

## Asymptomatic Atrial Fibrillation After Cryptogenetic Stroke Incidence, Clinical Significance, and Therapeutic Implications

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Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with a prevalence of 1% to 2% in the general population; this increases with age, reaching >8% in subjects over 80 years of age.<sup>1,2</sup> The arrhythmia is independently associated with an increased risk of stroke, which is about 5-fold higher in AF-affected patients than in controls.<sup>3</sup> AF is considered to be the cause of ischemic stroke in 15% to 17% of cases.<sup>3,4</sup> Interestingly, AF-related strokes cause higher mortality and disability than strokes unrelated to AF<sup>4,5</sup> and stroke risk is independent of the type of AF (paroxysmal, persistent, or permanent).<sup>6,7</sup> The rate of stroke caused by AF can be significantly reduced (by 60% to 70%) by the use of warfarin or novel oral anticoagulants.<sup>8,9</sup>

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AF is usually symptomatic, causing symptoms, such as palpitations, dyspnea, fatigue, angina, dizziness, and syncope.<sup>10</sup> Not rarely, however, the arrhythmia is not perceived at all by the patient and, in this case, is defined as asymptomatic, silent, undetected, occult, or subclinical AF.

According to the EURObservational Research Programme—AF (EORP-AF) Pilot General Registry, almost 40% of the AF patients who are seen in daily cardiology practice are completely asymptomatic, and another 30% have only mild symptoms.<sup>11</sup> The prevalence of silent AF varies in different clinical settings, ranging from 0% to 31% in postablation patients<sup>12,13</sup> to 16% to 25% as incidental finding at standard ECG,<sup>2,14</sup> 54% to 70% in patients treated with antiarrhythmic drugs, and<sup>15,16</sup> up to 51% to 74% in pacemaker/implantable cardioverter-defibrillator recipients.<sup>17,18</sup>

Stroke is the leading cause of long-term adult disability and mortality in the developed world. Approximately, 30% to 40% of all strokes are cryptogenetic or caused by unknown causes.<sup>19,20</sup> A possible explanation for these strokes is occult or subclinical AF. Several studies have shown that the incidence of silent AF after an undiagnosed stroke may be as high as 5% to 20%.<sup>21</sup> In daily clinical practice, it is important after cryptogenetic stroke to detect episodes of silent AF to start

appropriate anticoagulation therapy and reduce the risk of future events.

In this issue of *Circulation: Arrhythmia and Electro-physiology*, Dussault et al<sup>22</sup> report a systematic review and meta-analysis of electrocardiographic monitoring to detect AF after undiagnosed ischemic stroke or transient ischemic attack. The main purpose of the meta-analysis was to assess the relationship between the duration of ECG monitoring and the proportion of newly diagnosed AF. A total of 31 studies met the inclusion criteria (including 3 randomized controlled trials). The overall proportion of newly detected AF was 7.4%: 5.1% on short (<3 days) and 15% on long (>7 days) ECG monitoring. Extending ECG monitoring from 24 hours to 30 and 180 days increased the detection of AF from 4.2% to 15.2% and 29.15%, respectively. In the 3 randomized controlled trials,<sup>23–25</sup> long-term monitoring was associated with 7.26 odds of detecting AF in comparison with traditional short-term monitoring.

These results clearly show that more is better than less with regard to monitoring for the detection of asymptomatic AF after cryptogenetic stroke and support the recent guideline recommendation of at least 30 days of ECG monitoring after a stroke with undiagnosed cause.<sup>26</sup>

The main limitation of this article is the significant degree of heterogeneity observed among studies and the inability to detect the potential sources of this heterogeneity, despite subgroup analyses performed by the authors on prespecified variables. Indeed, many other factors, besides the length of monitoring, can influence the detection rates of AF in patients with cryptogenetic stroke. These include the definition of AF duration that constitutes an episode (>30 seconds, >2 minutes, >6 minutes, etc), the interval from the index stroke to the start of monitoring (from hours to days or months), and patient characteristics and selection (age and sex of patients, presence of comorbidities, type and burden of AF, value of CHADS<sub>2</sub> or CHA<sub>2</sub>DS<sub>2</sub>-VASc risk score systems, etc).

Despite this limitation, it is evident that silent AF is a common finding in patients with cryptogenetic stroke if prolonged electrocardiographic monitoring is performed soon after the index event, reaching ≤30% at 3 months if an implantable loop recorder is used.<sup>22</sup>

But what is the clinical and prognostic significance of silent AF after cryptogenetic stroke? At present, the literature is lacking in data on this issue; the only information we have is indirect and comes from patients treated with implantable electronic devices (pacemaker, implantable cardioverter-defibrillator, or CRT device) for an arrhythmic problem.<sup>17,18,27–31</sup> In these patients, detection of silent AF by the device is associated with an increased risk of thrombo-embolic events, with a hazard ratio ranging from 2.2 to 9.4.<sup>32</sup> According to a

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recent cohort study, asymptomatic AF is also associated with increased mortality (doubled compared with controls)<sup>33</sup>; the mortality is even higher than that observed in symptomatic AF (9.4% versus 4.2% at 1 year, in the EORP-AF Pilot General Registry).<sup>11</sup> However, it is not yet known what length of silent AF episodes or what amount of silent AF burden convey a substantial risk. Indeed, according to literature data, the length of asymptomatic episodes of AF that is associated with an increased risk of stroke varies from a minimum of 5 minutes in the Ancillary MOST (Mode Selection Trial)<sup>17</sup> to 6 minutes in the Asymptomatic AF and Stroke Evaluation in Pacemaker Patients and the AF Reduction Atrial Pacing Trial (ASSERT),<sup>30</sup> 1 hour in the SOS-AF (Stroke Prevention Strategies Based on AF Information From Implanted Devices) Project,<sup>31</sup> 3.8 hours in the Home Monitor CRT trial,<sup>29</sup> 5.5 hours in the prospective study of the clinical significance of atrial arrhythmias detected by implanted device diagnostics (TRENDS) trial,<sup>28</sup> to a maximum of 24 hours in the Italian AT500 Registry.<sup>18</sup> From these data, it seems evident that the episode duration and burden of asymptomatic AF that best predict subsequent stroke are still matters of debate and need to be addressed by future studies.

Another important issue is the relationship between silent AF and stroke; in other words, is silent AF the direct cause of the stroke or just a marker of an increased risk? The TRENDS, ASSERT, and the multicenter randomized study of anticoagulation guided by remote rhythm monitoring in patients with implantable cardioverter-defibrillator and CRT-D devices (IMPACT) trials have tried to answer this question by investigating the temporal relationship between device-detected AF and thrombo-embolic events.<sup>34–36</sup> In the majority of patients (73% to 94%), no AF was found on device recordings in the 30 days before the thrombo-embolic event. Moreover, when AF was detected, this happened >30 days before thrombo-embolic events in 29% to 50% of cases and after thrombo-embolic events in 3% to 16% of cases.<sup>32</sup> These results indicate that a proximate temporal relationship between asymptomatic AF and stroke occurrence does not exist and suggest that silent AF is not the direct cause of the stroke in the majority of cases of device-detected AF.

These results also call into question our current understanding of how AF causes embolic events. It is likely that multiple mechanisms contribute to stroke in patients with asymptomatic AF.<sup>34</sup> In some cases, stroke may be caused by stasis from an actual AF episode, in others, to chronic atrial and endothelial changes caused by multiple prior AF episodes; and in other cases again, to non-AF mechanisms. In these latter cases, it may be that the AF is simply a marker of increased stroke from any cause because of its relationship to other comorbidities, such as heart failure, hypertension, diabetes mellitus, occult atrial myopathy, endothelial dysfunction, or other vascular disease risk factors summarized by the CHA<sub>2</sub>DS<sub>2</sub>-VASc scoring system.

The uncertain causal relationship between asymptomatic AF and stroke also raises the issue of the therapeutic implications of this arrhythmia. From a therapeutic point of view, the detection of asymptomatic AF in patients with cryptogenetic stroke is important to establish the need for oral anticoagulation. In these patients, the detection of asymptomatic AF may allow early initiation of anticoagulation, instead of the usual care with antiplatelet therapy, and may lead to a reduction in the risk of recurrent stroke. However, it is important to point

out that no prospective randomized trials using oral anticoagulation have been performed in this field to date. Furthermore, the lack of a proximate temporal relationship between asymptomatic AF and stroke observed in the majority of patients in the ASSERT, TRENDS, and IMPACT trials<sup>34–36</sup> suggests that oral anticoagulation may not be systematically required for stroke prevention in asymptomatic patients. However, it is common opinion that anticoagulation is indicated in patients with cryptogenetic stroke and asymptomatic AF because a history of prior stroke already confers a high thrombo-embolic risk (CHA<sub>2</sub>DS<sub>2</sub>-VASc score of at least 2), which itself should prompt the use of oral anticoagulants according to current American and European guidelines.<sup>26,37</sup>

In conclusion, prolonged electrocardiographic monitoring, especially the use of an implantable loop recorder, enables silent AF to be detected in a high proportion of patients with cryptogenetic stroke (≤30%) and should be encouraged and preferred to conventional short-term monitoring. Although the prognosis of asymptomatic AF seems to be the same as—or even worse than—that of symptomatic AF, further trials are needed to establish the length and burden of silent AF episodes that convey a greater risk of stroke. Finally, despite the lack of randomized trials on the benefit of oral anticoagulation therapy, it is reasonable to prescribe this therapy for patients with cryptogenetic stroke and silent AF, who are, by definition, at high risk of recurrent thrombo-embolic events.

## Disclosures

None.

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