial fibrillation in patients after an ischaemic stroke**

Current guidelines from the European Stroke Organisation (2023)[16] recommend at least 48 h of monitoring. Although the effectiveness of prolonged cardiac monitoring using an implantable loop recorder or continuous portable ECG monitoring is unclear, it increases the chance to detect subclinical or device-detected atrial fibrillation, and many guidelines recommend use of an implantable loop recorder[16] or more than 2 weeks of portable ECG monitoring in patients with embolic stroke of unknown source.[17] The blood biomarker midregional pro-atrial natriuretic peptide might help to guide decision-making regarding the selection of patients who should undergo prolonged monitoring.[18]

Pharmacological prevention

The main goal of secondary prevention in patients with atrial fibrillation after ischemic stroke is the prevention of recurrent strokes by use of oral anticoagulation therapy, as recommended by guidelines such as those of the European Stroke Organisation,[30] the American Heart and Stroke Association,[31] and the Canadian Best Practice.[17] Long-term oral anticoagulation is highly effective to reduce the risk of ischaemic stroke in patients with atrial fibrillation in both primary and secondary prevention.[32] Since the early 2010s, direct oral anticoagulants (the direct factor Xa inhibitors apixaban, edoxaban, and rivaroxaban, and the direct thrombin-inhibitor dabigatran) have largely replaced vitamin K antagonists (eg, warfarin, marcoumar, acenocumarol, or phenprocoumon) as the mainstay of anticoagulation for ischaemic stroke prevention in patients with non-valvular atrial fibrillation.[33,34]

Beyond anticoagulation, the European Society of Cardiology guidelines[4] recommend a holistic approach for integrated care in patients with atrial fibrillation, the atrial fibrillation better care pathway (known as the ABC pathway: anticoagulation or avoid stroke, better symptom management, and cardiovascular and comorbidity optimisation), regardless of whether they have a history of ischaemic stroke or not. These guidelines[35] also include recommendations for the treatment of people with heart failure, which is common in patients with atrial fibrillation. According to recent findings from a randomised controlled trial, patients with rheumatic valve disease-related atrial fibrillation should be prescribed vitamin K antagonists, as rivaroxaban was associated with higher rates of cardiovascular outcome events and death in these patients.[36]

Timing of oral anticoagulation

Subgroup analyses from the pivotal randomised controlled trials comparing direct oral anticoagulants with vitamin K antagonists in patients with a history of ischaemic stroke and atrial fibrillation confirmed their safety and efficacy in this vulnerable subpopulation.[37–39]

The pivotal phase 3 trials excluded patients with a recent ischaemic stroke[40] because of a feared increased risk of intracranial bleeding complications, leading to substantial uncertainty about the optimal timing to initiate anticoagulant therapy after stroke. Therefore, balancing the risk of recurrent ischaemic stroke against the risk of early haemorrhagic transformation[41] of the infarcted brain tissue is a challenging clinical scenario.[42] Early anti-coagulation might increase haemorrhagic transformation of the infarcted brain tissue, resulting in additional neurological disability and death.[41,43] Early after the stroke, the blood–brain barrier can break down and infarcted tissue becomes prone to haemorrhagic transformation.[44,45] Anticoagulation might increase this risk of haemorrhagic transformation by promoting extravasation of blood and preventing clotting, but evidence to support this hypothesis is scarce. Historical data suggested that, without anticoagulation, the risk of early recurrent stroke could be as high as 1% per day in the first 10 days after a stroke.[46] Therefore, the benefits of anticoagulation are potentially high in this early phase, as the absolute risk of ischaemic stroke is high. In the absence of trials, emerging observational data have provided some guidance.[42,47–53] Taken together, these observational studies suggested that a substantial number of early recurrent ischaemic strokes

are presumably preventable by starting anticoagulation early, 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 increase adherence to treatment.

Several investigator-initiated trials have addressed timing of anticoagulation (table 1). Two of these trials have been completed. TIMING (NCT02961348)[54] was an open-label non-inferiority trial embedded in the Swedish national stroke registry, the Riksstroke. Patients were randomly assigned (1:1) to either early (≤4 days) or late (5–10 days) start of direct oral anticoagulation. 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 the COVID-19 pandemic, and enrolled only 888 of 3000 planned participants. The primary endpoint reached the pre-specified 3% non-inferiority margin. Of note, the proportion of ischaemic stroke was 3·11% in patients who started anticoagulation early, compared with 4·57% in patients who started late. None of the patients in either group had symptomatic intracranial bleeding. The majority of the patients included in this trial had a low National Institutes of Health Stroke Scale (NIHSS) score, indicating that early initiation of anticoagulants is safe in patients with mild stroke. ELAN (NCT03148457)[55,56] was an open-label randomised trial assigning 2013 participants in a 1:1 ratio to early anticoagulation (within 48 h 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 score on admission was 5 and at randomisation was 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 had thrombolysis before randomisation. Patients with parenchymal haemorrhage type 1 and 2 (but not those with haemorrhagic infarction type 1 and 2) or therapeutic

	TIMING (NCT02961348)[54]	ELAN (NCT03148457)[16,55,56]	OPTIMAS (NCT03759938)[57]	START (NCT03021928)
Status	Completed	Completed	Recruitment completed, awaiting results	Recruitment completed, results presented at the International Stroke Conference 2024 (Feb 7, 2024, Phoenix, AZ, USA), not yet published
Sample size	888 participants (planned 3000)	2013 participants	3648 participants	200 of 1500 planned participants (1000 patients with mild or moderate stroke and 500 with severe stroke)
Early start group	≤4 days after acute ischaemic stroke	<48 h after symptom onset (minor and moderate stroke) or at day 6 (±1 day) after symptom onset (major stroke)	≤4 days after acute ischaemic stroke	Time-to-treatment delay of 3, 6, 10, or 14 days for mild or moderate stroke; 6, 10, 14, or 21 days for severe stroke
Late start group	5–10 days after acute ischaemic stroke	Current recommendations (ie, minor stroke after day 3 [±1 day], moderate stroke after day 6 [±1 day], and major stroke after day 12 [±2 days])	7–14 days after acute ischaemic stroke	Time-to-treatment delay of 3, 6, 10, or 14 days for mild or moderate stroke; 6, 10, 14, or 21 days for severe stroke
Primary outcome	Composite outcome (recurrent ischaemic stroke, symptomatic intracerebral haemorrhage, or all-cause mortality)	Composite outcome (major bleeding, recurrent ischaemic stroke, systemic embolism, or vascular death)	Composite outcome at 90 days (recurrent symptomatic ischaemic stroke, symptomatic intracranial haemorrhage [including extradural, subdural, subarachnoid, and intracerebral haemorrhage and haemorrhagic transformation of the qualifying infarct], and systemic embolism)	Composite of any CNS haemorrhagic or other major haemorrhagic events and the ischaemic events of stroke or systemic embolism within 30 days of the index stroke
Time of assessment	90 days	30 days	90 days	30 days
Inclusion of patients with haemorrhagic transformation	Not reported	Yes (haemorrhagic infarction type 1 or type 2)	Yes (haemorrhagic infarction type 1 or type 2 and parenchymal haemorrhage type 1)	Upon investigator's judgement
Inclusion of patients with severe stroke	Yes (79 [9%] of participants)	Yes, per strata	Yes	Exclusion of patients with >50% infarct volume in the middle cerebral artery territory
Inclusion of patients on anticoagulation	Yes, if stopped >2 days before index stroke onset or INR <1·7 for VKA	Yes if INR <1·7 (for VKA) or low DOAC concentrations	Yes	Yes

DOAC=direct oral anticoagulants. INR=international normalised ratio. VKA=vitamin K antagonist.

Table 1: **Randomised controlled trials assessing the optimal timing of direct oral anticoagulantion after a ischaemic stroke in patients with atrial fibrillation**

anticoagulation at symptom onset were excluded. A primary-outcome event occurred in 29 participants (2·9%, of 1006) in the early-treatment group and 41 participants (4·1%, of 1007) in the later-treatment group (risk difference –1·18 percentage points, 95% CI –2·84 to 0·47) by 30 days. 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. Symptomatic intracranial haemorrhage occurred in four participants in the study (two in each treatment group [0·2%]) 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 in patients after a recent stroke. The major strengths of ELAN were 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 with heterogeneous imaging modalities provides additional reassurance about the validity and generalisability of the findings.

OPTIMAS (NCT03759938)[57] is a third large randomised trial. Enrolment completed on Feb 1, 2024. 3648 patients were randomly assigned 1:1 to early (within 96 h) or late (7–14 days) start of anticoagulant therapy after a recent stroke. OPTIMAS was designed as a non-inferiority trial, followed by a test for superiority if non-inferiority is established; the study includes patients with parenchymal haemorrhage type 1 (but not type 2) or ischaemic stroke occurring under oral anticoagulation before onset of the stroke symptoms. OPTIMAS results are awaited by end of 2024.

The design of these trials varies, but similar outcomes will allow an individual patient data meta-analysis (The 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 non-inferiority, safety, and superiority, including the investigation of anticoagulation in relevant subgroups (ie, according to 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 a novel therapeutic option on top of anticoagulation to prevent stroke in patients with atrial fibrillation.[58]

Although the first studies of rhythm versus rate control of heart beat produced neutral outcomes, including AFFIRM[59] (in which 70% of 4070 participants were taking warfarin) and AF-CHF[60] (88% of 1376 participants were taking warfarin), a mediator analysis of AFFIRM identified the presence of sinus rhythm as a key mediator of better outcomes, whereas withdrawal of anticoagulation, commonly done at that time in patients undergoing rhythm-control therapy, mediated poor outcome.[61] The ATHENA trial (60% of 4628 participants were taking warfarin) provided initial evidence that rhythm-control therapy using dronedarone, when delivered safely, can improve outcomes in people with atrial fibrillation,[62] including a reduction in the number of ischaemic stroke events in a post-hoc analysis.[63] Systematic early initiation of rhythm-control therapy has the potential to deliver safe and effective secondary thromboembolic event prevention.[64,65]

In 2020, the EAST-AFNET 4 trial[66,67] revitalised interest in rhythm-control therapy by showing that systematic early rhythm-control therapy reduced a composite of stroke, cardiovascular death, acute coronary syndrome, and hospitalisation for people with heart failure, compared with usual care, in patients with recently diagnosed atrial fibrillation at risk of stroke (table 2). Early rhythm control reduced a composite of death from cardiovascular causes, stroke, or hospitalisation with worsening of heart failure or acute coronary syndrome.[66,67] A mediator analysis looked at every feature that differed between randomised groups at the year 1 visit and analysed their association with events during the remaining follow-up of the trial.[66,67] The presence of sinus rhythm at 12 months explained 81% of the treatment effect, compared with usual care, during the remainder follow-up of 4·1 years. In patients who did not achieve sinus rhythm at 12 months despite early rhythm control therapy, there was no reduction in cardiovascular outcomes (HR 0·94, 95% CI 0·65–1·67).[66,67] 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] but no clear evidence exist for improved stroke prevention in completed trials.[73,76]

The aforementioned trials were conducted in participants with atrial fibrillation and were not specific to the setting of secondary prevention after ischaemic stroke. A prespecified subgroup analysis of EAST-AFNET 4 of data from participants with a history of ischaemic stroke found consistent results with the main trial.[77] The effect in the subgroup of participanst 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 people with multiple comorbidities,[78] a cohort that is not dissimilar to patients with atrial fibrillation and acute stroke.

	Left atrial appendage occlusion (LAAO)				Rhythm control	
	PROTECT-AF (NCT00129545)[68]	PREVAIL (NCT01182441)[69]	PRAGUE-17 (NCT02426944)[70,71]	LAOOS-III (NCT01561651)[72]	EAST-AFNET 4 (NCT01288352)[66,67]	RAFAS (NCT02285387)[16]
Trial characteristics						
Sample size	707 participants	407 participants	404 participants	4770 participants	2789 participants	273 participants
Intervention	Percutaneous LAAO	Percutaneous LAAO	Percutaneous LAAO	Surgical LAAO	Antiarrhythmic drugs or ablation	Antiarrhythmic drugs or ablation
Comparator	Warfarin	Warfarin	DOAC	No LAAO	No rhythm control	No rhythm control
Anticoagulation	Warfarin 50% (control group)	Warfarin 50% (control group)	DOAC 50% (control group)	82% (64% VKA, 18% DOAC)	2517 (90%) participants	255 (94%) participants
History of ischaemic stroke	131 (18%) participants	111 (28%) participants	129 (35%) participants	9% of participants	328 (12%) participants	273 (100%) participants
Outcomes						
Follow-up	3·8 years, mean	1·5 years, mean	3·5 years, median	3·8 years, mean	5·1 years	Outcome assessement for all participants at 12 months
Primary endpoint	Stroke, systemic embolism, and cardiovascular or unexplained death 8·4% (LAAO) *vs* 13·9% (warfarin), RR 0·60; 95% CI 0·41–1·05	Stroke, systemic embolism, and cardiovascular or unexplained death 0·064 (LAAO) *vs* 0·063 (warfarin), RR 1·07; 95% CI 0·57–1·89	Stroke, transient ischemic attack, systemic embolism, cardiovascular death, major or non-major clinically relevant bleeding, or complications related to procedure or device 10·99% (LAAO) *vs* 13·42% (NOAC), HR 0·84; 95% CI 0·53–1·31; p=0·44	Ischemic stroke or systemic embolism 4·8% (LAAO) *vs* 7·0% (OAC), HR 0·67; 95% CI 0·53–0·85	Primary death from cardiovascular causes, stroke, or hospitalisation with worsening of heart failure or acute coronary syndrome 3·9 *vs* 5·0 events per 100 patient-years HR 0·79 (96% CI 0·66–0·94; p=0·005)	Recurrent stroke at 3 months (2 [1·1%] *vs* 4 [4·2%]; HR, 0·257 [log-rank p=0·091]) and at 12 months (3 [1·7%] *vs* 6 [6·3%]; HR 0·251 [log-rank p=0·034])
Stroke	1·4 (LAAO) *vs* 1·1 (warfarin) events per 100 patient-years	1·9% (LAAO) *vs* 0·7% (warfarin)	1·9% (LAAO) *vs* 1·8% (DOAC)	4·6% (LAAO) *vs* 6·9 (no LAAO)	0·6% (rhythm control) vs 0·9% (no rhythm control)	See primary endpoint
Mortality	Cardiovascular or unexplained death 1·0 (LAAO) *vs* 2·4 per 100 years (warfarin)	Cardiovascular or unexplained death 2·6% (LAAO) *vs* 2·2% (warfarin)	All cause mortality 7·0% (LAAO) *vs* 7·8% (DOAC)	All cause mortality 22·6% (LAAO) *vs* 22·5% (no LAAO)	1·0% (rhythm control) vs 1·3% (no rhythm control)	Not reported

DOAC=direct oral anticoagulants. HR=hazard ratio. LAAO=left atrial appendage occlusion. OAC=any oral anticoagulation. VKA=vitamin K antagonist.

Table 2: **Trials investigating left atrial appendage occlusion or rhythm control in patients with atrial fibrillation**

The RAFAS trial (NCT02285387) was a randomised controlled trial in patients with acute stroke and atrial fibrillation that compared early rhythm-control therapy (within 2 months of stroke) to usual care. The trial found a lower incidence of ischaemic stroke at 12 months in participants receiving early rhythm control compared with those on usual care. However, the trial included several approaches for early rhythm control. Anti-arrhythmic drugs were introduced with a mean delay of 9 days after stroke, but invasive interventions (ie, electric cardioversion or ablation) were done more than 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 natural risk of stroke in these patients.[27,28,79] This raises questions whether there is a net clinical benefit of anticoagulation in these patients. Two randomised controlled trials have assessed safety and efficacy of anticoagulation with apixaban or edoxaban in patients with device-detected (by use of implantable cardiac devices) and short-lasting episodes of atrial fibrillation.[27,28] Although one trial testing edoxaban (NOAH-AFNET 6)[28] did not find a reduction in ischaemic stroke or systemic embolism compared with placebo, the other trial found a lower risk of stroke or systemic embolism with apixaban than with aspirin (ARTESiA).[27] Although the headline results appear divergent, the main findings are consistent across both trials. The low stroke incidence in patients with device-detected atrial fibrillation without anticoagulation might be the most consistent and surprising finding of NOAH-AFNET 6 and ARTESiA. A meta-analysis of data from both trials found a small (0·3% per year of treatment) but significant reduction in the risk of ischaemic stroke and systemic embolism with oral anticoagulation.[79] Both trials and the meta-analysis found an increased risk of major bleeding with anticoagulation.

More research is needed, but the low incidence of stroke might be related to the low arrhythmia burden in patients with device-detected atrial fibrillation, but without ECG-documented atrial fibrillation.[80] This finding supports the notion that a low burden of atrial fibrillation, because of natural history or achieved through rhythm control, is associated with a low risk of stroke.

Taken together, the evidence suggests that rhythm-control therapy initiated early after diagnosis of atrial fibrillation is safe and effective. Emerging data also suggest that these beneficial effects can be extended to patients with a history of ischaemic stroke, in whom the effects might be larger than in the general population, given the increased risk of recurrent stroke early after an ischaemic stroke. Initial data from RAFAS and the subgroup analysis of patients with a history of stroke from EAST-AFNET also provide reassuring evidence about the safety and efficacy of rhythm control if initiated early after a ischaemic stroke, but its optimal role and timing remain to be determined.

Non-pharmacological interventions

The occlusion of the left atrial appendage is a therapeutic option for the prevention of stroke in people with atrial fibrillation. About 90% of thrombi with potential to embolise are located in the left appendage, an observation initially made in a cohort of patients with non-valvular atrial fibrillation undergoing cardioversion.[81] Evidence from cardiac CT in patients with acute stroke has confirmed a high frequency of cardiac thrombi located in the left atrial appendage.[82]

The occlusion can be achieved by surgical ligation or percutaneous occlusion, which is most often done with either of the two US Food and Drug Administration-approved devices Amulet (Abbott, Abbott Park, IL, USA) and Watchman (Boston Scientific, Marlborough, MA, USA). Left atrial appendage occlusion has been primarily used as alternative treatment in people with atrial fibrillation ineligible for oral anticoagulation.[4] However, appendage occlusion has been tested in three randomised controlled trials in patients eligible for oral anticoagulation therapy (compared with vitamin K antagonists[68,69] in two of the trials and to direct oral anticoagulants[70] in one trial) and found to be non-inferior for efficacy.[83] Appendage occlusion was also found superior to vitamin K antagonists for safety and non-inferior when compared with direct oral anticoagulants.[71] No randomised controlled trial has investigated whether surgical or percutaneous left atrial appendage occlusion lowers the risk of recurrent stroke in patients with atrial fibrillation after stroke, despite oral anticoagulation. However, a large multicentre trial, LAAOS III[72] enrolled 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. A total of 4770 patients were randomly allocated to undergo or not undergo surgical left atrial appendage occlusion on top of usual care, which included oral anticoagulation. The primary outcome was the occurrence of ischaemic stroke or systemic embolism. After a mean of 3·8 years' follow up, 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 0·53–0·85). This difference in stroke and systemic embolism was larger beyond the perioperative timeframe (HR 0·58, 95% CI 0·42–0·80) and occurred despite that 75–80% of patients received oral anticoagulation in both groups throughout the duration of the study. This evidence suggests that surgical occlusion 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 optimise stroke prevention in people with atrial fibrillation who had a stroke, despite anticoagulation. However, surgical left atrial appendage occlusion is too invasive for people without other indications for heart surgery and will not be applicable to most patients with stroke. Percutaneous left atrial appendage occlusion is a less invasive alternative to surgical ligation, but whether the results of LAAOS III are applicable to percutaneous appendage occlusion is unclear. Potential drawbacks of percutaneous left atrial appendage occlusion include periprocedural complications, device-related thrombus formation (in about 2–5% of patients),[84] and residual leaks following device implantation. Table 2 summarises findings of completed trials that have investigated left atrial appendage occlusion. Future studies are needed to explore the potential role of percutaneous left atrial appendage occlusion to reduce the risk of recurrent stroke in patients that have a stroke while treated with anticoagulation. Ongoing randomised 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 subsequent section for a more detailed discussion of this group [COMPARE LAAO,[85] NCT04676880 and STROKE-CLOSE, NCT02830152]) or as an alternative to direct oral anticoagulant therapy in a general population of patients with atrial fibrillation (ie, not restricted to patients with a history of stroke [CHAMPION-AF, NCT04394546], or in patients after percutaneous-catheter ablation [OPTION, NCT03795298]).

A different approach to protect the brain from thromboembolism is offered by novel permanent carotid filter devices for percutaneous implantation,[86] which have been developed recently. Preclinical data seem promising, with continuous improvement of the device and implementation technique.[87] A first clinical study has been done in patients ineligible for oral anticoagulation.[88] Based on these data, a large phase 3 randomised 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 (INTERCEPT, NCT05723926).

Secondary prevention in patients with stroke despite anticoagulation

Although oral anticoagulation is a highly effective treatment that significantly reduces the risk of ischaemic stroke in people with atrial fibrillation (ie, by about two-thirds),[32] there is a residual risk of ischaemic stroke while on anticoagulation therapy. In the pivotal randomised controlled trials, the risk of ischaemic stroke in all participants (approximately 35% with history of stroke) was between 1–2% annually, depending on the study and treatment.[89–92] A large, nationwide 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] The study did not include participants in whom anticoagulation was stopped or paused for more than

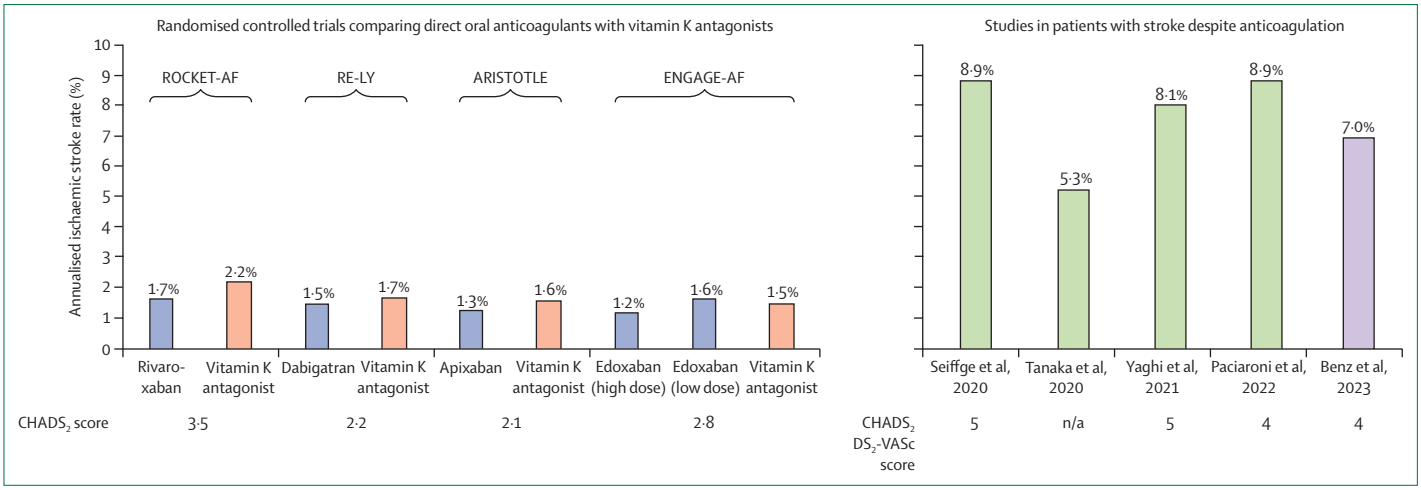

Figure: **Annualised rates of ischaemic stroke events in randomised controlled trials comparing vitamin K antagonists (red bars) with different direct oral anticoagulants (blue bars) and in studies of patients with stroke despite anticoagulant therapy (green bars [observational studies] and violet [IPDMA of the RCTs RE-LY, ARISTOTLE, ROCKET-AF, ENGAGE-AF, and AVERROES])**
IPDMA=individual participant data meta-analysis. RCT=randomised controlled trial. $CHAD_2$ score: congestive heart failure, hypertension, age ≥75 years, and diabetes mellitus, and a past history of transient ischemic attack or stroke. $CHADS_2$-VASC score: congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or TIA or thromboembolism, vascular disease, age 65–74 years and sex category (ie, female sex).

Panel 2: Case study: a patient with atrial fibrillation and ischaemic stroke despite anticoagulation

A 68-year-old woman with paroxysmal atrial fibrillation was admitted to our hospital after 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 5 mg twice a day, with the last intake 8 h before admission, and the calibrated anti-Xa activity was 140 ng/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 probable cause of the stroke and the patient successfully received carotid artery stenting 4 days after admission.

See Online for appendix

2 days for medical reasons (ie, peri-interventional, due to bleeding complications). The type of anticoagulant changed over time, reflecting the market share: the majority of patients with a stroke despite direct oral anticoagulant therapy now are those who have been on previous direct oral anticoagulant therapy, compared with the majority of patients in the decades before being on a previous vitamin K antagonist. Independent observational studies have found consistently high incidence of recurrent ischaemic stroke in patients with atrial fibrillation who had at least one index ischaemic stroke despite oral anticoagulant therapy (figure).[93–95] Therefore, these patients seem particularly vulnerable and in need of better prevention strategies.[96,97]

The aetiology of ischaemic stroke despite anticoagulation therapy in people with atrial fibrillation (excluding those patients in whom anticoagulation was stopped or paused for medical reasons) is heterogeneous and can include causes related to atrial fibrillation (ie, inadequate intensity of anticoagulation due to underdosing, non-compliance, failure to account for food interaction, particularly for rivaroxaban, or drug–drug interactions, inappropriate perioperative management, and cardioembolism despite anticoagulation) and causes unrelated to atrial fibrillation (ie, stroke caused by large vessel arteriosclerosis, cerebral small vessel disease, aortic arch disease, or occult cancer).[98] Based on expert consensus,[99,100] in these patients, ischaemic stroke is therefore classified into three categories: non-atrial fibrillation-related stroke aetiology (see case study in panel 2), medication error (panel 3), and cardioembolism despite anticoagulation (panel 4). A complete etiological work-up is therefore recommended to assess adequate drug dosing and adherence, as well as the presence of other potential causes of stroke unrelated to atrial fibrillation (appendix p 1). In particular, although on-label dose reductions are required in some patients with atrial fibrillation, the inappropriate use of off-label lower doses of direct oral anticoagulants is emerging as a common modifiable risk factor for atrial fibrillation-related stroke in current practice (appendix p 2).[97]

A survey among vascular neurologists in Germany found that the majority of physicians switched the type of anticoagulation in a patient who had a stroke despite anticoagulant therapy—ie, change from a vitamin K antagonist to a direct oral anticoagulant or change between different direct oral anticoagulants.[101] However, there is no evidence to support this strategy.[102–104] Expert opinion often suggests considering dabigatran 150 mg twice daily in this population, because this regimen was the sole one among direct oral anticoagulants to

***Panel 3:* Case study: a medication error**

An 83-year-old man with persistent atrial fibrillation was admitted to our hospital because of acute right side hemianopsia. MRI revealed occlusion of the left posterior cerebral artery P2 segment and a corresponding lesion on DWI and FLAIR imaging. The patient was on oral anticoagulation with apixaban 5 mg twice a day, without any reported interruption for medical reasons. The patient confirmed that he regularly took all pills from his medication blister, including in the morning on the day of his admission (ie, about 6 h before admission). Calibrated anti-Xa activity was not detectable (<30 ng/mL) though. After further investigations, the patient revealed that his wife usually prepared his medication blisters, even though she had been diagnosed with dementia. No apixaban tablet was found in the blister that she had prepared for the upcoming days. The patient was discharged on unchanged apixaban therapy and arrangements were made so that his medication blisters were prepared by the local pharmacy.

DWI=diffusion-weighted imaging. FLAIR=fluid-attenuated inversion recovery.

***Panel 4:* Case study: cardioembolism despite anticoagulation in a patient with atrial fibrillation**

A 73-year-old man with persistent atrial fibrillation was admitted to our 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 20 mg per day and his last intake was 12 h before admission. Calibrated anti-Xa activity was 90 ng/mL at admission. The patient received intravenous thrombolysis and mechanical thrombectomy, experiencing major improvements. Additional clinical exams did not provide any evidence for non-atrial fibrillation-related causes of his stroke. The patient was continued on rivaroxaban. After interdisciplinary discussion involving neurologists and cardiologists, the patient was offered percutaneous left atrial appendage occlusion, on top of oral anticoagulation with rivaroxaban. The intervention was successfully done 4 weeks after stroke onset, and the patient continued his treatment with rivaroxaban (with additional short-term clopidogrel 75 mg for 6 weeks).

significantly reduce the risk of ischaemic stroke relative to warfarin in the RE-LY trial,[105] but there are no head-to-head comparisons with other direct oral anticoagulants to support this recommendation. Furthermore, observational studies found no association between a change of anticoagulation therapy and decreased risk of recurrent stroke.[94,97,102–104] Additional antiplatelet therapy, often initiated 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 longer interruptions in antithrombotic treatment after bleeding events.[97,102,103,106] 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 assessing permanent bilateral carotid filters (INTERCEPT) or percutaneous left atrial appendage occlusion (ELPASE, NCT05976685, funded by the Swiss National Science Foundation) on top of direct oral anticoagulant therapy. Patients with stroke will be enrolled also in the Fourth Left Atrial Appendage Occlusion trial (LAAOS-4, NCT05963698), together with 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 (table 3). In the absence of evidence, a personalised approach assessing individual risk profiles and targeting the most likely cause of stroke seems reasonable.

Direct factor XI and XIa inhibitors

A novel generation of oral anticoagulants is being investigated in phase 2 and 3 randomised controlled trials. Direct factor XI and XIa inhibitors target proteins in the coagulation cascade. Due to the primary role of factor XIa in thrombus amplification, but its subsidiary role in haemostasis, it is hypothesised that inhibition of factor XI and XIa can prevent thrombus formation with minimal associated increase in spontaneous major bleeding events. Promising preclinical data, mendelian randomisation analyses, and epidemiological data showing reduced risk of ischaemic stroke and venous thromboembolism with reduced factor XI concentrations, have led to the development of various compounds targeting factor XI and XIa for clinical application. Asundexian[107] and milvexian[108] are two small molecules that are oral direct inhibitors of factor XIa and abelacimab is a highly selective, fully humanised monoclonal antibody targeting factor XI that has to be administered once monthly subcutaneously. Dose finding phase 2b studies testing these medications for prevention of venous thromboembolism in patients undergoing total knee arthroplasty (milvexian[109]), safety in people with atrial fibrillation (asundexian),[110] reduction of major adverse cardiovascular events after acute myocardial infarction (asundexian),[111] and secondary stroke prevention following non-cardioembolic stroke (asundexian[112] and milvexian[113]) have been completed. In the PACIFIC-AF trial, 876 participants with atrial fibrillation were enrolled and randomly assigned to apixaban or two different doses of the factor XI inhibitor asundexian. Ratios of incidence proportions (measured as relative differences) 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 the pooled

	INTERCEPT (NCT05723926)	ELAPSE (NCT05976685)	LAAOS-4 (NCT05963698)
Intervention	Permanent bilateral carotid artery filter on top of DOAC therapy (plus antiplatelet therapy for 6 months)	Percutaneous left atrial appendage occlusion (any approved device) on top of DOAC therapy (plus antiplatelet therapy for 6 weeks)	Percutaneous left atrial appendage occlusion with device
Comparator	Standard DOAC therapy	Standard DOAC therapy	Local, standard medical care (any anticoagulation)
Sample size	2000 participants	482 participants (adaptive design)	4000 participants
Estimated percentage of patients with breakthrough strokes	66%	100%	Unknown (patients with breakthrough stroke are eligible among other patients at high risk of stroke)
Primary endpoint	Large vessel anterior circulation ischemic stroke	Composite of ischaemic stroke, systemic embolism, and cardiovascular death	Composite of ischaemic stroke and systemic embolism
Follow-up	44 months	Minimum 6 months, and maximum 48 months	4 years (estimated average)
Current status	Vanguard trial in preparation	First patient recruited in Q1/2024	First patient recruited in Q4/2023

DOAC=direct oral anticoagulant therapy.

Table 3: **Trials in patients with atrial fibrillation and stroke despite anticoagulation therapy**

	NASPAF-ICH (NCT02998905)	SoSTART (NCT03153150)	APACHE-AF (NCT02565693)	ENRICH-AF (NCT03950076)	ASPIRE (NCT03907046)	PRESTIGE-AF (NCT03996772)	STATICH (NCT03186729)	A3ICH (NCT03243175)	STROKECLOSE (NCT02830152)
Trial status	Completed	Completed	Completed	Recruiting	Recruiting	Completed	Recruitment completed, in follow-up	Recruitment completed, in follow-up	Recruiting
Sample size	30 participants	203 participants	101 participants	1200 participants	700 participants	319 (of 350 planned) participants	65 (of 500 planned) participants	300 participants	750 participants
Intervention	Any DOAC	Any oral anticoagulation	Apixaban	Edoxaban	Any DOAC	Any DOAC	Any DOAC	Apixaban and LAAO	LAAO
Control	Aspirin	Usual care*	Usual care*	Usual care*	Aspirin	Usual care*	Usual care*	Usual care*	Any medical treatment (including DOAC)
Primary endpoint	Recurrent stroke of any type (ischaemic stroke or intracerebral haemorrhage)	Recurrent symptomatic intracranial haemorrhage	Non-fatal stroke (ischaemic stroke, intracerebral haemorrhage or subarachnoid haemorrhage) or vascular death	Any stroke and major haemorrhage	Any stroke or death	Any stroke	Fatal or non-fatal symptomatic intracerebral haemorrhage	Fatal or non-fatal major cardiovascular ischaemic or haemorrhagic events	Any stroke, systemic embolism, life-threatening or major bleeding and all-cause mortality
Follow-up	≥6 months	≥12 months	≥6 months	≥6 months	≥12 months	≥12 months	≥6 months	24 months	≥6 months
Findings	Not reported	Inconclusive	Inconclusive	Ongoing	Ongoing	Not reported	Not reported	Ongoing	Ongoing

DOAC=direct oral anticoagulants. LAAO=left atrial appendage occlusion. *Any antiplatelet agent or no antithrombotic treatment.

Table 4: **Randomised controlled trials investigating stroke prevention in patients with atrial fibrillation and history of intracranial haemorrhage**

data from the asundexian groups versus apixaban. The incidence of ischaemic events was similar in all three groups, albeit the study was underpowered and very few ischaemic vascular events occurred during follow-up. Based on these promising safety results, phase 3 trials of stroke prevention in people with atrial fibrillation of asundexian (OCEANIC-AF, NCT05643573) and milvexian (LIBREXIA-AF, NCT05757869) have being launched, but the trial testing asundexian was prematurely stopped after an interim analysis found no efficacy. Promising results from a phase 2b study of abelacimab, compared with rivaroxaban, showed a 67% reduction in the primary endpoint of major or clinically relevant non-major bleeding. Abelacimab is currently being investigated in people with atrial fibrillation deemed ineligible for anticoagulation, but patients with a stroke are excluded from this trial (NCT05712200).

Secondary prevention after intracerebral haemorrhage

Atrial fibrillation is frequent in patients with intracerebral haemorrhage,[114] affecting around 25% of patients,[115] and probably mainly related to prevalence of overlapping risk factors (eg, arterial hypertension and old age). Anticoagulation therapy is frequently withheld in

patients with a history of intracerebral haemorrhage because of the possibility that anticoagulation might increase the risk of recurrent intracerebral haemorrhage. Furthermore, anticoagulation-associated intracerebral haemorrhage might be associated with greater risk of death and disability compared with intracerebral haemorrhage not related to oral anticoagulation therapy.[116,117] However, growing evidence shows that, in patients on oral anticoagulation therapy with bleeding in the brain due to underlying cerebral small vessel disease, anticoagulation seems to be a complicating factor rather than a sufficient or necessary cause of bleeding.[118] Further observational data consistently found that patients with intracerebral haemorrhage, especially those with atrial fibrillation, are at high risk of ischemic events.[119,120] In these patients, the frequency of ischemic stroke usually exceeds that of recurrent intracerebral haemorrhage. Further observational data also suggest that resumption of anticoagulation might be associated with ischaemic stroke prevention without an increase in risk of intracranial haemorrhage, regardless of the underlying small vessel disease and haematoma location, which are seen as predictors of future risk of recurrent intracerebral haemorrhage.[121–123] These observations have led to several randomised controlled trials investigating stroke prevention strategies in patients with atrial fibrillation and a history of intracerebral haemorrhage. Five trials have so far been completed with two trials published (APACHE-AF and SoSTART), one not published (NASPAF-AF), and two trials completing recruitment and currently in follow-up (STATICH and PRESTIGE-AF; table 4), but their findings are preliminary.[124,125] An 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 (ie, the significant reduction of ischaemic stroke and systemic embolism) is consistent with that established in patients without intracranial haemorrhage.[126] However, the number of patients was insufficient to reliably estimate the risk of bleeding in this vulnerable population and large adequately powered trials are needed. The data safety and monitoring board of the largest ongoing trial (ENRICH-AF) 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.[127] The results of these trials are eagerly awaited and planned collaborations for an individual patient data meta-analysis providing sufficient statistical power for meaningful subgroup analyses are underway (COCROACH).[126]

Conclusions and future directions

Atrial fibrillation is a major cause of ischaemic stroke and is associated with substantial mortality and morbidity.

Search strategy and selection criteria

We searched PubMed and MEDLINE and relevant clinical trial registries (ie, ClinicalTrials.gov and ISRCTN) for trials in English published between January 2013, and June 2023. We focused on papers in the 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, and (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.

Secondary prevention strategies include direct oral anticoagulants and their early initiation after a stroke appears to be safe and might reduce the risk of recurrence; further data from recently completed trials awaiting publication (eg, OPTIMAS) and individual patient data meta-analysis (CATALYST) are needed regarding some patients with specific characteristics. Rhythm control reduces the risk of ischaemic stroke on top of anticoagulation, but the optimal timing and best approach (anti-arrhythmic drugs, electric cardioversion, or ablation) need to be determined. Close collaboration between neurologists and cardiologists 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 these patients, non-atrial fibrillation related causes should be considered along with medication issues (non-adherence or inadequate dosing). Switching anticoagulation seems ineffective based on observational data, and adding antiplatelet therapy on top of anticoagulation is probably 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; their safety and efficacy in secondary prevention after ischaemic stroke is under evaluation in large trials. Novel pharmacological therapies targeting factor XI and XIa are being tested in phase 2 and phase 3 trials and might provide similar efficacy with enhanced safety, relative to available direct oral anticoagulants. Furthermore, stroke prevention in patients with atrial fibrillation after intracerebral haemorrhage is being investigated in several trials testing different strategies such as direct oral anticoagulants and left atrial appendage occlusion.

Contributors

DJS and VaC designed the review paper with inputs from all coauthors. 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 figure. All authors provided critical revisions to the final manuscript.

Declaration of interests

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