# Ischemic Stroke Prevention in Patients Atrial Fibrillation and a Recent Ischemic Stroke, TIA, or Intracranial Hemorrhage; a World Stroke Organisation (WSO) Scientific Statement.

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| Journal: | *International Journal of Stroke* |
| Manuscript ID | IJS-10-24-12849.R2 |
| Manuscript Type: | Review |
| Date Submitted by the Author: | 16-Dec-2024 |
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| Keywords: | Stroke, Prevention, statement, brain and heart, atrial fibrillation, evidence, guideline |
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DOI: 10.1177/17474930241312649

# Ischemic Stroke Prevention in Patients Atrial Fibrillation and a Recent Ischemic Stroke, TIA, or Intracranial Hemorrhage; a World Stroke Organisation (WSO) Scientific Statement

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**Keywords**

Atrial fibrillation, stroke, transient ischemic attack, anticoagulants, prevention, detection, recommendation.

**Word count**



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**Figures and tables**



**Supplementary File**



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DOI: 10.1177/17474930241312649

## ABSTRACT

**Background.** Secondary stroke prevention in patients with atrial fibrillation (**AF**) is one of the fastest growing areas in the field of cerebrovascular diseases. This Scientific statement from the World Stroke Organization Brain & Heart Task Force provides a critical analysis of the strength of current evidence this topic, highlights areas of current controversy, identifies knowledge gaps, and proposes priorities for future research.

**Methods.** We select topics with the highest clinical relevance and perform a systematic search to answer specific practical questions. Based on the strength of available evidence and knowledge gaps, we identify topics that need to be prioritized in future research. For this purpose, we adopt a novel classification of evidence strength based on the availability of publications in which the primary population is patients with recent (<6 months) cerebrovascular events, whether the primary study endpoint is a recurrent ischemic stroke, and the quality of the studies (e.g., observational vs. randomized controlled trial).

**Summary.** Priority areas include AF screening, molecular biomarkers, AF subtype classification, anticoagulation in device-detected AF, timing of anticoagulation initiation, effective management of breakthrough strokes on existing anticoagulant therapy, the role of left atrial appendage closure, novel approaches, and antithrombotic therapy post-intracranial hemorrhage. Strength of currently available evidence varies across the selected topics, with early anticoagulation being the one showing more consistent data.

**Conclusion.** Several knowledge gaps persist in most areas related to secondary stroke prevention in AF. Prioritizing research in this field is crucial to advance current knowledge and improve clinical care.





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## INTRODUCTION

Atrial fibrillation (**AF**) is a cardiac arrhythmia affecting approximately 59.7 million individuals globally as of 2019, which represents a 111% increase from 1990.[1] Population-based projections estimate a 2-3 fold increase in the global prevalence of AF by 2050-2060 due to population growth, ageing, and advanced AF detection methods.[2] AF is associated with a 5-fold risk for ischemic stroke (**IS**)[3], present in 18-30% of acute IS cases,[4-6] and its prevalence in IS hospitalizations has increased to 22% in North America in recent decades.[4,6] Several aspects of AF diagnosis and management have advanced significantly in the last decade. This position statement aims to review current evidence, classify its strength, and identify priority areas for future research.

## METHODS

The writing group selected relevant topics with clinical impact to be addressed in this document. We performed a systematic search for each topic (**Table S1**). Statements were organized in sections focused on the diagnosis and management of AF patients with a recent IS, intracranial hemorrhage (**ICH**), or transient ischemic attack (**TIA**). Sections for which newer evidence was available or more controversial were discussed more extensively than others. The aim was to evaluate the strength of current evidence and identify knowledge gaps for future research instead of providing clinical recommendations. We implemented a novel classification of evidence focused on clinical needs for physicians managing patients with acute IS. As such, we classified levels of evidence based on whether data addressed patients with a



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DOI: 10.1177/17474930241312649

recent cerebrovascular event defined as ≤6 months (as opposed to remote cerebrovascular events) before inclusion in randomized controlled trials (**RCTs**) or observational studies (**Figure 1**). The classification of strength of evidence also prioritized studies in which recurrent IS was the primary endpoint or a prespecified secondary endpoint. Members of the Writing Group and the World Stroke Organization Brain & Heart Task Force reviewed each statement and their level of evidence. If a co-author disagreed with a statement, the wording and level of evidence adjudication were revised until reaching consensus. All authors approved the final version of each statement and level of evidence adjudication.

## AF SCREENING

AF is associated with AF recurrence and IS risk, and thus, prolonged cardiac monitoring (**PCM**) is used to screen for subclinical AF. In patients with IS and TIA, RCTs have shown significantly increased AF detection using external devices and implantable cardiac monitors (**ICM**) (**Table S2**) than standard-of-care diagnostics. None of the RCTs on PCM was designed to test whether PCM reduces IS recurrence, and all were underpowered to show a significant effect. A study-level meta-analysis of 6 clinical trials with 68556 patient-months of follow-up showed no association between PCM use and IS recurrence (incidence rate ratio -**IRR**- 0.90; 95%CI 0.71-1.15), recurrent IS or TIA (IRR 0.97; 95%CI 0.80-1.18), or recurrent IS/ICH/TIA (IRR 0.99; 95%CI 0.80-1.20).[7] It must be noted that type of cardiac monitoring (e.g., external vs implantable), duration (7 days to ≅3 years), and timing of initiation (3 days to 6 months) were heterogeneous



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DOI: 10.1177/17474930241312649

across studies. Two RCTs are currently evaluating whether different intensities of PCM reduce stroke risk in patients with a recent IS or TIA (NCT04371055, NCT05134454).

## BLOOD BIOMARKERS FOR IMPROVING AF SCREENING

Measuring blood biomarkers capable of identifyng patients more likely to have PCM-detected AF could potentially streamline AF screening. Blood biomarkers can be classified into cardiac, thrombotic, and inflammatory.[8]

### *Cardiac Biomarkers*

Elevated cardiac troponin has been associated with increased AF detection (AUC 0.660-0.697) in several observational studies (**Table S3**).[9] Natriuretic peptides are released from the cardiac atria or ventricles under strain.[8,10] Although both N-terminal pro b-type natriuretic peptide (**NT-proBNP**) and midregional pro-atrial natriuretic peptide (**MR-proANP**) are associated with AF diagnosis post-stroke[11-15], **NT-proBNP** is less atrial-specific than MR-proANP. In the **BIOSIGNAL** (Biomarker Signature of Stroke Aetiology) study, which prospectively measured MR-proANP in 1759 patients within 24 hours of acute IS onset. Log$_{10}$MR-proANP levels were strongly associated with new AF diagnosis (aOR 35.3, 95%CI 17.6-71.0).[15] A simple model with age and MR-proANP showed good discrimination (AUC 0.810) and higher net benefit than existing clinical AF risk scores.



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*Thrombosis Biomarkers*

Anti-thrombin III, D-dimer, and the **MOCHA** profile (markers of coagulation and hemostatic activation, including serum d-dimer, prothrombin fragment 1.2, thrombin-antithrombin complex, and fibrin monomer) have been associated with new AF detection, underlying malignancy, and stroke recurrence, with a good predictive ability when associated with left atrial volume index (AUC 0.800).[14,16] The AUC of thrombotic markers for AF detection was 0.700 in another study and appeared to be a stronger association with underlying malignancy and venous thromboembolism.[17]

*Inflammatory and novel biomarkers*

In a larger systematic review and meta-analysis, there was only a non-significant trend toward association with AF detection among people with C-reactive protein higher levels.[10] Novel biomarkers, including Bone morphogenic protein 10[18], symmetric dimethylarginine[19], and soluble suppression of tumorigenicity-2[20] have been associated with AF detection in stroke patients but more evidence is needed. Cytokines (e.g. IL-4, IL-6, IL-10, tumor necrosis factor, interferon-gamma, etc.) have been associated with AF relative to sinus rhythm. IL-17 have been implicated in the pathogenesis of AF[21], and IL-6 is associated with increased AF incidence in patients undergoing cardiac surgery[22,23] and with AF recurrence after electrical cardioversion[24]. We did not identify any studies evaluating the role of cytokines for predicting AF detection in patients with a recent IS or TIA.



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DOI: 10.1177/17474930241312649

## CLASSIFICATION OF AF SUBTYPES

### *Stroke recurrence rates according to the timing of AF diagnosis*

The timing of AF detection relative to stroke onset and the intensity of monitoring determine the characteristics of the detected AF, with a gradient of stroke risk ranging from very high in patients with AF known before stroke onset to significantly lower risk in PCM-detected AF.[25] AF known before stroke occurrence is detected incidentally on 12-lead ECGs performed during routine physical examination or when patients become symptomatic before they experience a stroke. Therefore, by the time it is diagnosed on an ECG, it has matured long enough to become a symptomatic high-burden arrhythmia. In contrast, AF detected on opportunistic PCM pursued post-stroke is generally an earlier and lower-burden arrhythmia.[25]

Based on meta-analyses of RCTs and observational studies, AF in patients with a recent IS or TIA has been categorized into three main subtypes based on the timing of AF diagnosis: AF known before stroke onset or "Known AF" (**KAF**), AF newly-detected post-stroke on 12-lead ECG, and AF detected after stroke (**AFDAS**) on PCM, ranging from short (24h or 48h Holter) to long-term (≥7 days).[2] The rationale behind this categorization is that KAF has a higher prevalence of risk factors and vascular comorbidities, more severe left atrial substrate, greater AF burden, and higher risk of stroke recurrence than AFDAS.[7,27] AF newly detected on 12-ECGs post-stroke has a 5-fold higher risk of stroke recurrence than PCM-detected AF and is considered a pre-existing AF that remained undiagnosed until stroke occurrence despite being high-burden, with risk profile similar to KAF.[28] Therefore, newly 12-lead ECG-detected AF at any time-point





DOI: 10.1177/17474930241312649

post-stroke should not be considered AFDAS and has a similar long-term risk of stroke as KAF (**Figure 2**).[26] AFDAS is always PCM-detected.

## PREVENTION OF RECURRENT ISCHEMIC STROKE

The pillars of IS prevention in AF are the management of risk factors, anticoagulation, rate/rhythm control, and minimizing the risk of bleeding. Patients with a recent IS or TIA usually undergo PCM, which adds a layer of complexity due to the wide range of AF burden found in this population.

### *Management of risk factors*

Strong evidence from RCTs supports that optimizing the control of risk factors is crucial for IS prevention, regardless of the presence of AF.[29] In patients with AF, the strongest evidence from RCTs has shown that physical activity, reducing alcohol intake, and treating hypertension, sleep-disordered breathing, obesity, and diabetes can reduce AF incidence and recurrence.[30,31] No specific RCT has assessed the effect of risk factor management on recurrent IS in AF patients with a recent IS or TIA.

### *RCTs of anticoagulants in ECG-detected AF*

Robust evidence from multiple large RCTs and meta-analyses of RCTs demonstrates that vitamin K antagonists (**VKA**) reduce IS risk by approximately 67% compared to placebo or no therapy, and the risk of stroke (ischemic and hemorrhagic) by 38% relative to Aspirin.[32] In more recent RCTs, direct oral





DOI: 10.1177/17474930241312649

anticoagulants (**DOACs**) were at least as effective as VKAs for the prevention of IS (RR 0.92, 95%CI 0.83-1. 02), resulted in a 52% lower risk of ICH (RR 0.48; 95%CI 0.39-0.59), and 19% lower risk of stroke/SE (0.81; 95%CI 0.73-0.91) in patients with and without a remote stroke/TIA.[33]

*Secondary Analyses of RCTs of anticoagulants in device-detected AF*

**NOAH-AFNET 6** (Non-vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes) reported neutral findings in a randomized trial comparing edoxaban 60 mg daily versus placebo or aspirin for the prevention of stroke, systemic embolism (**SE**), or cardiovascular death in patients 65 years of age or older with subclinical device-detected AF lasting ≥6 minutes and at least one risk factor.[34] It was stopped early due to excess major bleeding with edoxaban and had a low number of stroke events, potentially limiting the trial's power to detect differences in the primary efficacy outcome. In contrast, the **ARTESiA** (Apixaban for Stroke Prevention in Subclinical Atrial Fibrillation) trial reported superior prevention of stroke or SE with random assignment to apixaban 5 mg twice daily compared with aspirin 81 mg daily in patients 55 years of age or older with subclinical device-detected AF lasting 6 minutes to 24 hours.[35] An aggregate meta-analysis of the two trials demonstrated that oral anticoagulation with these agents reduced IS risk (relative risk [RR], 0.68 [95% CI, 0.50-0.92]) and reported consistent estimates of treatment effect between the two trials ($I^2$=0%).[36] However, less than 10% of participants in these trials had a history of IS or TIA. Subanalyses from NOAH-AFNET 6 and ARTESiA comparing the effect of DOACs versus aspirin or placebo



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DOI: 10.1177/17474930241312649

on IS recurrence risk in patients with remote IS or TIA were conflicting (**Table S4**). In both trials, DOACs significantly increased major bleeding risk.

Concerns have been raised by experts[37-39] and recent guidelines[31] regarding a one-size-fits-all approach for anticoagulation in IS or TIA patients with device-detected subclinical AF lasting <24 hours. A more comprehensive and personalized approach considering the interplay of AF burden, atrial substrate, and time between stroke occurrence and AF diagnosis has been proposed for patients with AFDAS. For instance, the **B²AD-RISK** scheme, which comprises the longitudinal measurement of biomarkers (B), AF burden (B), atrial substrate (A), age and sex demographics (D), and risk factors (R), is currently being tested in a pilot study (NCT0658970).[26]

*Early Rhythm Control*

The **EAST-AFNET 4** (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial) trial randomized 2789 patients with AF diagnosed within the previous 12 months to early rhythm control (**ERC**) with antiarrhythmic drugs or ablation vs standard of care. The primary composite efficacy outcome of cardiovascular death, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome was less frequent in the ERC group (HR 0.79, 95%CI 0.66-0.94). Patients receiving ERC had a lower risk of stroke than the control group (HR 0.65, 95%CI 0.44-0.97). Several observational studies and a subanalysis of EAST-AFNET 4 in patients with prior IS or TIA have shown similar results.[40] A small open-label, randomized,



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multicenter RCT including 300 patients with acute IS and AF within 2 months of stroke onset. This study found lower recurrent IS rates in patients undergoing ERC than in those receiving usual care (HR 0.251; 95%CI 0.063-1.003).[41] **EAST-STROKE** (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial in Acute STROKE) will test a similar approach in patients with recent ischemic cerebrovascular events (NCT05230550).

## TIMING OF INITIATION OF ANTICOAGULATION

Clinicians considering early initiation of anticoagulation therapy must balance the potential benefit of improved recurrent stroke prevention on the one hand and the potential harm of symptomatic ICH on the other hand. Observational studies found that DOAC therapy is initiated early (median within 4 days) after a recent stroke in clinical routine even in the absence of RCT data and despite more conservative historical guideline recommendations.[42-47] Several registry-based observational studies were conducted to answer the 'timing question' in various populations (**Table S5**).[42-47] These studies found no strong evidence of a heightened ICH risk in patients with early initiation of anticoagulation. However, most studies artificially split timing to make a comparison but the real finding is that most people already started early applied different definitions of early and late timing ranging from ≤2 days to ≤7 days, they had retrospective designs with risk of confounding by indication and had no standardized procedure for early or later treatment selection.



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DOI: 10.1177/17474930241312649

Three RCTs specifically addressed the topic of early or late initiation of DOACs. The **TIMING** (Timing of Oral Anticoagulant Therapy in Acute IS With Atrial Fibrillation) was a registry-based noninferiority RCT that randomized 888 IS patients (median NIHSS 4) with AF admitted within 72 hours of symptom onset to either early (≤4 days) or delayed (5-10 days) start of DOAC treatment.[48] Early DOAC initiation was non-inferior to delayed start (IS rates 3.1% versus 4.6%), and no patient in either group experienced a symptomatic ICH. **ELAN** (Early versus Late Initiation of Direct Oral Anticoagulants in Post-IS Patients with Atrial Fibrillation) is the largest RCT comparing early versus later initiation of DOAC treatment in AF-related IS.[49] The time frame for early or late start of DOAC treatment was defined according to the infarct size on neuroimaging.[49] Patients with minor or moderate stroke randomized to early initiation of DOACs were started within 48 hours, and patients with major stroke on day 6 or 7 (n=1006). The primary outcome, a composite of recurrent IS, SE, major extracranial bleeding, symptomatic ICH or vascular death within 30 days, occurred in 2.9% versus 4.1% in the early and late groups, respectively. Numerically, fewer patients in the early group had recurrent IS within 30 days (1.4% versus 2.5%). Two patients in each group had symptomatic ICH. The **OPTIMAS** (Optimal Timing of Anticoagulation After Acute Ischaemic Stroke) trial was a phase 4, multicenter, parallel-group, randomized controlled trial applying an open-label intervention and blinded endpoint adjudication.[50] It used a hierarchical non-inferiority-superiority gatekeeper design (sequentially assessing a non-inferiority margin of 2 percentage points and then proceeding to test for superiority) to compare early initiation of DOACs (within 4 days after stroke onset) versus delayed initiation (7-14 days following stroke onset) in 3621 patients with AF and IS.[50] The primary endpoint was a composite of recurrent



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DOI: 10.1177/17474930241312649

IS, symptomatic ICH, stroke of unknown type, or systemic embolism at 90 days in a modified intention-to-treat analysis. Early DOAC initiation within 4 days post-IS was noninferior to delayed initiation for the composite primary endpoint. Early initiation was not superior to late initiation.

CATALYST (CollAboration on the optimal Timing of anticoagulation after ischaemic stroke and Atrial fibrillation: prospective individuaL participant data meta-analYsiS of randomized controlled Trials) is an individual participant data meta-analysis of RCTs investigating the optimal timing of DOAC initiation after acute IS in patients with AF. CATALYST included data from 5411 patients from TIMING, ELAN, OPTIMAS, and START.[51] The primary endpoint was a composite of recurrent IS, symptomatic intracerebral hemorrhage, or unclassified stroke at 30 days. Early DOAC initiation (within 4 days) was superior to later initiation (≥5 days) for the primary endpoint at 30 days (2.12% vs. 3.02%, OR 0.70, 95% CI 0.50-0.98). Symptomatic intracerebral hemorrhage rates were low in both the early and late groups: 0.45% and 0.40%, respectively. At 90-days primary endpoint events were numerically lower in the earlier than the later group, but without reaching statistical significance. The CATALYST meta-analysis supports the initiation of DOACs early after acute IS in patients with atrial fibrillation.

## MANAGEMENT OF BREAKTHROUGH STROKES ON ANTICOAGULATION

Data from RCTs and population-based studies show that approximately 1% of patients on DOACs experience a breakthrough IS annually.[52] Recurrent IS risk is particularly high in patients with breakthrough



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DOI: 10.1177/17474930241312649

stroke raging between 5 and 9% annually.[53] While suboptimal adherence to anticoagulants is still common[54], breakthrough strokes can occur even with the best medication compliance and prescribing practices.[53] Several aspects must be considered before labeling a breakthrough event as DOAC failure-related. The specific cause of breakthrough strokes can be identified by applying a comprehensive and systematic investigation, which in turn can help tailor secondary prevention strategies (**Figure 3**).[55]

*Identification of Competing Stroke Mechanisms*

The proportion of breakthrough strokes explained by competing mechanisms other than AF ranges between 24% and 35%.[56,57] While some series have shown that competing mechanisms are more frequent in AF patients on anticoagulants at the time of the event than among those off anticoagulation,[57] others have shown a similar prevalence on and off anticoagulation[58]. Among competing causes, the most frequently reported are large (18-61%) and small (25-26%) artery disease[56-58]. Cancer-related coagulopathy is a potential competing mechanism. Approximately 7% of patients with AF have cancer and this is associated with an increased risk of IS (e.g. breast).[59] If cancer-related coagulopathy is suspected, further targeted investigations should be undertaken if the results are likely to change treatment.

*Anticoagulant adherence or dosing failure*

Adherence or dosing issues represent 32% of all breakthrough strokes.[56] Poor adherence and persistence are the leading causes of inefficient anticoagulation in patients with AF. In a meta-analysis of 48





DOI: 10.1177/17474930241312649

observational studies including 594784 AF patients, the pooled proportion of good adherence to oral anticoagulants at 12 months, defined as >80% of days covered or medication possession ratio, was only 68%.[54] Similarly, the pooled proportion of persistence on anticoagulation at 12 months was 62%.[54] Both non-persistence (HR 4.6; 95%CI 2.8-7.4) and poor adherence (HR 1.4; 95%CI 1.06-1.8) were associated with increased stroke risk.[54] Other causes of inefficient anticoagulation beyond the scope of this work but still of clinical importance include poor absorption, underdosing, drug-drug interactions, and inappropriate interruption surrounding surgical procedures.[60]

*Poor management of risk factors*

As discussed previously, the management of risk factors is an essential component of stroke prevention, which is sometimes suboptimal, explaining a proportion of stroke recurrences.[29] Although not a stroke mechanisms, part of the risk of stroke recurrence, can be explained by poor risk factors control.

*AF-related residual risk*

The most frequent cause of breakthrough strokes in patients on optimal anticoagulation and no competing mechanisms is cardioembolism from AF-related residual risk (44%).[56] This risk is explained by AF-specific structural and functional factors, including left atrial appendage (**LAA**) morphology (e.g., LAA shape[61], berry angle[62], and orifice size[63]) and flow[64]. Approximately 90% of cardiac thrombi in patients with AF originate in the LAA.[65] The prevalence of LAA thrombus among individuals receiving DOACs is approximately



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DOI: 10.1177/17474930241312649

329 2.3%.[66] Among AF patients on DOACs, LAA thrombi seem to be more frequent in those with a prior stroke
330 than among those without[67] and the general population[66]. These LAA features can be investigated with
331 transesophageal echocardiography, cardiac computed tomography, and cardiac magnetic resonance
332 imaging.
333
334 ***Secondary stroke prevention in patients with breakthrough strokes***
335 Given the high risk of early recurrence, secondary stroke prevention in patients with breakthrough strokes
336 is essential. There are no data from RCTs evaluating whether switching a DOAC to a different DOAC or a
337 VKA at the time of experiencing a breakthrough stroke reduces recurrent stroke risk. A study-level meta-
338 analysis of 6 retrospective observational studies comprising 12159 patients suggests that remaining on a
339 DOAC instead of switching from DOACs to VKA is associated with lower IS recurrence risk (RR 0.55;
340 95%CI 0.43-0.70) and lower risk of ICH (RR 0.37, 95%CI 0.25-0.55), but with increased risk of death (RR
341 1.85; 95% CI 1.06-3.24).[68] This analysis is subject to the limitations of retrospective observational studies.
342 In observational studies, adding an antiplatelet agent to anticoagulants was not associated with lower IS
343 risk reduction.[56] In a subanalysis of RCTs, adding an antiplatelet agent was linked to increased ICH risk[69],
344 and a meta-analysis of RCTs and observational studies showed overall increased bleeding risk[70]. Evidence
345 is missing for short-term addition of antiplatelet agents in patients with competing large-artery stroke
346 mechanism. The Frail Atrial Fibrillation (**FRAIL AF**) trial randomized frail individuals (≥75 years of age and
347 a Groningen Frailty Indicator score ≥3) with AF who were receiving VKAs to continue VKA therapy vs.


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DOI: 10.1177/17474930241312649

348 switching to a DOAC.[71] The primary outcome of major or clinically relevant nonmajor bleeding complication
349 was more frequent in the DOAC (HR 1.69; 95%CI 1.23-2.32), without differences in the risk of
350 thromboembolic events at 12 months of follow-up. The proportion of patients with a previous stroke and the
351 risk of IS were not reported.
352
353 A potential novel option for patients with breakthrough stroke is LAA occlusion as a matched observational
354 cohort study found a lower risk of recurrent stroke compared to standard of care DOAC therapy alone in
355 patients with breakthrough stroke (HR 0.33, 95%CI 0.19-0.58).[72] Although promising, a major limitation of
356 this data is that for the LAA occlusion patients, follow-up started from the moment of the LAA occlusion
357 procedure bypassing the high-risk early post stroke time period, while for the non-LAA occlusion cohort,
358 follow-up started immediately after the index event (inclusive of the high-risk early post stroke time period)
359 introducing substantial bias in favour of LAA occlusion. As such, uncertainty remains and this approach is
360 currently being investigated in randomized controlled trials (NCT05976685, NCT05963698).
361
362 **LEFT ATRIAL APPENDAGE CLOSURE AND OTHER INTERVENTIONS**
363 The left atrial appendage (**LAA**) is the primary cardioembolic structural source in AF patients.[5] As such,
364 LAA closure (**LAAC**) has been tested in several RCTs as a potential strategy for stroke prevention in
365 patients with AF.
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367 ***Studies of Percutaneous LAAC vs VKAs***

368 The **PROTECT-AF** (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial
369 Fibrillation) trial compared VKAs vs percutaneous LAAC in 707 anticoagulant-naïve AF with a $CHADS_2$
370 score ≥1.[7] LAAC met prespecified criteria for noninferiority and superiority (rate ratio -RR- 0.60, 95%CI
371 0.41-1.05) for its primary efficacy endpoint (composite of stroke, SE, and cardiovascular/unexplained
372 death).[73] The **PREVAIL** (Prospective Randomized Evaluation of the Watchman LAA Closure Device In
373 Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) trial compared VKAs vs LAAC in 407
374 anticoagulant-naïve AF patients with a $CHADS_2$ score ≥2 or 1 and another risk factor.[74] Percutaneous LAAC
375 was non-inferior to warfarin for IS prevention or SE >7 days post-closure but did not achieve the
376 prespecified noninferiority threshold for the composite endpoint of stroke, SE, and cardiovascular or
377 unexplained death.[74] A prospective registry found no difference in outcomes in patients with and without
378 a prior stroke.[75]

379

380 ***Studies of Percutaneous LAAC vs DOACs***

381 The **PRAGUE-17** (Left Atrial Appendage Closure vs. Novel Anticoagulation Agents in Atrial Fibrillation) trial
382 included 402 AF patients with at least one of the following: bleeding requiring intervention or hospitalization;
383 breakthrough stroke while on anticoagulants or $CHA_2DS_2$-VASc score ≥3 + HAS-BLED score ≥2. Patients
384 were randomized to percutaneous LAAC vs DOACs.[76] LAAC was non-inferior to DOAC in preventing the
385 composite outcome of stroke, TIA, SE, cardiovascular death, major or nonmajor clinically relevant bleeding,





DOI: 10.1177/17474930241312649

386 or procedure-/device-related complications. There were no significant differences between groups in the
387 risk of IS or TIA (HR 1.13, 95%CI 0.44-2.93) or major/non-major bleeding (HR 0.81, 95%CI 0.44-1.52). An
388 propensity-matched analysis comparing percutaneous LAAC vs DOACs in 587 patients with AF and a prior
389 stroke (median time between stroke and LAAC of 7.6 months) showed no differences in the rates of IS and
390 ICH, but a lower risk of the primary composite outcome of IS, major bleeding, and all-cause death.[77]
391
392 *Trials of Surgical LAAC*
393 The **ATLAS** (AtriClip Left Atrial Appendage Exclusion Concomitant to Structural Heart Procedures) pilot
394 trial included patients undergoing non-mechanical valve and/or coronary artery bypass grafting without
395 preoperative AF or needing anticoagulation, $CHA_2DS_2$-VASc score ≥2, and HAS-BLED score ≥2.[78] A total
396 of 562 patients were randomized to surgical LAA exclusion (**LAAE**) vs no exclusion.[78] The proportion of
397 patients with postoperative AF was 44.3%. The proportion of thromboembolic events was 3.4% in LAAE
398 patients and 5.6% in the no-LAAE group.[78] **LAAOS III** (Left Atrial Appendage Occlusion Study) randomized
399 4770 AF patients with a $CHA_2DS_2$-VASc score ≥2 undergoing cardiac surgery to surgical LAAE vs no-
400 LAAE.[79] Surgical LAAE reduced the risk of stroke or SE compared to no-LAAE (HR 0.67; 95% CI 0.53-0.85)
401 in a population where 80% of patients continued to receive oral anticoagulation.[79] Results were consistent
402 in interaction analysis for patients with and without prior IS, TIA or SE.[79] The results from LAAOS III have
403 catalyzed several ongoing trials testing the combination of mechanical therapy (percutaneous LAAC or


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DOI: 10.1177/17474930241312649

carotid filter devices) combined with oral anticoagulation for improved stroke prevention in AF patients who remain at high risk for stroke despite anticoagulation.[53]

### *Percutaneous Carotid Filters*

Vine™ is a novel permanent common carotid filter system that is implanted percutaneously under ultrasound guidance. It has been designed to prevent emboli >1.4 mm that result in large vessel occlusions from reaching the anterior circulation, which is affected by the majority of AF-related ischemic strokes.[80,81] On the basis of a promising phase 2 program establishing the feasibility and safety of the device, in which there were no strokes due to large vessel occlusion following carotid filter implantation in over 268 patient-years of follow-up (106 participants), the **INTERCEPT** (Carotid Implants for PreveNtion of STrokE ReCurrEnce From Large Vessel Occlusion in Atrial Fibrillation Patients Treated With Oral Anticoagulation) RCT (NCT05723926) will be testing the superiority of bilateral carotid filter implantation + DOAC vs. DOAC alone in patients with AF and stroke within the past year.[82,83]

## SECONDARY PREVENTION IN AF AND PREVIOUS ICH

Patients with a previous ICH, particularly intracerebral hemorrhage, have an inherently high risk of recurrent ICH. Therefore, the decision to start or reinstate antithrombotic therapy in these patients is challenging.

### *Anticoagulation*



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DOI: 10.1177/17474930241312649

Observational studies suggest that resumption of anticoagulation after ICH may be associated with reduced thromboembolic events without an offsetting increase in the risk of ICH recurrence.[84] In an individual patient-level meta-analysis combining information from three small early phase RCTs and subgroup data of a single phase III RCT totalling 412 patients with an ICH and AF, treatment with oral anticoagulation did not lead to a significant reduction in the primary outcome of any stroke or cardiovascular death.[85] Patients who reinitiated anticoagulation had a lower frequency of recurrent IS (4% vs. 19%) and major ischemic cardiovascular events, including IS, SE, pulmonary embolism, and myocardial infarction (4% vs. 19%). However, anticoagulation had numerically higher ICH recurrence events (6% vs. 3%).[85] Ongoing phase 3 clinical trials testing the safety and efficacy of anticoagulation in ICH survivors with AF will provide more evidence to inform clinical decision-making in the future (**Table S6**).

The **ENRICH-AF** (Edoxaban for Intracranial Haemorrhage Survivors with Atrial Fibrillation trial) trial is comparing standard dosing edoxaban with non-anticoagulant medical treatment for stroke prevention in intracranial hemorrhage survivors with atrial fibrillation.[86] Following an initial safety review of the first 699 patients—where 174 (25%) presented with lobar intracranial hemorrhage and 34 (5%) with isolated convexity subarachnoid hemorrhage—the trial's Data Safety Monitoring Board advised halting the enrollment of those with these two hemorrhage subtypes that are typically caused by underlying cerebral amyloid angiopathy. They additionally recommended discontinuing study drug immediately in this subgroup of patients.[86] The data leading to this recommendation has yet to be published, and no treatment



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DOI: 10.1177/17474930241312649

interactions were identified in patients with lobar or isolated convexity subarachnoid hemorrhage in the abovementioned meta-analysis.[85] Further data from ongoing RCTs where patients with CAA-related intracranial hemorrhage remain eligible, and repeated meta-analyses will be important to clarify net-benefit in these high risk patients.

*Antiplatelet therapy*

Antiplatelet monotherapy, while inferior to anticoagulation, offers a modest 23% reduction in the risk of thromboembolic events in patients with AF relative to placebo.[32] **RESTART** (REstart or STop Antithrombotics Randomised Trial) included 537 participants with ICH and a prior history of ischemic vascular disease.[87] Antiplatelet therapy did not increase the risk of recurrent ICH at a median follow-up of 2 years. Still, it significantly reduced the risk of major ischemic vascular disease, although it must be noted that only 25% (134/537) of the patients had AF.[87] The effect of Aspirin compared to no treatment or placebo in a population exclusively comprising AF patients with a prior ICH has not been tested in an RCT.

*LAAC in patients with ICH*

Meta-analyses have indicated that LAAC may have similar efficacy to warfarin in lowering the risk of IS, but the risk of ICH may be significantly lower with LAA closure.[88] Data on the head-to-head comparisons between LAAC and DOACs in patients with prior ICH are lacking. Additionally, given that studies evaluating LAAC excluded patients with ICH, it is unclear if these results can be extrapolated to patients with ICH.



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DOI: 10.1177/17474930241312649

461

462 *Timing of antithrombotic therapy post-ICH*

463 Clinical equipoise exists on the optimal timing of antithrombotic therapy after ICH. Literature-based

464 estimates on the optimal timing of OAC following intracranial hemorrhage range broadly from 3 days to 30

465 weeks.[89,90] While antiplatelet medications were started at a median of 76 days (IQR, 29-146) in the

466 RESTART trial[87], observational data are inconclusive.[91]

467

468 **KNOWLEDGE GAPS AND FUTURE DIRECTIONS**

469 Despite significant advances in stroke prevention in patients with AF, several knowledge gaps have been

470 identified in this position statement. Relevant ongoing RCTs and observational studies addressing these

471 gaps are listed in the supplementary file (**Table S6**). This group has identified several research questions

472 of clinical relevance that should be addressed in future studies (classified with a level of evidence C, D, E,

473 or F in **Table 1**).

474

475 ***AF Screening &*** **Classification of AF Subtypes**

476 Differences between subtypes of AF and their specific risk of IS outcomes are well-established. However,

477 the clinical impact of this classification has not yet been demonstrated. Future studies assessing who the

478 interplay between timing of AF detection, intensity of monitoring, AF burden, risk factors, and blood

479 biomarkers impact on stroke recurrence risk are needed. It is also crucial to understand how AF burden



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DOI: 10.1177/17474930241312649

and left atrial substrate progress over time. Given the increased risk of ICH resulting from the addition of antiplatelet agents to DOACs, there are concerns about potential harm when screening for AF in patients with an established competing cause (e.g., severe carotid artery stenosis). Therefore, the clinical implications of detecting AF in patients with a defined cause of stroke remains to be determined and adding oral anticoagulants to antiplatelet therapy in this population should be investigated in RCTs. One of the most pressing uncertainties, due to its potential impact on health care costs and clinical outcomes, is the ideal duration of monitoring for AF detection in patients with a recent ischemic cerebrovascular event. Whether a single device approach or a stepwise combination of short-term followed by longer term cardiac monitoring in selected patients is unknown.

*Blood Biomarkers*

Evidence supporting the role blood biomarkers, mainly natriuretic peptides, suggests they could be incorporated into clinical practice to select patients who may benefit from PCM. Additionally, due to the association with AF-related outcomes, using natriuretic peptides may also help identify patients who could benefit from anticoagulation if AF is detected. RCTs specifically addressing these questions are needed. The results of the **MOSES** (MidregiOnal Proatrial Natriuretic Peptide to Guide SEcondary Stroke Prevention) trial are awaited. Other blood biomarkers are at earlier stages of investigation or are less specific for AF detection (NCT03961334).



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DOI: 10.1177/17474930241312649

499 ***Secondary Stroke Prevention in AF & Management of Breakthrough Strokes***

500 Given the increasing use of PCM, one of the main uncertainties is whether oral anticoagulation can reduce
501 stroke recurrence risk in patients with a recent IS or TIA and device-detected AF lasting <24 hours and not
502 confirmed on 12-lead ECG are lacking, relative to antiplatelet therapy. Early rhythm control therapy has
503 proven to be effective in patients with remote cerebrovascular events. However, no large, multicenter RCT
504 has demonstrated its benefit in patients with a recent IS or TIA. EAST-STROKE study will address this
505 question. There is no clear strategy for the management of patients with breakthrough strokes. Several
506 strategies are being tested, including switching from a DOAC to a VKA vs. staying on a DOAC, carotid filter
507 implantation + DOAC, and LAAO vs LAAO + DOAC therapy.

508

509 ***Resuming or Starting Anticoagulation Post-ICH***

510 Whether resuming or starting anticoagulation in patients with a previous ICH is safe, improves survival or
511 effectively provides net benefit, remains unknown. The results of **PRESTIGE-AF** (PREvention of STroke
512 in Intracerebral haemorrhaGE Survivors With Atrial Fibrillation, NCT03996772) and **RENRICH-AF**, which
513 have completed recruitment, are awaited, and the **ASPIRE** (Anticoagulation in ICH Survivors for Stroke
514 Prevention and Recovery, NCT03907046) and **A3ICH** (Avoiding Anticoagulation After IntraCerebral
515 Haemorrhage, NCT03243175) trials are ongoing. The role of other approaches such as LAAO vs.
516 antiplatelet therapy or anticoagulation, require further investigation.

517



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In summary, many uncertainties remain on how to screen for AF and how to prevent AF-related strokes in varying scenarios. Funding agencies should prioritize research on these fields. Academic-industry partnerships are also strongly encouraged to advance knowledge.





DOI: 10.1177/17474930241312649

## DISCLOSURES

LAS Speaker/consulting honoraria from Boehringer Ingelheim, Pfizer, Bayer, AstraZeneca, Medtronic

ACC Speaker honoraria from BMS, Pfizer, AstraZeneca, and Boehringer Ingelheim

MK Speaker/Consulting honoraria from Astra Zeneca, BMS, Medtronic

NBS Consulting honoraria from Medtronic

VC Speaker/consulting honoraria from Boehringer Ingelheim, Pfizer, Bayer, EVER PHARMA, Daiichi Sankyo

C-YH Speaker honoraria from Boehringer Ingelheim, Daiichi Sankyo, Pfizer, Bayer, Medtronic

MJH Speaker honoraria from Sanofi

DJS Speaker/consulting honoraria from Pfizer and AstraZeneca

MCB Speaker/consulting honoraria from J&J, Anthos Therapeutics, Merck.

JFS Speaker honoraria from BMS, Pfizer, AstraZeneca.

AS Speaker/consulting honoraria from AstraZeneca, Bayer AG, Daiichi Sankyo Ltd, Javelin Inc.

Other authors: no disclosures relevant to this work

## ACKNOWLEDGEMENTS

We thank Dr. Alba Hernandez Pinilla and Ioannis Farah for their contribution to the systematic search of current evidence and ongoing studies.

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DOI: 10.1177/17474930241312649

## FUNDING

LAS Kathleen and Dr Henry Barnett Chair in Stroke Research

ACC David Cargill Trust Clinical Senior Research Fellow.

JFS Support from Deutsche Herzstiftung e.V.

MK Swiss National Science Foundation (NR 182267, NR 213471) and Swiss Heart Foundation

Other authors: no funding relevant to this wok.





DOI: 10.1177/17474930241312649

568 **Figure 1.** Classification of levels of evidence

569

| | Primary population is patients with recent (≤6 m) IS/TIA/ICH | Subgroup analysis for patients with recent (≤6 m) IS/TIA/ICH | Primary population or subgroup analysis for remote IS/TIA/ICH |
|---|---|---|---|
| **The statement's outcome is a primary study endpoint** | | | |
| Consistent fata from ≥2 RCTs or meta-analyses of RCTs | A1 | A3 | B1 |
| Data from a single RCT | A2 | A4 | B2 |
| Consistent data from meta-analyses of observational studies, large prospective observational studies, or stroke registries | B1 | B2 | B3 |
| Data from ≥1 retrospective observational studies | C1 | C2 | C3 |
| **The statement's outcome is a secondary study endpoint** | | | |
| Consistent Data from ≥2 RCTs or meta-analyses of RCTs | A2 | A4 | B4 |
| Data from a single RCT | A3 | B2 | C1 |
| Consistent data from meta-analyses of observational studies, large prospective observational studies, or stroke registries | B2 | B3 | C3 |
| Data from ≥1 retrospective observational studies | C2 | C3 | C4 |
| **Insufficient data** | | | |
| Inconsistent, underpowered, or conflicting data OR no studies or subgroup analyses in patients with IS/TIA/ICH and AF | D | | |
| Expert opinion | E | | |
| More data are needed, and no solid expert opinion | F | | |

**Level A:** strong. **Level B:** moderately strong. **Level C:** weaker. **Levels D, E, F:** conflicting or uncertain.

570

571

572 **RCT:** randomized controlled trial. **IS/TIA/ICH:** ischemic stroke, transient ischemic attack or intracranial

573 hemorrhage.

574



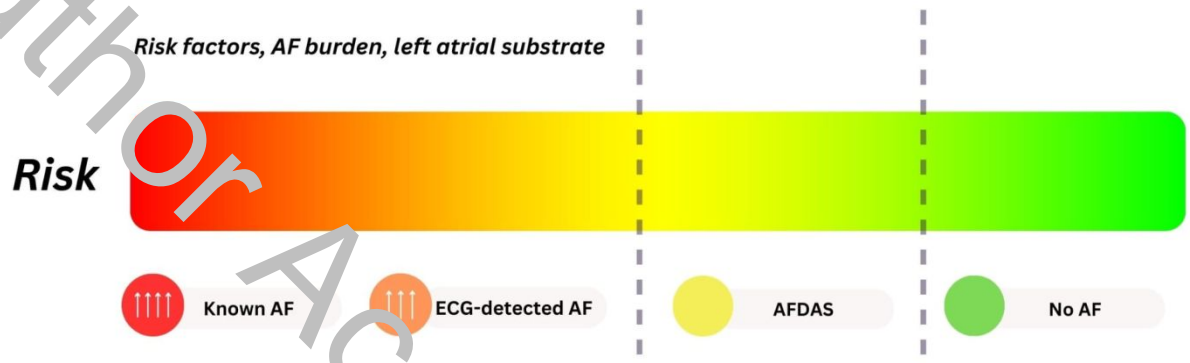


DOI: 10.1177/17474930241312649

575 **Figure 2.** AF risk based on the timing of detection and intensity of cardiac monitoring

576

577




578

579 **AF:** atrial fibrillation. **ECG:** 12-lead electrocardiogram. **AFDAS:** atrial fibrillation detected after stroke.

580





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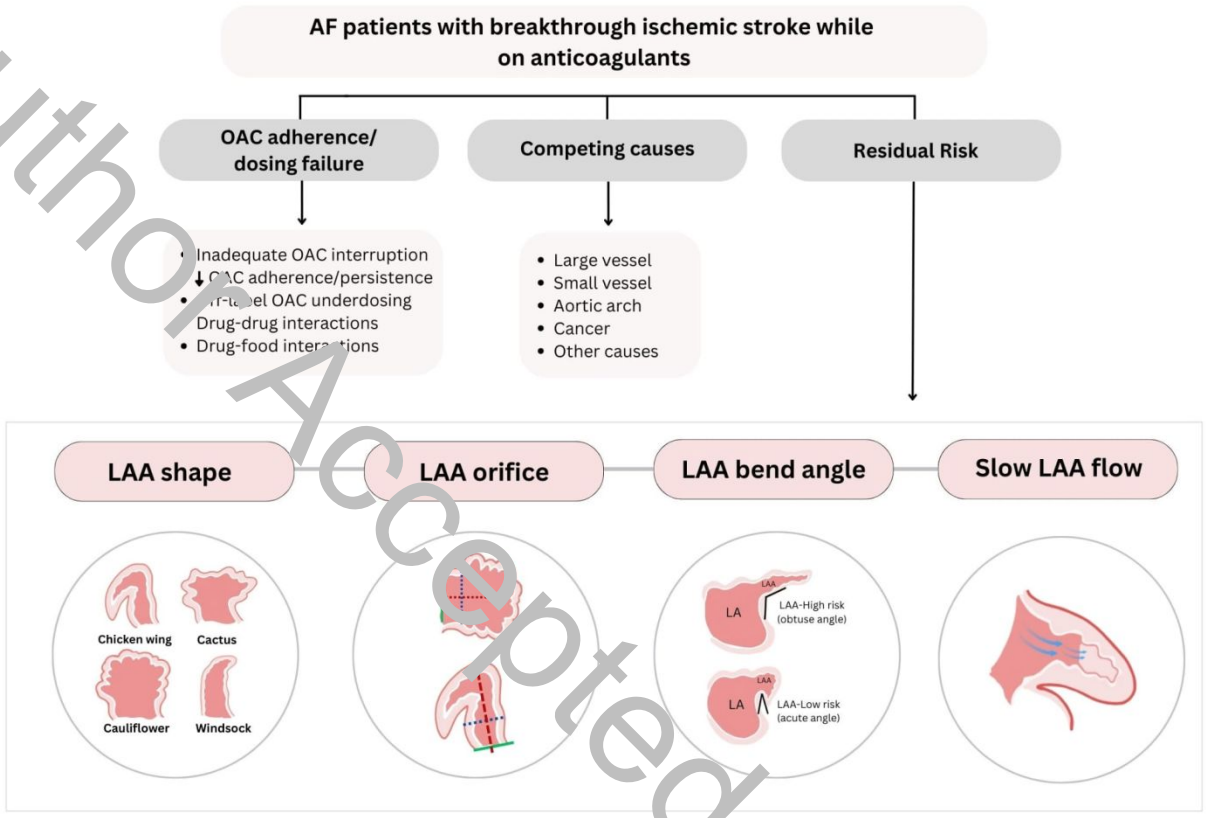
581 **Figure 3.** Etiological investigation of breakthrough strokes




582

583 **OAC:** oral anticoagulant. **AF:** atrial fibrillation. **LAA:** left atrial appendage.

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DOI: 10.1177/17474930241312649

587 **Table 1.** WSO Brain & Heart Task Force statements on AF in patients with recent IS, TIA and ICH
588

| Section | No | Statement | Level of Evidence |
|---|---|---|---|
| AF Screening | 1 | PCM increases AF detection compared to usual care. | A1 |
| | 2 | Longer monitoring is associated with higher AF detection rates. | A1 |
| | 3 | The ideal duration of PCM in patients with recent IS/TIA is unknown. | E |
| | 4 | No strong evidence supports that PCM in recent IS/TIA patients reduces stroke recurrence. | A2 |
| Biomarkers for guiding AF screening | 5 | Cardiac troponin and natriuretic peptides NT-proBNP and MR-proANP are associated with AF detection. Other novel molecular biomarkers for AF prediction require further testing. | B1 |
| Classification of AF subtypes | 6 | Based on differences in burden, risk factors, left atrial substrate, and embolic risk, AF in patients with recent IS/TIA can be classified into known AF, ECG-detected AF, and AFDAS, which is always detected on PCM. | B2 |
| Secondary stroke prevention | 7 | Optimizing the management of risk factors, including hypertension, diabetes, obesity, sleep-disordered breathing and excessive alcohol use in patients with recent IS/TIA with AF can reduce AF burden progression and recurrence post-ablation but there is no direct evidence supporting a reduction of IS recurrence risk in patients with AF. This evidence is unlikely to be generated, as improved risk factors control has been shown to reduce the risk of stroke in patients with and without AF. | D |
| | 8 | Anticoagulation significantly reduces IS risk in patients with previously known AF. Subanalyses in patients with remote IS/TIA show no significant interaction. | A4 |
| | 9 | DOACs are at least equally effective as VKAs for the prevention of recurrent IS in patients with a remote cerebrovascular event, with a significantly lower risk of intracranial hemorrhage and stroke and systemic embolism. | A4 |
| | 10 | Data on the efficacy of anticoagulation in reducing stroke recurrence risk in patients with a remote IS/TIA and device-detected AF lasting <24 hours and not always confirmed on 12-lead ECG are based on secondary analyses of RCTs and show conflicting results. | D |





DOI: 10.1177/17474930241312649

| | | | |
|---|---|---|---|
| | 11 | Data on the benefit of anticoagulation relative to ASA/placebo in reducing stroke recurrence risk in patients with a recent IS/TIA and device-detected AF lasting <24 hours and not confirmed on 12-lead ECG are lacking. | F |
| | 12 | Individualized management of anticoagulation in patients with a recent IS/TIA and AFDAS lasting <24 hours, and a longitudinal assessment of the interplay and combined effect of all determinants of IS risk (e.g., AF burden, risk factors, atrial substrate) and ICH risk (e.g., brain infarct size, microbleeds) instead of a one-size-fits-all approach has been recommended by experts and guidelines until further evidence is available. | E |
| | 13 | Early rhythm control reduces the risk of IS recurrence if applied within 12 months of AF diagnosis in patients with and without remote IS. A small RCT showed lower IS recurrence rates. | A2 |
| | 14 | The minimum AF burden, alone or in combination with other factors (e.g. atrial substrate, risk factors), that requires anticoagulation in patients with a recent IS/TIA is unknown | D |
| **Timing of reinitiation of anticoagulation** | 15 | Early anticoagulation post-IS is associated with a potentially lower risk of IS recurrence and similar bleeding compared with later anticoagulation. Ongoing RCTs and updated meta-analyses are awaited. | A1 |
| **Management of breakthrough stroke** | 16 | A thorough and systematic investigation of competing stroke mechanisms and causes of AF-related residual risk is required in patients with breakthrough strokes on anticoagulants. | B2 |
| | 17 | There is no definite evidence that switching anticoagulants makes a difference in any direction regarding IS recurrence risk in patients with a breakthrough stroke on anticoagulation. | B2 |
| | 18 | Adding long-term antiplatelet agents to anticoagulants in patients with a recent IS/TIA and AF can increase ICH risk and offers no additional protection against IS recurrence. | B2 |
| | 19 | Percutaneous LAAO ± DOACs was associated with lower IS recurrence rates than persisting on a DOAC after a breakthrough stroke in a single retrospective observational study. | C1 |





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DOI: 10.1177/17474930241312649

| | | | |
|---|---|---|---|
| **LAA closure** | **20** | Percutaneous LAAC is non-inferior to DOACs for the prevention of the composite of stroke, TIA, SE, cardiovascular death, major or nonmajor clinically relevant bleeding, or procedure-/device-related complications in selected patients with and without a remote stroke. No differences between treatments were found in the risk of IS/TIA or major bleeding. There are no RCTs or subgroup analyses from RCTs in patients with a recent or remote IS/TIA/ICH. | **C3** |
| | **21** | Surgical LAA exclusion reduced the risk of IS/SE in patients with and without remote IS/TIA undergoing cardiac surgery for another reason. | **B2** |
| | **22** | Studies are needed for assessing novel protection devices or the combination of different strategies as standard-of-care management in patients with a prior IS/TIA. | **F** |
| **Intracranial hemorrhage** | **23** | No robust data from RCTs supports that anticoagulation can be safely initiated or resumed in patients with AF and a prior ICH without increasing the risk of a recurrent ICH. An individual patient-level meta-analysis from 4 RCTs showed that DOACs post-ICH result in significantly less major ischemic cardiovascular events compared to no anticoagulation. The number of recurrent ICHs was higher among patients with anticoagulation. The composite of major vascular events and death was inconclusive due to small sample size. Results of ongoing RCTs are awaited. | **D** |
| | **24** | In patients with AF and prior ICH, there is insufficient data regarding the timing of anticoagulation resumption. | **F** |
| | **25** | Currently, there are no robust data on the safety and efficacy of other interventions, such as antiplatelet therapy and LAAC, for preventing IS in AF with a previous ICH. | **F** |

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