Atrial Fibrillation and the Risk of Stroke
Does Timing Matter?

Parin J. Patel, MD; Rajat Deo, MD, MTR

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.\(^1,2\) 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.

Multiple studies using CIEDs have demonstrated that short durations of asymptomatic AF are associated with an increase in thromboembolic risk.\(^3,4\) 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\(_2\) score 2.3) without any history of clinical AF.\(^4\) 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.\(^4\) 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.\(^5\)

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.\(^6\) 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\(_2\) 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.\(^7\)

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.\(^7\) 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\(^8\) 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 \(\approx\)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.\(^9\) 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...
120 before the stroke. There were 13 patients (7% of patients with stroke), who had ≥5.5 hours of AF recorded on at least 1 day in the control period only. Furthermore, 3 patients (1.6% of patients with stroke) had ≥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 ≥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 al12 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 CHA2DS2-VASc score was 4.8; however, <50% were prescribed warfarin therapy. The annualized stroke rate in the TRENDS 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 CHA2DS2-VASc score was 4.8; however, <50% were prescribed warfarin therapy. The annualized stroke rate in the TRENDS 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.

In summary, the study by Turakhia et al12 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.

References


Key Words: Editorials • anticoagulation • arrhythmias, cardiac • atrial fibrillation • cardiac implantable electronic devices • stroke
Atrial Fibrillation and the Risk of Stroke: Does Timing Matter?
Parin J. Patel and Rajat Deo

*Circ Arrhythm Electrophysiol.* 2015;8:1002-1004
doi: 10.1161/CIRCEP.115.003367

*Circulation: Arrhythmia and Electrophysiology* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3149. Online ISSN: 1941-3084

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circep.ahajournals.org/content/8/5/1002

**Permissions:** Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation: Arrhythmia and Electrophysiology* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

**Reprints:** Information about reprints can be found online at:
http://www.lww.com/reprints

**Subscriptions:** Information about subscribing to *Circulation: Arrhythmia and Electrophysiology* is online at:
http://circep.ahajournals.org//subscriptions/