Screening for Atrial Fibrillation With a Wearable Device

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The formative, landmark descriptions of the prevalence and risk of atrial fibrillation (AF) in the Framingham Heart Study were based on "spot" 12-lead electrocardiograms.[1] In terms of surveillance, this was largely unchanged from centuries of recording an irregular pulse by palpation and required a very high frequency of sustained arrhythmia to detect AF. However, the last decade has seen a substantial increase in the potential tools available for detection of infrequent AF, including a variety of "wearable" technologies.[2-6] The ready availability of both medical and consumer-based technologies for diagnosis of AF is driving a major shift in the approach from characterizing AF as a binary diagnosis—present or absent—to one on a continuum (based more on frequency of arrhythmia).[7]

Related article page 146

In this issue of *JAMA*, Steinhubl et al[8] present the results of the mHealth Screening to Prevent Strokes (mSToPS) randomized clinical trial. Using a novel clinical research design,[9] the authors deployed a direct-to-patient approach for monitoring individuals who were at risk of developing AF but with no known clinical history of AF. Patients with either older age or additional risk factors for AF were randomly assigned to undergo monitoring with self-applied continuous electrocardiographic monitoring initiated immediately after enrollment (n = 1364) or to undergo monitoring after a 4-month delay (n = 1291).

The study demonstrated that 2 weeks of immediate active monitoring yielded a higher rate of AF diagnosis compared with delayed monitoring at 4 months (3.9% vs 0.9%, respectively; absolute difference, 3% [95% CI, 1.8%-4.0%]). Importantly, simply contacting patients and informing them that they qualified for randomization due to their risk factors did not inherently increase their likelihood of subsequent diagnosis (compared with a matched, uncontacted, control cohort). In the observational phase of the study, the rates of health care utilization, including increased use of anticoagulation for stroke prevention, were higher among actively monitored patients than matched controls.

What are the clinical implications of the study by Steinhubl et al? As with any screening protocol, it is important to consider the context. In this study,[8] the inclusion criteria were such that the study population was enriched for risk of developing AF. The study participants were older or had significant risk factors for AF, stroke, or both. Several prior studies have demonstrated feasibility of AF screening in different populations using a variety of medical and consumer devices.[2-6] The population in the current study[8] may be most similar to that of the Assessment of Remote Heart Rhythm Sampling Using the AliveCor Heart Monitor to Screen for Atrial Fibrillation (REHERSE-AF) Study, in which at-risk patients were recruited in the United Kingdom and instructed to self-record their rhythm 1 to 2 times weekly (and with symptoms) using a hand-held device.[6] This monitoring strategy resulted in a 3.7% rate of AF diagnosis at 12 months, which is similar to that of the mSToPS detection rate at 4 months (3.9%-5.1% in the active monitoring group with 2 weeks of continuous monitoring).

Therefore, the mSToPS data suggest that immediate, continuous screening for 2 weeks may be equivalent to weekly or biweekly, 30-second rhythm monitoring over a 12-month period in a population of similar risk. This is further supported by the timing of detection in the mSToPS cohort: among patients with AF detected on 2-week monitoring, nearly one-quarter had AF on day 1 and nearly 40% had AF detected within the first 3 days (including both the early and delayed active monitoring groups). The detection of AF in the mSToPS study also compares favorably with a cohort of higher-risk patients with cryptogenic stroke in the Study of Continuous Cardiac Monitoring to Assess Atrial Fibrillation After Cryptogenic Stroke (CRYSTAL-AF), who underwent continuous monitoring with an implantable loop recorder, which detected AF in 8.9% at 6 months, an expectedly higher frequency given their uniform history of stroke.[10] Given the significant variation in device technology, screening algorithms, availability, and health system considerations, these data are informative for the design of research and screening protocols moving forward and could broaden the approaches to screening in these patients.[11]

However, before the findings of mSToPS can be incorporated into clinical practice, 2 major questions must be considered with regard to structured AF screening: (1) does earlier or more sensitive detection of AF improve clinical outcomes? (2) And if so, is it cost-effective? There is good evidence that earlier AF detection could affect clinical outcomes across 4 key aspects of AF care[12]: (1) aggressive management of modifiable risk factors, (2) rate control, (3) symptom control, and (4) stroke prevention. Multiple AF risk factors, including hypertension, diabetes, and sleep apnea, each require treatment, and earlier AF detection could prompt more attentive and effective treatment of these conditions. Furthermore, there is strong support for significant improvements in AF outcomes with comprehensive AF risk factor management.[12] Among symptomatic patients who are candidates for rhythm control, both medical (antiarrhythmic) and interventional approaches (ie, catheter ablation) have consistently demonstrated more favorable outcomes among patients with intermittent AF (and less advanced disease).[13]

The net clinical benefit of stroke prevention for patients with lower-burden (AF duration between minutes up to 24 hours) or subclinical AF is more complicated. While oral anticoagulation has been shown to reduce stroke and improve survival among patients with AF and additional risk factors for stroke,[14] recent work has also suggested a

substantial risk of stroke among patients with low-burden AF and no risk factors.[15] Data from randomized trials are necessary to test whether the benefits of treatment with oral anticoagulation outweigh the risks in patients with subclinical or low-burden AF. Some evidence will come from studies such as the Apixaban for the Reduction of Thromboembolism in Patients With Device-Detected Sub-clinical Atrial Fibrillation (ARTESIA) trial, which will study apixaban vs aspirin in patients with subclinical AF (AF ≥6 minutes but none >24 hours) detected by implantable devices.[16] In the future, the optimal approach to stroke prevention may require integrating the patient's underlying risk factor profile (ie, CHA_2DS_2-VASc score) and the frequency and amount of AF (AF burden).

Whether screening for AF is cost-effective is a more complex question and depends on the target population, local practice patterns, screening approach, and the effects on outcomes. While several studies have suggested various screening protocols to be cost-effective in different health systems, these studies have been based largely on assumptions regarding stroke risk reduction in these patients, which will require additional trials to confirm (as noted above).[11] The mSToPS investigators' 3-year analysis of cost differences in these groups will be informative because patients in the actively screened group had higher health care utilization at 12 months. An ongoing AF screening study using smartwatches will also help address some of these important questions (https://clinicaltrials.gov/ct2/show/NCT03335800).

Although innovative in its design, the mSToPS trial has some limitations. The delayed-screening cohort was compared with a control group derived from administrative data, of which the diagnostic sensitivity for AF is inherently lower than for patients who are actively, electrocardiographically monitored (however, the authors' sensitivity analyses demonstrated consistent findings). Additionally, there were significant differences between patients who consented through direct-contact recruitment vs those invited to participate in the study but did not consent. Also, about a third of patients who did consent did not wear the monitoring patch (n = 917/2655), and there were significant differences between those who did and did not use it. While this limits the external validity, it also suggests AF detection should have been even higher in the actively monitored groups. These are important considerations for future studies with similar designs.

In summary, the mSToPS trial by Steinhubl et al[8] provides strong support for the use of 2 weeks of continuous rhythm monitoring to screen for AF in at-risk populations, given the detection rate of up to 5% at 4 months. This appears to detect a substantial proportion of patients who might be detected using more inconvenient, invasive, costly, or longer monitoring approaches. While existing epidemiologic and outcomes data support interventions for risk factors and symptoms of AF early in the disease process, clinical trials demonstrating improvement in cardiovascular outcomes, such as reduced occurrence of stroke, will be necessary to take action and screen for AF at the population level.

ARTICLE INFORMATION

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Intravenous Alteplase for Mild Nondisabling Acute Ischemic Stroke
A Bridge Too Far?

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Treatment of patients with stroke has changed substantially during the past 25 years. In 1995, the NINDS rt-PA trial showed among selected patients with acute ischemic stroke who were treated with intravenous alteplase within 3 hours of known stroke onset or last known well time had reduced disability at 3 months.[1] In 2008, the ECASS III trial demonstrated benefit of intravenous alteplase among selected patients treated up to 4.5 hours after known stroke onset or last known well time.[2] Benefit from alteplase treatment occurred despite higher rates of symptomatic intracranial hemorrhage compared with placebo (6.4% vs 0.6% in the NINDS rt-PA trial; 2.4% vs 0.3% in ECASS III).[1,2] More recently, thrombectomy has been shown to substantially reduce morbidity in selected patients with ischemic stroke.[3]

Related article page 156

Experience with intravenous alteplase in acute ischemic stroke has defined many clinical situations in which the overall benefit of reducing disability with treatment outweighs the risk of hemorrhage.[4] However, situations remain for which data are insufficient. One involves acute ischemic stroke with initially mild neurologic deficits. Many of these patients who are not treated with alteplase do well, but up to 15% may experience early worsening of signs and symptoms and approximately 30% have some degree of disability at 3 months.[5,6] For such patients who are treated with intravenous alteplase, the risk of symptomatic intracranial hemorrhage is still 2% to 3%.[7] A meta-analysis of 9 trials of intravenous alteplase in acute ischemic stroke showed a significant reduction in functional disability at 3 months for patients with mild stroke.[8] These patients were not further categorized by whether their acute neurologic deficits were disabling. Current guidelines from the American Heart Association/American Stroke Association (AHA/ASA) recommend intravenous alteplase administration within 3 hours for patients with mild but disabling stroke symptoms but are indecisive about those with nondisabling symptoms.[4] It is this latter group of patients that has posed a persistent therapeutic dilemma: treat because they might get worse or do not treat because of the risk of symptomatic intracranial hemorrhage?

In this issue of *JAMA*, Khatri and colleagues report the results of the PRISMS trial of intravenous alteplase vs aspirin administered within 3 hours of known stroke onset or last known well time for patients with acute ischemic stroke and initially mild, nondisabling deficits.[9] A National Institutes of Health Stroke Scale (NIHSS) score of 5 or lower was used to define mild stroke. The NIHSS is an 11-item scale with scores ranging from 0 to 42 and higher scores indicating worse neurologic deficits.[10] Patients can achieve a score of 5 or lower with different neurologic deficits and constitute a heterogeneous group. For example, the following deficits would all score 5 or lower: complete paralysis of 1 leg (score of 4), complete aphasia (score of 3), mild arm weakness with mild sensory loss (score of 2), mild dysarthria (score of 1), and double vision (score of 0). Thus, PRISMS eligibility also required that deficits be judged "not clearly disabling"; ie, that they would not prevent a patient from performing basic activities of daily living (bathing, ambulating, toileting, hygiene, and eating) or returning to work. The primary end point was favorable functional outcome—a modified Rankin Scale (mRS) score of 0 or 1—at 90 days. An mRS score of 0 indicates no symptoms; an mRS score of 1 indicates no significant disability despite symptoms and that a patient is able to carry out all usual duties and activities.[11]

PRISMS was designed to detect a 9% absolute difference in the proportion of participants with favorable outcome with 80% power. The study was terminated early by the sponsor without unblinding because of poor recruitment when one-third of the projected 948 study participants had been enrolled. Among the 313 patients in PRISMS, 78% who received alteplase vs 81% who received aspirin achieved an mRS score of 0 or 1 at 90 days (adjusted risk difference, −1.1%; 95% CI, −9.4% to 7.3%).[9]

These numerically similar outcomes between the 2 groups are quite a departure from the 10% difference observed in