

## Atrial Fibrillation and the Risk of Stroke Does Timing Matter?

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Stroke is the most concerning complication of atrial fibrillation (AF) as it leads to significant morbidity and mortality. Given the aging population and increasing burden of cardiovascular comorbidities, the overall prevalence of AF is increasing across the world.<sup>1,2</sup> In addition, evolving medical technology and cardiac implantable electronic devices (CIED) have enhanced our ability to identify subclinical AF. These devices have the potential to identify asymptomatic AF patients, who are at risk for thromboembolic complications and may benefit from anticoagulation therapy.

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Multiple studies using CIEDs have demonstrated that short durations of asymptomatic AF are associated with an increase in thromboembolic risk.<sup>3-9</sup> One of the initial studies that evaluated the burden and timing of subclinical AF as a risk factor for stroke was the Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT), which consisted of 2580 hypertensive patients (mean CHADS<sub>2</sub> score 2.3) without any history of clinical AF.<sup>4</sup> All patients had dual-chamber devices, and the primary analysis assessed atrial arrhythmias for >6 minutes in the 3-month postprocedural period. Approximately 10% of participants had AF identified during this timeframe. After a median follow-up of 2.5 years, the annualized thromboembolic rate was 1.7% in those individuals with CIED-detected AF when compared with 0.7% in controls, corresponding to a 2.5-fold increased hazard of stroke associated with AF episodes >6 minutes in duration.<sup>4</sup> In addition to correlating the overall burden or duration of AF and stroke risk, the ASSERT investigators evaluated the timing of AF episodes and thromboembolic risk. Of the 51 patients from the ASSERT study that had an ischemic stroke or other embolic event, only 51% or 26 patients had subclinical AF. Of these 26 patients with AF, only 4 had AF within 30 days and only 1 had AF at the time of the stroke.<sup>10</sup>

Another important study that provided similar insight with respect to the burden and timing of paroxysmal AF and stroke

risk included TRENDS, which was a prospective, observational cohort of 2813 patients with at least 1 stroke risk factor.<sup>3</sup> The primary analysis of this study evaluated whether CIED-detected AF over a 30-day period was associated with thromboembolic risk. Nearly 15% of this population had a previous thromboembolic event, 20% had a history of AF, and the mean CHADS<sub>2</sub> score was 2.2. After a mean follow-up of 1.4 years, there were 40 thromboembolic events including 20 ischemic strokes. The investigators demonstrated a trend toward increased stroke risk with AF episodes lasting at least 5.5 hours during the 30-day period before the stroke event.<sup>3</sup> Further analysis evaluated the temporal relation of CIED-detected AF and stroke in TRENDS and demonstrated that only 11 of the 40 patients who developed a thromboembolic complication had an episode of AF within a month of the event.<sup>11</sup> Similar to the ASSERT study, the majority of patients with stroke (73%) did not have any CIED-detected atrial arrhythmias in the month before the stroke.

The limited number of thromboembolic events in previous studies precludes a thorough understanding on whether AF episodes are temporally related to increases in the risk of stroke. The current study by Dr Turakhia et al<sup>12</sup> addresses this issue by evaluating continuous cardiac rhythm monitoring over 120 days before an ischemic stroke in 187 patients. The unique study design and robust analysis deserve additional examination. First, administrative and electronic medical records for ≈10000 patients from the Veterans Affairs Healthcare System were linked to the Veterans Affairs National Cardiac Device Surveillance Program's remote monitoring data, which included an individual's daily AF burden. Furthermore, the case-crossover design is a unique and informative approach for studying the transient effects of AF on the risk of stroke.<sup>13</sup> This study design is similar to a case control analysis; however, instead of a separate control population, each subject contributes an exposure time to both a case and control period. As a result, this study design is highly efficient because each case serves as its own control (ie, matched). One challenge in matched designs is that the number of discordant pairs, which are the instances where there is a difference in AF burden between the case and the control period, is a key driver of statistical power. Thus, it is important to select exposures of interest that not only exhibit variability within a wide time window but also select control periods that are sufficiently distant in time from the case period to minimize their association with the outcome of interest (ie, stroke).

In the primary analysis, these investigators identified 187 patients with ischemic strokes and at least 120 days of continuous monitoring before the event. Exposure time in the case period corresponded to days 1 to 30 before the stroke, and exposure time in the control period reflected days 91 to

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120 before the stroke. There were 13 patients (7% of patients with stroke), who had  $\geq 5.5$  hours of AF recorded on at least 1 day in the case period only. Furthermore, 3 patients (1.6% of patients with stroke) had  $\geq 5.5$  hours of AF recorded on at least 1 day in the control period only. The odds ratio for ischemic stroke associated with an AF burden  $\geq 5.5$  hours in the case versus control period was 5.22 after adjustment for warfarin use. These investigators also evaluated 5-day time periods to develop a better understanding between the proximity of AF and odds of stroke. The case period was divided into 12 sequential 5-day increments (days 1–5; days 6–10, etc) spanning the 60-day period before the stroke and compared with 6 matched 5-day control periods corresponding to days 91 to 120 before the stroke. The risk of stroke was highest within 5 days of the episode of AF, and the risk declined steadily with longer periods after the episode of AF.

The findings from the current analysis suggest a temporal association between the proximity of AF and the risk of ischemic stroke. These findings seem to contradict the analyses from the ASSERT and TRENDS studies in which the majority of AF-related, thromboembolic events did not have an episode of AF in the month before the event. Both ASSERT and TRENDS had a limited number of thromboembolic events compared with the 187 ischemic strokes evaluated in the current analysis. As such, the study by Turakhia et al<sup>12</sup> provides important insight into the temporal correlation between several hours of AF and stroke risk. Some caution remains necessary while interpreting the longer term risks of stroke in patients with clinical or CIED-detected AF. Arrhythmia evaluation in the current study was limited to the 120-day period before the stroke event. In ASSERT, CIED-detected AF was associated with thromboembolism after  $>2$  years of follow-up. Thus, the control period of the present study is likely undersampled, and it will be important to assess whether AF episodes occurring before the 120-day cutoff and a longer duration of time influence the temporal relationships between AF and stroke.

The current analyses also question whether CIED-detected AF confers the same risk of stroke as clinical AF. Nearly 40% of the individuals in this study had a history of AF, and their mean CHA<sub>2</sub>DS<sub>2</sub>-VASc score was 4.8; however,  $<50\%$  were prescribed warfarin therapy. The annualized stroke rate in this analysis was 1.6% and is significantly lower than what we would have expected based on inadequate anticoagulation treatment.<sup>1</sup> One partial explanation may be that anticoagulation use was underascertained. It is also interesting to note that this lower stroke rate is consistent with the observed, event rates from other CIED studies.<sup>3,4</sup> As such, the natural question is whether CIED-detected AF is inherently different from clinically detected AF. The original analysis of the CHADS<sub>2</sub> scoring system and stroke event rate and subsequent refinements including validation studies place the stroke rates up to 3-fold higher than what was observed in the current and other CIED studies.<sup>14–17</sup>

From a clinical stand point, current guidelines regard the risk of thromboembolism as independent of the frequency or duration of AF.<sup>1</sup> Although CIED-detected AF seems to be associated with a lower thromboembolic event rate than clinical AF, it seems appropriate to prescribe anticoagulation especially for patients at intermediate to high risk based on

the various risk scores. One interesting question will be how does AF burden influence anticoagulation therapy in lower risk individuals such as those with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 0 or 1? One previous study proposed that AF burden helped to determine stroke risk in patients who were otherwise considered low thromboembolic risk.<sup>9</sup> In an analysis of  $>550$  patients with dual-chamber pacemakers, thromboembolism developed in 14 patients over a 1-year follow-up. A higher, 24-hour burden of AF was associated with an increased thromboembolic risk for patients with a CHADS<sub>2</sub> score of 1 or 2. AF burden, however, did not help to differentiate stroke risks among individuals with a CHADS<sub>2</sub> score that was equal to 0 or  $>2$ . Additional studies and trials will be necessary to assess whether CIED-detected AF may help to stratify thromboembolic risk, especially in low to intermediate risk patients.

Several ongoing studies are evaluating anticoagulation use that is guided by the detection of paroxysmal AF using electronic devices. The Oral Anticoagulation Therapy (OAT) Pilot Study (ClinicalTrials.gov identifier NCT01959425) is a relevant trial that focuses on high-risk AF patients (CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 3$ ), who have undergone successful ablation and remain free of AF after 3 months. AF in this study is defined as either a clinical episode or asymptomatic AF of  $>30$  seconds on remote monitoring. Eligible participants are randomized to continued anticoagulation or withdrawal of anticoagulant therapy. The primary outcome is a first thromboembolic event over a 1-year period. In addition, the TACTIC AF (Safety Study on Stopping Anticoagulation Medication in Patients With a History of Atrial Fibrillation; ClinicalTrials.gov identifier NCT01650298) is a CIED-guided, safety study on discontinuing anticoagulation therapies in patients with a history of AF. The study is enrolling patients with a CIED and paroxysmal AF, who are receiving novel oral anticoagulation therapy, and will assess whether it is safe to discontinue anticoagulation based on information from the CIED.

In summary, the study by Turakhia et al<sup>12</sup> is thought provoking and suggests a transient, temporal risk of ischemic stroke after several hours of AF. Additional studies will help to determine whether the burden and timing of CIED-detected AF can help to stratify thromboembolic risk and tailor anticoagulation therapy. The advent of rapidly acting oral anticoagulants certainly provides the opportunity for intermittent medication use that is guided by the detection of AF, especially in lower risk populations. Studies should also assess more broadly whether CIED-detected AF results in an increase in other cardiovascular events and hospitalizations especially in selected populations.

## Disclosures

None.

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