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How and When to Screen for Atrial Fibrillation after Stroke: Insights from Insertable Cardiac Monitoring Devices

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The introduction of insertable cardiac monitoring devices has dramatically altered our understanding of the role of intermittent atrial fibrillation in cryptogenic stroke. In this narrative review we discuss the incidence, timing and relationship between atrial fibrillation and cryptogenic stroke, how to select patients for monitoring and the value and limitations of different monitoring strategies. We also discuss the role of empirical anticoagulation, and atrial fibrillation burden as a means of tailoring anticoagulation in patients at high risk of bleeding.

Keywords Stroke; Atrial fibrillation; Cryptogenic; Ischemia

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Introduction

The prevention of stroke caused by atrial fibrillation (AF) is a major health priority. AF has been found to increase the risk of stroke by 3-5 fold and strokes associated with AF have a poorer prognosis with increased rates of disability and mortality.^{1,2} Furthermore, survivors of strokes related to AF are at an increased risk of recurrent strokes.³

Paroxysmal AF (PAF) poses many clinical challenges due to its transient and often asymptomatic nature. As a result it is frequently a silent risk factor that may not be detected on routine investigations.⁴⁻⁹ The prevalence and prognostic value of subclinical or occult AF is difficult to assess. Although traditionally PAF was thought to incur a similar risk of embolism as permanent AF,^{10,11} recent studies have shown a reduced risk of stroke with PAF.^{12,13} Despite this apparent lower risk, treatment of PAF with

anticoagulation is still warranted and the length of AF is not currently used as a tool to select patients for anticoagulation.¹⁴

The detection of AF after ischemic stroke or transient ischemic attack (TIA) in any form is paramount, as it will strongly influence therapeutic decisions. Ischemic strokes occurring in the absence of AF (or other major cardiac sources) are best treated with antiplatelet medication; however, when AF is detected the treatment should be changed to anticoagulation. The commencement of anticoagulation following stroke in patients with AF has been found to be highly effective to prevent recurrent strokes.^{15,16}

In this narrative review we canvas the topical and often controversial subject of PAF in cryptogenic stroke (CS). We will discuss the incidence, timing and relationship between AF and CS, how to select patients for monitoring and the value and limitations of different monitoring strategies. We will also discuss the

role of empirical anticoagulation, and AF burden as a means of tailoring anticoagulation in patients at high risk of bleeding.

CS versus Embolic Stroke of Undetermined Source (ESUS)

CS refers to ischemic strokes which lack a clearly determined mechanism.¹⁷ The reported incidence of CS varies considerably across studies from 20%–40% of all strokes. This wide variation can in part be explained by the lack of a generally accepted definition of CS.¹⁸ The TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification identifies three situations where a patient may be deemed to have had a CS (or stroke of undetermined origin in TOAST terminology).¹⁹ Firstly, if the diagnostic assessment is incomplete, secondly if no cause is found despite extensive assessment and thirdly if no single cause can be isolated because there are multiple plausible causes of stroke identified. In this review we will focus on the second group of patients where no cause was found despite extensive assessment. Even within this group the term CS is not used in a standardized fashion, nor is the work up after stroke universally agreed upon. In order to circumvent these limitations, the concept of ESUS has been established to refer specifically to the subset of cases where the etiology of the stroke has been investigated following

a standardized pathway but the cause remains unknown.¹⁸ In order to be diagnosed with ESUS, patients must have undergone a series of investigations which include imaging of the brain (CT/MRI), an electrocardiogram, a transthoracic echocardiogram, a twenty-four hour Holter cardiac rhythm monitor and imaging of both the extra- and intra-cranial arteries supplying the area of brain ischemia. ESUS is diagnosed in patients with non-lacunar brain infarcts without intracranial or extracranial atherosclerosis (> 50% stenosis of the arteries supplying the area of ischemia) or a major-risk cardioembolic source and where no other specific cause of stroke is identified (Table 1).²⁰

The majority of the current literature refers to CS, however, this term is problematic as it is non-specific and does not label the reason why a cause of stroke was not identified or specify the work-up performed. ESUS is arguably a more useful and specific term when referring to patients who have undergone a work-up that has failed to reveal most common etiologies of stroke. The restricted definition of ESUS is also more useful in clinical trials.

These semantic differences aside, the risk of recurrent stroke after ESUS or CS is at least as high as other forms of ischemic stroke and appropriate secondary preventive measures are needed in this large population of patients.²¹

Incidence of AF detection after CS

There has been a wide variation of reported incidence AF following stroke ranging from 10%–30% of strokes.^{7,9,22–25} Some of this variation can be explained by the differences in study design, inclusion and exclusion criteria, differing monitoring strategies and the lack of consistency in follow-up duration. The highest incidence of AF has been identified using insertable cardiac monitoring (ICM) devices over an extended duration in patients with CS (Table 2).^{22,26,27}

The EMBRACE trial, a large prospective trial, studied 572 patients with CS or TIA, aged > 55 years and without a pre-existing diagnosis of AF. Patients were randomly assigned to undergo non-invasive ambulatory electrocardiography monitoring with

Table 1. Cryptogenic stroke (CS) versus embolic stroke of undetermined source (ESUS)

CS
Diagnostic assessment incomplete; or
No cause found despite extensive assessment; or
Multiple potential causes, e.g., concurrent atrial fibrillation and relevant high grade stenosis of precerebral artery
ESUS
Stroke etiology remains unknown despite all of following investigations:
Brain imaging (CT/MRI)
Electrocardiogram
Transthoracic echocardiogram
24-hour Holter cardiac monitor
Imaging of extra and intra-cranial arteries

Table 2. Summary of studies/trials that investigated the incidence of atrial fibrillation detection following cryptogenic stroke

Study	Sample size	Study design	Incidence of AF detection
EMBRACE trial	n = 572	Randomized control study	At 90 days: 16.1% of intervention group (non-invasive ambulatory electrocardiogram monitoring) vs. 3.2% of control group
CRYSTAL AF trial	n = 441	Randomized control study	At 6 months: 8.9% of intervention group (insertable cardiac monitor [ICM]) vs. 1.4% of control group 12 months: 12.4% of intervention group vs. 2% of control group 36 months: 30% of intervention group vs. 3% of control group
Ziegler et al. (2015)	n = 1,247	Retrospective cohort analysis	30 days: 4.6% of patients with ICM 182 days: 12.2% of patient with ICM

either a 30-day event triggered recorder (intervention group) or a conventional 24-hour monitor (control group). This study identified a detection rate of AF of 16.1% in the intervention group compared with 3.2% in the control group within 90 days of randomization (95% confidence interval [CI], 8.0–17.6; $P < 0.001$).²⁸

CRYptogenic Stroke And underLYing AF (CRYSTAL AF) trial, a randomized control study which assessed whether long-term monitoring with an insertible cardiac monitor was more effective than conventional follow-up in patients with CS, found that by six months 8.9% of the patients in the ICM group compared to 1.4% in the control group had been diagnosed with AF.²² CS in the CRYSTAL AF trial was diagnosed differently than in EM-BRACE: transesophageal echocardiography, intracranial vascular imaging and coagulation tests (in selected patients) were mandatory in addition to Holter/telemetry. By twelve months, the incidence of AF detection increased to 12.4% in the ICM group compared with 2% in the control group, and at 36 months, the rates of AF detection were 30% in the continuous monitoring arm versus 3% in the control group.²²

One recent study examined a large ($n = 1,247$), real-world population of patients with ICMs inserted for detection of AF following loosely defined criteria CS.²⁹ This study found an increased rate of detection of AF compared with the CRYSTAL AF trial. Detection rate of AF was 4.6% and 12.2% at 30 and 182 days respectively.²⁹ This represents a 37% relative increase in the rate of detection at 6 months compared with the CRYSTAL AF trial.

A recent systematic review and meta-analysis suggest that AF may be detected in up to 25% of TIA and stroke patients.²⁵

Timing of AF and stroke

The temporal relationship between occult AF and stroke is controversial.^{30,31} The detection of AF on cardiac monitoring does not prove causality and while in the majority of situations it could represent the etiology of the stroke, alternative explanations and stroke mechanisms may occur.³² Occult AF may be an incidental finding in a population that shares many common risk factors with ischemic stroke.³³ Alternatively, it has been postulated that AF may be the consequence of certain types of stroke.³¹ Strokes involving the insular cortex are at increased risk of generating neurogenic AF. Strokes in this region, which has a substantial role in the regulation of cardiac rate and rhythm, lead to changes in sympathovagal balance and may result in an arrhythmogenic effect. In such cases the risk of AF is significantly higher in the initial post-stroke period, however, may subside to a level of baseline population risk after a few weeks as the neurogenic autonomic and inflammatory mechanisms triggering AF dissipate. This finding has potential implications for treat-

ment. This mechanism of AF is possibly transient, self-limiting and non-recurrent thus potentially may not necessitate life-long anticoagulation. In practice, however this potential mechanism is difficult to prove and currently there is no evidence that patients with new onset AF in the context of insular infarction should be treated differently.

Evidence to support a temporal link between AF and ischemic stroke has been questioned in smaller studies^{34,35} Recently, however, a larger cohort study in patients with implantable devices found a strong association between AF burden of > 5.5 hours and short term risk of ischemic stroke (odds ratio 4.21; 95% CI, 1.53–3.44).³⁰ The risk was highest in the initial 5–10 days following the episode of AF and by 30 days following the event was no longer elevated. The finding of a marked but short-term increased risk of stroke may provide evidence for targeted intermittent anticoagulation using rapidly acting anticoagulants, exclusively during the high-risk period for stroke prevention.³⁶ Trials are planned to compare intermittent, monitoring based “on demand” anticoagulation versus chronic anticoagulation, especially in patients with a low burden of AF.

Threshold of AF burden

There is no general agreement or consistent data to determine the relationship between the duration of AF detected on monitoring and the stroke risk, with different studies quoting different thresholds of AF required to increase risk. In a non-stroke population the TRENDS study found that a burden of greater than 5.5 hours on any given day during the preceding 30 days conferred double the risk of thromboembolism.¹¹ Low atrial tachycardia/AF burden (< 5.5 hours on each preceding day) resulted in a thromboembolism risk similar to not having AF/atrial tachycardia. However, other studies have quoted a much lower burden to increase stroke risk. The SURPRISE study found that 1–4 hours increased risk and the MOST study identified that atrial tachyarrhythmia of more than five minutes at least doubled the incidence of stroke or death.^{37,38}

Identifying patients at risk of AF after CS or TIA

Identifying a key patient population that would be likely to benefit from long-term cardiac monitoring is important so as to increase the yield of the investigation and ensure cost-effectiveness. However, within the literature there remains considerable contention regarding which risk factors are clinically useful. A number of proposed risk factors have been considered including clinical features, electrocardiographic parameters, echocardi-

graphic abnormalities and radiographic evidence.

A number of clinical features that may represent independent risk factors for a new diagnosis of AF after TIA or stroke have been studied. These include age, diabetes mellitus, arterial hypertension, dyslipidemia, smoking, CHADS₂ score and CHA₂DS₂-VASc score.

Advanced age has been consistently identified as an independent risk factor for AF post CS and this finding has been presented in a number of different studies.^{6,24,39,40} A recent study investigated predictors of AF in CS or TIA in 221 patients who received an ICM. This study evaluated a number of demographic and clinical features and found that increased age was the only clinical feature that was independently associated with increased incidence of AF during follow-up.⁴⁰ This finding was supported by other studies.^{24,39}

While CHADS₂/CHA₂DS₂-VASc score has been found to increase the risk of AF,⁴¹ this parameter has not been recognized as a significant risk factor in the post-CS setting.^{24,40} This may be due to sample size issues or the high prevalence of elevated CHADS₂/CHA₂DS₂-VASc score in this secondary prevention population.

Electrocardiographic findings could be a simple and effective method for selecting patients who should undergo further monitoring. There is growing evidence for the importance of atrial premature contractions.^{5,28,42} A recent prospective cohort sub-analysis of the EMBRACE study found that the number of atrial premature beats on a routine 24-hour Holter electrocardiogram was a strong dose-dependent predictor of prevalent subclinical AF.²⁸ The detection rate incrementally increased from <9% in patients with < 100 atrial premature beats per 24 hours, to 40% among patients with 1,500 atrial premature beats.²⁸ A prolonged PR interval on electrocardiogram was independently associated with increased risk of detecting AF in CS or TIA.⁴⁰

Echocardiographic parameters have been explored for their role in increasing the likelihood of AF following CS.^{43,44} Interestingly, compared to patients with a left atrium within the normal limits, moderate to severe left atrial enlargement increased the risk of recurrent cryptogenic or cardioembolic stroke, however, no interaction has been found between left atrial enlargement and AF.⁴⁴ This study suggests that the effect of left atrial enlargement on recurrent CS and cardioembolic stroke may be mediated by a mechanism independent of AF.⁴⁴ Unfortunately, no continuous cardiac monitoring was performed in this study to conclusively prove this contention. In addition to size, left atrial morphology has been evaluated. A single lobed left atrial appendage predominated in CS patients.⁴⁵ Morphologic features of the left atrial appendage may predispose or protect against embolism in patients with established AF.⁴⁶ Four types of left atrial morphology

have been identified: cactus, chicken wing, windstock and cauliflower. Different left atrial appendage morphologies have been correlated with a different risk of stroke or TIA, however, there have been conflicting results as to which morphology confers the most significant stroke risk. Di Biase et al.,⁴⁶ in a retrospective study found that while the chicken wing was the most prevalent morphology, it was least associated with stroke or TIA. The risk of previous stroke or TIA was similar across all other morphologies. In contrast, a prospective study performed by Korhonen et al found a significantly increased prevalence of the "chicken wing" morphology in the stroke subgroup compared with the control group.⁴⁵ The marked discrepancy between these studies may in part be explained by different classification criteria's and overlap between some morphological classes.

Particular radiographic features identified on CT or MRI have been identified as significant for predicting a likely cardioembolic source of stroke. These patterns include multiple areas of acute infarcts, infarcts involving multiple vascular territories and multiple chronic infarcts. However, these radiographic changes have not been consistently identified in the post-CS setting and may be more in keeping with established AF as opposed to occult AF. A retrospective analysis of the brain imaging of 212 patients with CS in the ICM arm of the CRYSTAL AF trial found no clear topographical pattern of acute infarction significantly associated with AF detection after CS.⁴⁷ However, other features such as the identification of coexisting chronic and acute infarcts or leuko-araiosis were found to have a 2-3 times higher rate of AF.⁴⁷ The finding that prior infarction seen on neuroimaging is independently associated with AF is supported by Favilla et al.²⁴

Finally, biochemical markers such as natriuretic peptides are increased in AF and cardioembolic strokes.^{48,49} Pro-B-type natriuretic peptide levels may be highly predictive of incident AF in patients in sinus rhythm and after CS.^{49,50}

Despite significant advances, at present, the decision to strongly pursue AF after TIA or ischemic stroke remains a clinical decision guided by stroke neurologists as to which patients are at increased risk of AF and should undergo further monitoring. No single feature is able to conclusively disprove the presence of AF. Of course, the decision to continue monitoring also depends on the treatment implication of finding AF. It is agreed to investigate only CS patients where the risk-benefit balance would favor the initiation of anticoagulation if AF would be identified.^{7,33}

Monitoring strategies to identify AF after CS or TIA

Having selected appropriate patients for further monitoring of AF after CS, there is currently no uniform consensus on which

modality to use.⁸ A variety of techniques have been utilized including in-hospital monitoring, serial electrocardiographs, Holter monitors, external event or loop recorders²² and more long-term modalities such as cardiac event monitors, recordings from pacemakers or implantable cardiac defibrillations, patient-triggered daily electrocardiographs and mobile cardiac outpatient telemetry.²⁴

External monitoring modalities (for example intermittent hand-held electrocardiogram recordings or long term Holters/mobile cardiac outpatient telemetry) are reliant on patient compliance.^{6,51} Compliance declines if monitoring is prolonged. A systematic review and meta-analysis of three randomized controlled trials and 13 observational studies revealed a significantly higher AF detection with implantable loop recorder devices compared to wearable devices.⁵²

Accepting continuous monitoring strategy as the "gold" standard detection method, it is now possible to compare currently available intermittent techniques and determine its sensitivity with the gold standard using simulation technique. Compared to continuous rhythm monitoring in 168 ICM patients of the CRYSTAL AF trial, such a simulation study found that long-term continuous electrocardiographic monitoring with ICMs was significantly more effective than with any of the simulated intermittent monitoring strategies. For instance the sensitivity of a 30-day event recorder for AF was only 22.8%.²⁶ The rates of AF may have been lower in CRYSTAL AF because it was performed in a clinical trial population and patients were studied relatively late after the stroke.

The current guideline for patients who have experienced an acute CS or TIA is for prolonged rhythm monitoring for 30 days within six months of the index event with a low degree of evidence rating.²³ A monitoring period of 30 days may not be optimal as in CRYSTAL AF more than half of the AF episodes were detected after the initial month of monitoring.²² As such important opportunities for secondary stroke prevention with the introduction of anticoagulation may be missed if monitoring is not prolonged.⁸

Whilst implantable loop recorders are likely to be the most reliable method of screening for occult AF, these devices are slightly invasive and expensive and thus should be used in a select patient population according to the patients risk profile.^{53,54}

Empirical anticoagulation

In light of the inherent difficulties with diagnosing occult AF and the significant opportunity for secondary stroke prevention, empirical anticoagulation in patients with CS has been considered.^{20,55} However, the trends towards reduction in ischemic

stroke are offset by increases in major intra- and extra-cranial hemorrhages, especially with vitamin K antagonists. While novel oral anticoagulants carry a decreased risk of bleeding compared with warfarin, approaching the risk of aspirin, the treatment effect with the novel oral anticoagulants in patients with sinus rhythm remains unknown.⁵⁶ Furthermore, anticoagulation has not been proven to be superior to antiplatelet therapy in patients without AF. Three major trials are currently investigating a strategy of novel oral anticoagulants versus aspirin in patients with ESUS.

Targeted anticoagulation in patients at high risk of bleeding

In patients who are at a significantly increased risk of bleeding, for example patients with high HAS-BLED scores, patients receiving concurrent antiplatelet therapy or those with end stage renal disease, long term anticoagulation may not be safe. With new technologies such as ICM devices, it is possible to monitor for AF burden and make a more accurate and individualized risk-benefit assessment. An option for minimization of anticoagulant risk could be the transient use of oral anticoagulation linked to onset and offset of an episode of AF in patients at high risk of bleeding and low burden of AF. One such study used data from real-world practice setting in patients with AF and ICM devices.⁵⁷ Up to 87% of patients had a low AF burden, classified as presence of AF in < 1% of the time and were therefore eligible to discontinue anticoagulation. During follow-up, no strokes were observed and bleeding occurred only in patients who remained on anticoagulation. This small study provides some initial evidence to support the safe cessation of oral anticoagulation in patients who are at increased risk of bleeding and are being continuously and objectively monitored for AF.

Conclusion

The ability to detect and monitor the presence of AF accurately after TIA and stroke has changed our understanding of the mechanisms underlying CS. These devices will have an impact in the years to come on how the secondary prevention of stroke can be optimized.

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