Title

Are device-detected atrial high-rate episodes a risk marker for stroke?

Journal

Nature Cardiovascular Research, 2(12)

Authors

Hanna, Peter
Buch, Eric
Shivkumar, Kalyanam

Publication Date

2023-12-01

DOI

10.1038/s44161-023-00383-y

Peer reviewed

Published in final edited form as:
Nat Cardiovasc Res. 2023 December ; 2(12): 1097–1098. doi:10.1038/s44161-023-00383-y.

Are device-detected AHREs a risk marker for stroke?

Peter Hanna, MD, PhD[1,2], **Eric Buch, MD, MS**[1], **Kalyanam Shivkumar, MD, PhD**[1,2]

[1]University of California Los Angeles (UCLA) Cardiac Arrhythmia Center, UCLA, Los Angeles, CA, USA

[2]Neurocardiology Research Program of Excellence, David Geffen School of Medicine, UCLA, Los Angeles, CA, USA

STANDFIRST:

Continuous cardiac rhythm monitoring via cardiac implantable electronic devices and other wearable monitors has identified an increased number of patients with asymptomatic atrial fibrillation. However, not all patients with device-detected AHREs are alike, and fine-tuning risk assessment may help identify those patients that benefit the most from anticoagulation."

Although screening for atrial fibrillation (AF) in the general population has not been shown to improve health outcomes,[1] continuous cardiac rhythm monitoring via cardiac implantable electronic devices (CIEDs) provides a unique opportunity to detect AF with remarkable sensitivity. However, CIED data presents a conundrum of whether to initiate anticoagulation in patients with atrial tachyarrhythmias other than sustained AF or atrial flutter. These atrial high-rate episodes (AHREs) are found in 30 to 60% of patients with CIEDs and may represent a precursor to atrial fibrillation (AF) that merits anticoagulation.[2] The Asymptomatic AF and Stroke Evaluation in Pacemaker Patients and the AF Reduction Atrial Pacing Trial (ASSERT) showed that, in 2580 patients 65 years or older with hypertension and no history of AF, AHREs (defined as episodes of atrial rate >190 beats per minute for at least 6 minutes) identified on pacemaker or implantable cardioverter-defibrillator was associated with twice the risk of ischemic stroke over a mean follow-up of 2.5 years.[3] Despite this strong association, it remains unclear whether oral anticoagulation reduces stroke risk in patients with device-detected AHREs.

Kirchof *et al.* recently published a double-blind, double-dummy, randomized trial of patients 65 years or older with AHREs detected on their implanted cardiac devices that sought to answer whether patients with AHREs would benefit from anticoagulation.[4] In this study across 18 European countries, 2536 patients 65 years or older were randomized in a 1:1 ratio to receive edoxaban or placebo. The median CHA_2DS_2-VASc score was 4, AHREs generally showed atrial rates greater than 200 beats per minute, and ECG-diagnosed AF developed in 462 patients (8.7% per patient-year). After a median follow-up of 21 months, the study was terminated early due to safety concerns and evidence of futility on

---

Address for correspondence: Kalyanam Shivkumar MD PhD, UCLA Cardiac Arrhythmia Center, 100 UCLA Medical Plaza, Suite 660, Los Angeles, CA 90095, Fax: 310-825-2092.

Competing Interests: University of California, Los Angeles has patents developed by KS relating to cardiac neural diagnostics and therapeutics. KS is a consultant for Nference Inc & Anumana Inc. PH and EB have no disclosures.

interim assessment. A primary outcome event, defined as a composite of cardiovascular death, stroke, or systemic embolism, occurred in 83 patients (3.2% per patient-year) in the edoxaban group vs 101 patients (4.0% per patient-year) in the placebo group (hazard ratio [HR] 0.81; 95% confidence interval [CI], 0.60 to 1.08; p=0.15). A safety outcome event, defined as a composite of death from any cause or major bleeding, occurred in 149 patients (5.9% per patient-year) in the edoxaban group vs 114 patients in the placebo group (4.5% per patient-year; HR 1.31; 95% CI, 1.02 to 1.67; p=0.03).

The findings in the current study mirror those from ambulatory ECG monitoring studies. The AF Detected by Continuous Electrocardiogram Monitoring Using Implantable Loop Recorder to Prevent Stroke in High-Risk Individuals (LOOP) study was a randomized controlled trial in which patients aged 70–90 years with at least one additional stroke risk factor and asymptomatic AF greater than 5 minutes identified by insertable cardiac monitor were anticoagulated.[5] While continuous monitoring with an insertable cardiac monitor increased the number of patients diagnosed with asymptomatic AF, anticoagulating those patients did not significantly decrease the primary endpoint of stroke or systemic arterial embolism (HR, 0.80; 95% CI, 0.61–1.05).

These trials highlight the challenges of identifying clinically relevant AHREs. CIED-detected AHREs do not necessarily represent AF and could be caused by oversensing or other atrial tachyarrhythmias that warrant close evaluation of the electrograms.[2] Arrhythmias such as atrial tachycardia that result in rapid but organized atrial activation might confer a lower risk of thromboembolism. Furthermore, the ASSERT study demonstrated that those patients with longer AHRE greater than 24 hours had significantly higher risk of ischemic stroke or systemic embolism with an absolute risk of 3.1% per year, similar to the risk of clinical AF.[6] The median duration of AHREs at 2.8 hours in the current study may explain the lack of demonstrated benefit of anticoagulation.

Identifying those patients in whom AHREs are clinically relevant is fraught with challenges. The use of the CHA_2DS_2-VASc score, a risk assessment tool validated in patients with a diagnosis of AF,[7] has not been validated in predicting stroke risk in patients with AHREs. While the event rate of ischemic stroke of about 1% per patient-year in both groups in the current study is on par with those described in other studies of AHREs,[2] this is about one-fifth of what would be expected in a cohort of AF patients with a CHA_2DS_2-VASc score of 4.[8] In assessing stroke risk, one may suppose that patients seemingly at higher risk of stroke may derive greater benefit from anticoagulation. Conversely, the LOOP study subgroup analysis indicated that patients without prior stroke who were anticoagulated had reduced rates of ischemic stroke compared to those patients with prior stroke.[9] Overall, the low event rate, which was in part due to the early termination of the study, stymied the power to detect a small benefit of anticoagulation. By comparison, the STROKESTOP study, a multicenter, parallel group, unmasked randomized controlled trial in 7165 patients undergoing intermittent ECG monitoring over a 14-day period demonstrated a statistically significant but small benefit of anticoagulation in patients with silent AF after a median follow-up of 6.9 years.[10] The recently published ARTESIA randomized controlled trial did demonstrate a 37% relative reduction in stroke or systemic embolism with the use of apixaban (0.78% per patient-year versus 1.24% per patient-year in the placebo (aspirin)

group) for subclinical AF lasting 6 minutes to 24 hours after a shorter median follow-up of 3.5 years.[11] However, apixaban use also resulted in increased major bleeding (1.71% per patient-year in the apixaban group vs 0.94% per patient-year in the aspirin group).

The increasing amount of data available to the clinician via CIEDs and newer wearable monitors presents a dilemma. While such monitoring has identified an increased risk of stroke, demonstrating benefit of anticoagulation has been challenging. Fine-tuning risk assessment such as identifying predictors of those patients that subsequently develop ECG-diagnosed AF or differentiating AHREs based on frequency or duration may help identify those patients that benefit the most from anticoagulation. In contrast to the present study, just over three decades ago, several randomized controlled trials (AFASAK, SPAF, BAATAF and SPINAF)[12] evaluating anticoagulation in atrial fibrillation were terminated early due to clear demonstration of clinically significant benefit. Akin to the observation at the time that lone atrial fibrillation is associated with low risk of stroke, AHREs may similarly be associated a low risk that is challenging to improve upon with anticoagulation.[13]The low event rates associated with AHREs suggests that larger studies with longer follow-up times would be needed to show even a small benefit. While it may be tempting for clinicians to treat AHRE similarly to AF, current data suggest that these may be distinct arrhythmia patterns with different risk profiles.

Acknowledgements:

PH was supported by AHA Career Development Award 23CDA1039446. KS was supported by NIH P01HL164311 and R01HL162921

References

1. Force, U.S.P.S.T., et al. JAMA 327, 360–367 (2022). [PubMed: 35076659]
2. Freedman B, et al. Circulation 135, 1851–1867 (2017). [PubMed: 28483832]
3. Healey JS, et al. N Engl J Med 366, 120–129 (2012). [PubMed: 22236222]
4. Kirchhof P, et al. N Engl J Med 389, 1167–1179 (2023). [PubMed: 37622677]
5. Svendsen JH, et al. Lancet (London, England) 398, 1507–1516 (2021). [PubMed: 34469766]
6. Van Gelder IC, et al. Eur Heart J 38, 1339–1344 (2017). [PubMed: 28329139]
7. Lip GY, Nieuwlaat R, Pisters R, Lane DA & Crijns HJ Chest 137, 263–272 (2010). [PubMed: 19762550]
8. Friberg L, Rosenqvist M & Lip GY Eur Heart J 33, 1500–1510 (2012). [PubMed: 22246443]
9. Diederichsen SZ, et al. JAMA Neurol 79, 997–1004 (2022). [PubMed: 36036546]
10. Svennberg E, et al. Lancet (London, England) 398, 1498–1506 (2021). [PubMed: 34469764]
11. Healey JS, et al. N Engl J Med (2023).
12. Shivkumar K, Jafri SM & Gheorghiade M Prog Cardiovasc Dis 38, 337–342 (1996). [PubMed: 8552791]
13. Chesebro JH, Fuster V & Halperin JL N Engl J Med 323, 1556–1558 (1990). [PubMed: 2233936]