Everything Counts in Large Amounts
Device-Detected Atrial High-Rate Arrhythmias

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Although the risk of stroke associated with paroxysmal atrial fibrillation (AF) is comparable to that with persistent (or permanent) AF, the lower representation of patients with paroxysmal AF in clinical trials reduces the confidence of the risk estimate.1 As a group, patients with paroxysmal AF are heterogeneous but typically younger, with less advanced associated cardiovascular disease than those with persistent or permanent AF. Episodes of AF occur daily in some patients but in others are separated by months or even years, and the duration of episodes varies considerably as well. Nevertheless, the threshold burden of paroxysmal AF required to justify chronic anticoagulant therapy has not been clearly defined, and prophylactic therapy is prescribed less consistently for patients with this form of the arrhythmia.2,3 Clinical practice guidelines currently recommend prophylactic antithrombotic therapy based on the axiom that paroxysmal and persistent AF carry similar risks of thromboembolism. The anticoagulation decision is based on clinical features other than the pattern, chronicity, or duration of AF, specifically the presence or absence of associated valvular heart disease, prior thromboembolism, advanced age, hypertension, diabetes, impaired left ventricular function, or heart failure.4

Even in patients with symptomatic AF, asymptomatic episodes are common.5 In studies of unsolicited patients based on standard surface ECG recordings, the prevalence of asymptomatic AF ranged from 5% to 20%.5,6 Among the challenges in antithrombotic therapy is identifying patients with asymptomatic paroxysmal AF. Longer-term Holter and event monitoring increases the detection of asymptomatic AF, and in the Prevention of Atrial Fibrillation After Cardioversion (PAFAC) trial, nearly 70% of episodes of paroxysmal AF detected by transtelephonic monitoring were asymptomatic.7 Implanted dual-chamber cardiac arrhythmia devices, including pacemakers, cardioverter-defibrillators, and resynchronization devices (CRTs), are capable of continuously monitoring the rhythm. In a study of patients with paroxysmal AF and implanted pacemakers, 38% of episodes of atrial high-rate activity (AHRE; tantamount to AF or atrial flutter) lasting 48 hours or longer were asymptomatic.8 During 24 months of observation in a multicenter study, the incidence of AHRE, most of which was asymptomatic, was 89% and 46% in patients with and without previously documented atrial tachyarrhythmias, respectively.9 The sensitivity and specificity of AHRE detected by arrhythmia devices depend on multiple factors, including criteria for rate and duration, method of detection, atrial and far-field sensitivity, thresholds for mode-switching and other programmed parameters, and certain characteristics of the atrial arrhythmias.10-12 In the MOST trial, the incidence of device-detected AHRE defined by atrial rates of 220 bpm or more lasting 5 minutes or longer was 51% of 312 patients, similar to other studies of patients with pacemakers.13 Detection of this degree of AHRE correlated with a higher stroke rate, and multivariable analyses adjusting for other prognostic factors demonstrated that detection of AHRE raised the risk of death 2.5-fold, the risk of death or nonfatal stroke by a factor of 2.8, and the risk of developing overt AF to nearly 6 times that of patients without AHRE. Another study suggested an increased risk of thromboembolism in patients with device-detected AHRE lasting a day or longer, and the risk rose significantly with the number of stroke risk factors.14 These results are concordant with those in the Italian AT-500 Registry cohort of elderly patients with bradycardia and antiarrhythmic agents, in whom the adjusted risk of thromboembolism was increased 3.1-fold in patients with device-detected AHRE of >24 hours during follow-up.15

In this issue of Circulation: Arrhythmia and Electrophysiology, Glotzer et al16 shed additional light on the importance of atrial tachyarrhythmia burden in predicting thromboembolic events. The purpose of the TRENDS study was to evaluate the relationship between long-term detection of AHRE and thromboembolic events among patients with stroke risk factors and implanted dual-chamber cardiac pacemakers. The overall rate of ischemic events was low in this cohort (1.3% per year), perhaps because some patients were treated with anticoagulant medication (an uncontrolled variable). In a secondary analysis, patients who displayed AHRE (atrial rates >175 bpm lasting >20 seconds) for <5.5 hours on a single day during a 30-day period experienced a clinical thromboembolism rate of 1.1% per year, whereas the event rate among those with a greater burden of AHRE was 2.4% per year. After statistical adjustment for stroke risk factors, an AHRE burden <5.5 hours per day over 30 days was associated with a risk of thromboembolism similar to that of...
patients entirely free of AHRE, whereas the risk doubled among patients with AHRE during more than 5.5 hours per day over a comparable period. It is important to emphasize, however, that the difference in hazard ratio for the groups with low versus high AHRE burdens was not statistically significant.

Whether AHRE are the proximate cause of stroke or a marker of stroke risk independent of the cardiac rhythm is an important, unresolved question. In addition, the duration of AHRE that confers an increased risk of stroke is unclear. The data conveyed by Glotzer et al\textsuperscript{16} must be considered hypothesis-generating. In view of the low echo time rate and lack of statistical significance, the results are not sufficient to dictate whether we should start screening patients for asymptomatic paroxysmal atrial tachyarrhythmias. In addition, the designs of future studies should take into account the low event rate of this cohort, which might be higher if patients with dual-chamber CRT devices are included.

Despite the emerging data, there are multiple unanswered questions. We still do not know why stroke risk appears to be almost the same in patients with paroxysmal and persistent AF. One answer may be that the 2 arrhythmia patterns are manifestations of similar structural, fibrotic heart disease that has different clinical manifestations at various stages. If the period immediately after cessation of AF is particularly risky for thromboembolism, frequent rhythm shifts in patients with paroxysmal AF might overcome the lower stroke risk they enjoy during prolonged periods of sinus rhythm. These issues and others are ripe for further investigation, and device-detected AHRE is an appealing surrogate for paroxysmal AF to facilitate such studies.

When combined with appropriate analysis algorithms, an array of long-term ECG monitoring tools, such as digital Holter recorders, ECG garments, implanted pacemakers, implantable cardioverter-defibrillators, CRTs, or dedicated implanted ECG monitoring devices, offer highly sensitive means of detecting short episodes of AF. Whether these AHRE have the same prognostic relevance as AF detected by standard techniques is not clear. In addition, a high proportion of patients with paroxysmal AF are younger individuals with “lone AF” in the absence of identifiable heart disease who are unlikely to require implanted arrhythmia devices. Fortunately, their risk of thromboembolism is low, so detection of asymptomatic episodes has fewer implications for antithrombotic therapy than for the identification of patients at risk of developing persistent AF over time, during which the risk of stroke also appears to rise.\textsuperscript{17} Conversely, identification of asymptomatic paroxysmal AF/AHRE in older patients with associated cardiovascular disease may identify individuals at risk of stroke, with corresponding implications for antithrombotic therapy. Such patients may also become candidates for earlier intervention to prevent recurrent AF.

Further research is needed to define more precisely the critical duration of AHRE associated with a significantly increased risk of stroke and whether a frequency or duration of AHRE is associated with the development of sustained AF. A multicenter, randomized trial of remote surveillance technology in patients with an implanted dual-chamber defibrillator or a resynchronization device is testing the hypothesis that initiation and withdrawal of oral anticoagulant therapy guided by continuous ambulatory monitoring of the atrial electrogram will improve clinical outcomes by reducing the combined rate of stroke, systemic embolism, and major bleeding compared with conventional clinical management\textsuperscript{18} Intrinsic to this assessment is whether active monitoring of the atrial rhythm affords advantages in terms of other aspects of therapy, including administration of antiarrhythmic drugs. Information of this type ultimately bears on the clinical value of wireless remote surveillance of the cardiac rhythm and may define the critical threshold of AHRE burden warranting therapeutic intervention.

The irregular and seemingly unpredictable distribution of AF episodes and their relationship to the type and severity of underlying heart disease make these investigations methodologically challenging. Clinical strategies involving antithrombotic therapy for stroke prevention in patients with pacemakers or other arrhythmia devices should consider not only the frequency and duration of AHRE but also the patient’s risks of thromboembolism and bleeding. As a consequence, we must learn much more about the complex relationship between thromboembolic risk and the burden of atrial tachyarrhythmias such as AF before the information gleaned from implanted cardiac devices can be factored into this aspect of clinical practice.

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References


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