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REVIEW ARTICLE

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Atrial fibrillation and cryptogenic stroke. What is the current evidence? Role of electrocardiographic monitoring

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Abstract

The diagnosis of cryptogenic stroke is made by exclusion. However, current evidence supports the role of atrial fibrillation episodes as a cause of this condition. Prospective data have demonstrated the benefits of long-term electrocardiographic monitoring to identify atrial fibrillation in association with cryptogenic stroke. This aim of this article was to analyze the contemporary evidence for the possible relationship between atrial fibrillation and cryptogenic stroke and the role of continuous electrocardiographic monitoring to clarify this hypothesis.

KEYWORDS
atrial fibrillation, atrial fibrillation burden, cryptogenic stroke, electrocardiogram, monitoring devices

1 | INTRODUCTION

About 15% to 40% of all ischemic strokes have no identifiable etiology.[1] These cases are defined as cryptogenic stroke (CS). The diagnosis of CS is made by exclusion. In clinical practice, the diagnosis of CS is considered in 3 circumstances: (i) when the diagnostic assessment is incomplete, (ii) when a single cause cannot be determined because there are several reasonable causes, or (iii) when despite extensive assessment, there is no identifiable cause.[2]

Recent studies suggest that atrial fibrillation (AF) is a possible cause of CS. Most of these studies are based on continuous electrocardiographic (ECG) monitoring. However, there is no consensus on the usefulness of ECG monitoring in this setting and many questions about the association between AF and CS remain. We therefore review the evidence favoring an association between AF and CS with emphasis on future steps that make help reaching definitive conclusions.

2 | WHAT WE HAVE LEARNED FROM ECG MONITORING IN PATIENTS WITH CS?

Following a transient ischemic attack (TIA) or stroke event, paroxysmal AF is detected by a single 12-lead electrocardiogram or 24-hour Holter recording in 2% to 4%. If ECG monitoring extends to 24-72 hours, the incidence of AF increases to 18%.[3] Dahal et al[4] carried out a meta-analysis of 4 randomized controlled trials including a total of 1149 patients. Their analysis showed that in comparison with short-term monitoring (≤ 48 hours), prolonged monitoring (≥ 7 days) increases the detection rate of AF episodes lasting ≥ 30 seconds after a CS or TIA (2.5% vs 13.8%, $P < .00001$). The advantage of long-term ECG monitoring over conventional follow-up using serial electrocardiograms or 24-hour Holter was confirmed in the CRYSTAL-AF [5] study. In this investigation, detection rates of new AF with an implanted long-term monitoring recording device were significantly higher than following conventional monitoring: 8.9% vs 1.4% at 6 months, 12.4% vs 2,0% at 12 months, and 30.0% vs 3.0% at 36 months ($P < .001$ for all comparisons).

Although there are recommendations to perform at least 24 hours of ECG monitoring to rule out AF following an ischemic stroke, some studies suggest that this recommendation is poorly accomplished in clinical practice. Edwards et al[6] evaluated the use of ECG monitoring following an ischemic stroke among 17 398 patients from the Ontario Stroke Registry studied between 2003 and 2013. They found that only 30.6% of patients received a 24-hour Holter monitoring and less than 1% received ECG monitoring longer than 48 hours. Based on these results, the researchers concluded that (i)

there is a gap between evidence and practice that favors the overdiagnosis of CS and (ii) the potential underdiagnosis of AF results in missed opportunities for secondary prevention of cerebral infarction with anticoagulants.

3 | WHAT IS THE MEANING OF FIRST EPISODE OF AF AFTER A CS? CAUSALITY, ASSOCIATION, OR RISK FACTOR?

The mere presence of AF discovered within days, weeks, or months following a CS does not establish the etiology of cardiogenic embolism. In fact, there are no published studies that establish this causality. Furthermore, there is evidence that stroke, including lacunar infarcts, may trigger AF episodes.[7]

The ASSERT study [8] included 2580 patients with implanted pacemakers or defibrillators with long-term ECG monitoring capabilities. Fifty-one patients developed a stroke or a systemic embolism. The authors could not find a straightforward temporal relationship between these events and the occurrence of AF. Twenty-six patients with stroke or systemic embolism had subclinical AF. Fourteen cases of this group suffered the arrhythmia 30 days before the index event, 4 patients had AF within 30 days to the index event, and 8 cases showed AF to 101 days after the occurrence of stroke. A recent review article mentions the lack of evidence on the true clinical significance of AF diagnosed de novo in cases of CS. However, there is accumulating evidence on the role of AF burden and the benefits of the anticoagulants use to prevent a new stroke. It should also be noted that there is a clear benefit in the use of anticoagulants in patients with ischemic stroke or prior transient ischemic attacks in whom AF is demonstrated. In this case, the decision of anticoagulation is based on the implementation of the CHA2DS2-VASc score, even if the mechanistic basis of this result is not entirely clear.[9]

Prolonged ECG recordings identify patients with low AF burden (<1% of the monitoring time).[10] This type of AF has a low risk of stroke albeit higher than that of patients without AF. In fact, among patients with 2 years of continuous ECG monitoring as little as one hour of AF doubles the risk of ischemic stroke.[11] Nowadays, there is no consensus whether patients with low AF burden in the setting of a CS will benefit from anticoagulant or antiplatelet drugs. Further studies are needed to clarify this topic. However, Bridge et al[10] propose the use of intermittent anticoagulation in patients at high risk of bleeding and low AF burden who are also continuously and reliably monitored. In this study, there were no patients with stroke, and bleeding events were manifested only in patients who used continuous anticoagulation.

4 | WHICH PATIENTS WILL BENEFIT FROM PROLONGED ECG MONITORING?

Poli et al[12] conducted a study in patients with CS/TIA and assigned them to receive an implantable prolonged ECG monitoring device based on the presence of known risk factors for AF. The authors concluded that selecting patients using this strategy allows identification of AF in 1 of 3 patients within 1 year of monitoring. The stronger predictors of AF after CS were atrial size >45 mm and the presence of atrial ectopic beats. Thijs et al[13] found that the best predictors of AF were (i) a prolonged PR interval and (ii) advanced age. However, they recognized their moderate predictive ability to discriminate patients with and without AF after CS.

A recent review article summarized the main conditions that predispose to develop low AF burden.[10]

1. Increasing age.
2. High CHA2DS2-VASc scores.
3. Cerebral infarction with typical topographic features such as cortical location or multiple vascular territories.
4. Suspicious of left atrial disease (left atrial dilatation, distension, size and morphology of left atrial appendage, P wave dispersion, frequent atrial premature beats, and high levels of NT-proBNP).

Another investigation found that the total atrial conduction time measured by Doppler echocardiography using the PA-TDI interval predicts hidden AF in patients with CS with a sensitivity of 93.8% and specificity of 90.5%. After a multivariate analysis, the last parameter was an independent predictor of hidden AF.[14]

There are other proposed schemes for prediction of paroxysmal AF following an ischemic stroke. One of the best one studied is the iPAB score, which includes a personal history of arrhythmia or antiarrhythmic drug use, atrial dilatation, and elevation of brain natriuretic peptide.[15]

The evidence regarding the monitoring time to be employed in patients with CS for detecting AF is still inconclusive. A recent consensus document recommends "extended ECG monitoring" in patients with CS to detect undiagnosed AF. This expert panel proposes a careful evaluation of each patient prior to device use based on cost-efficacy, patient's acceptance, and compliance.[16] Further investigations are necessary to achieve definitive conclusions, but the recommendation by Montalvo et al[17] of 30 days of ECG monitoring after a CS appears to be a feasible choice in clinical practice.

5 | CONCLUSIONS

Some studies support the relationship between AF and CS, but further studies are necessary to reach definitive conclusions. The use of prolonged ECG monitoring devices is an attractive option for identifying patients with silent AF and for establishing the association between both AF and CS. The degree of AF burden, detected by prolonged ECG monitoring, ultimately dictates the optimal anticoagulation regimen (continuous vs. intermittent anticoagulation following detection of AF episodes) for the prevention of stroke.

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CONFLICT OF INTERESTS

Authors declare no Conflict of Interests for this article.

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