The article by Halcox et al describes the REHEARSE-AF study (Assessment of Remote Heart Rhythm Sampling Using the AliveCor Heart Monitor to Screen for Atrial Fibrillation), a randomized trial of screening for atrial fibrillation (AF) with a smartphone-based single-lead electrocardiographic capture system in 1001 patients ≥65 years of age with a CHA2DS2-VASc score of ≥2 and without a history of AF. Patients were randomized either to biweekly electrocardiographic recordings with the iPhone device (iECG group; n=500) or to routine care (control group; n=501) over a 12-month period. Not surprisingly, more patients with AF were identified in the iECG group (n=19) than in the control group (n=5).

The data from this study confirm results from studies with implanted pacemakers, cardioverter-defibrillators, and loop recorders and other AF screening studies that, in patients unknown to have AF, particularly those with cardiovascular comorbidities, the more we look for AF, the more we will find it. As Sophocles mused more generally, “Look and you will find—what is unsought will go undetected.” But is there a need to know about asymptomatic episodes of so-called subclinical AF (SCAF)? What are the implications of such a finding?

Clinical AF is associated with increased rates of stroke, heart failure, mortality, hospitalization, and cognitive decline, much of which may present suddenly and constitute irretrievable harm. Therefore, there is a strong prima facie argument that it would help to know the onset of AF as soon as possible, but that is true only if we have therapeutic strategies that can prevent the adverse consequences of AF both safely and effectively. Anticoagulation for AF leads to a reduction in stroke and mortality and perhaps halts the decline of cognitive function and the onset of dementia. It seems that a solid case might be made to look for AF and to react to its discovery by recommending anticoagulation. But is it that simple?

The AF detected by continuous monitoring with implanted devices, or frequent electrocardiographic sampling as in the REHEARSE-AF study, may not have the same adverse consequences as in patients who present with clinically symptomatic AF. We have learned that paroxysmal and perhaps persistent forms of AF may have less risk of stroke than permanent AF. There also seems to be a direct relationship between stroke and the duration of episodes of AF or the overall burden of AF. Do the possibly short and infrequent bouts of atrial high-rate events (AHREs), or SCAF, imply a clinically significant incidence of adverse consequences?

Several studies of patients with implantable devices have tried to quantify the duration of AF that would merit oral anticoagulation on the basis of the incidence of stroke or systemic embolism. They all showed an increased rate of stroke associated with AHREs. Representative data from these studies indicate that the duration of the AF is of particular importance. The MOST study (Atrial Diagnostics Ancillary Study of the Mode Selection Trial; a retrospective study) found that AF as short as 5
minutes was associated with an increased risk of stroke.\textsuperscript{5} The TRENDS study (A Prospective Study of the Clinical Significance of Atrial Arrhythmias Detected by Implanted Device Diagnostics), in which nearly half of the patients had a history of clinical AF before study enrollment, found that patients with moderate stroke risk and AHREs $\geq 5.5$ h/d in a 30-day period appeared to have double the thromboembolic risk.\textsuperscript{6} The ASSERT study (Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial) in hypertensive patients found that episodes of AF lasting $>6$ minutes, compared with no episodes, were associated with a 2.5-fold risk of ischemic stroke or systemic embolism.\textsuperscript{15} Then, the Detection of AHREs by Continuous Home Monitoring study in patients with heart failure found that, compared with patients without detected AHREs, patients with detected AHREs $>3.8$ h/d were 9 times more likely to develop a thromboembolism.\textsuperscript{16} Most recently, a revisit of the ASSERT study data examined the duration of device-detected SCAF and the occurrence of stroke. Those investigators found that the risk of ischemic stroke or systemic embolism in patients with SCAF duration between 6 minutes and 24 hours was not significantly different from that in patients without SCAF. Only SCAF $>24$ hours was associated with an increased risk of ischemic stroke or systemic embolism.\textsuperscript{17} It was concluded that SCAF $>24$ hours was associated with an increased risk of ischemic stroke or systemic embolism. And despite all of the above, there is the recognition that short AHREs are sometimes/often only a prelude to longer episodes, most recently reported by the RATEF Registry study (Registry of Atrial Tachycardia and Atrial Fibrillation Episodes).\textsuperscript{7}

Another puzzle is that asymptomatic episodes of SCAF detected by continuous monitoring in many, if not most, studies seem not to correlate closely with the timing of stroke.\textsuperscript{6,8,15} It may be that AF and thrombus formation might occur some days, weeks, or even months before the clot dislodges from the atrium and causes an embolic stroke, but it is difficult to incriminate AF as the stroke mechanism when the AF occurs only after the stroke. In addition, there are many causes of ischemic stroke other than AF, none of which is unlikely in patients with AF. However, 1 large study,\textsuperscript{18} which combined a clinical database and a data-monitoring database, clearly demonstrated that there was a much higher likelihood of finding AF $\geq 5.5$ hours' duration within the days preceding the stroke than at other times.

If we accept that episodes of AHREs or SCAFs revealed by monitoring increase the risk of stroke and may be mechanistically involved, the next question is whether these embolic events occur frequently enough and long enough to justify attempting stroke prevention with anticoagulant therapy. For all the above studies, the absolute risk of stroke was much lower than expected.\textsuperscript{19} For instance, in the relatively longer ASSERT study (mean follow-up, 3 years), the percentage of patients with a thromboembolic event was 1.20%, and the percentage of patients with AF detected before their thromboembolic event was 0.70%. Modeling studies have concluded that ischemic event rates of $\geq 0.9$/y (direct oral anticoagulants) and 1.7$/y$ (vitamin K antagonist therapy) are needed to justify anticoagulation for AF because of the major bleeding associated with anticoagulant therapy.\textsuperscript{20} It is therefore far from clear that anticoagulation is justified, especially for episodes of AF $<24$ hours in duration.

Two randomized controlled trials are currently underway to explore this issue. ARTEsIA (Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation; unique identifier: NCT01938248)\textsuperscript{21} randomizes apixaban against aspirin in patients with AHREs, and in NOAH (Non-Vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes; unique identifier: NCT02618577),\textsuperscript{22} similar patients receive edoxaban or placebo, with blind aspirin treatment available for patients receiving placebo with an indication for aspirin. Neither trial will report for some years, which leaves the clinician still uncertain as to how to manage these patients.\textsuperscript{22} European guidelines have strongly recommend using the discovery of AHREs to perform “further ECG monitoring to document AF before initiating AF therapy” unless the thrombogenic risk of the patient or patient preference warrants anticoagulation.\textsuperscript{23}

How does the REHEARSE-AF study help? Halcox and colleagues used biweekly, short recordings to identify AF in patients at risk of thrombogenesis. Is using intermittent, short iECG recordings rather than implantable device monitoring a “poor man’s” version of arrhythmia monitoring? Certainly, the frequent iECG recording, well outside the clinical norm, will tend to reveal infrequent arrhythmia, but the short recording period gives little idea of the duration of the arrhythmia, and mere identification is not enough. Finally, the results of the REHEARSE-AF study also serve to focus on issues seen in virtually all the previous AHRE studies. First, the adverse event rate (stroke and systemic embolism) in the 1001 participants was quite low (0.02%). Second, of the 16 total strokes, 14 were either causally unrelated to AF or of undetermined origin.

As far as choosing whether to anticoagulate the patient, we might as well follow the advice of Yogi Berra: “When you come to a fork in the road [decision], take it [guess].” Perhaps it is better not to look for it. After all, “what is left unsought will not be discovered.” But we cannot leave it there, thinking “out of sight, out of mind,” because what Victor Hugo actually wrote was “When a man is out of [his] sight [blind], it is not too long before he is out of [his] mind [crazy],” and we would not want that nor all the other adverse complications of AF to come tumbling down on our patients just because we were not prepared to look, find, and further evaluate what can be discovered with simple clinical techniques. Clearly, we have more work to do.
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FOOTNOTES
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