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Editorial

Screening for Atrial Fibrillation—Refining the Target

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Atrial fibrillation (AF) profoundly affects individual patients and the health system at large. The substantial morbidity, mortality, and health-related expenditures associated with this exceedingly common arrhythmia cannot be underestimated.[1] Indeed, the association between AF and increased risk of stroke (often debilitating) is well established.[2]

As such, screening for AF is of paramount interest to public health. In 2018, the US Preventive Services Task Force (USPSTF) found that available evidence was insufficient to assess the balance of benefits and harms of using the electrocardiogram (ECG) to screen for AF; moreover, they reported that ECG screening may not detect more AF than usual care (ie, pulse palpation).[3] The USPSTF is now broadening the scope of its initial recommendation: for adults aged 50 years and older without a diagnosis or symptoms of AF and without a history of transient ischemic attack or stroke, "the current evidence is insufficient to assess the balance of benefits and harms of screening for AF" (I statement).[4,5]

At the same time, through a rigorous systematic review, the USPSTF recognizes that there is adequate evidence that intermittent screening strategies and continuous screening may identify undiagnosed AF more effectively than usual care.[4,5] However, the central issue rests on the inadequate evidence base for the benefits that can result from broad AF screening. The outcomes that may result—specifically, initiating anticoagulant therapy from incidentally discovered AF or even early rhythm control strategies—may result in harm.

Future opportunities lie in refining the populations considered for screening. For example, a 2019 USPSTF recommendation states that abdominal aortic aneurysm screening is not recommended for all patients but rather the high-risk subset of men who are aged 65 to 75 years and previously smoked.[6] Similarly, for lung cancer screening, the USPSTF recommends low-dose chest computed tomography only for individuals aged 50 to 80 years who have a 20 pack-year smoking history and currently smoke or have quit within the past 15 years.[7] Although AF is more prevalent than these conditions, it is plausible that screening an entire population above a specific age threshold will fail to demonstrate merit compared with an approach of targeted screening.

As the new USPSTF recommendation notes,[4,5] the evidence base for optimal screening and the effectiveness of treatment is limited. This is, in large part, because available studies offer different approaches regarding optimal screening, deriving stroke risk, and informing treatment thresholds. Understandably, studies approach screening using a binary screening for AF (ie, present or absent). Our current practice is to measure risk in terms of ordinal stratification scores. However, identifying patients with or without AF and assessing their stroke risk with a number is misaligned with the remarkable heterogeneity in patients with AF.[8] AF lies along a spectrum of importance, and several studies have suggested that assessing the burden of AF, rather than the presence or absence, may be a better approach.

One such study is the recently published LOOP trial,[9] which enrolled approximately 6000 older patients without AF with a median CHA_2DS_2-VASc score of 4 and randomized them to implantable loop recorder (ILR) monitoring or usual outpatient care. The intervention group was focused on early AF detection, whereas the primary end point was a clinical outcome: time to first stroke or systemic arterial embolism. The study included a recommended intervention of anticoagulation if AF greater than 6 minutes was discovered. Patients were followed-up for approximately 5 years.

Not surprisingly, detected AF was significantly higher in patients with an ILR (32% vs 12%). Among those with a diagnosis of AF, 30% of patients with ILRs received anticoagulation vs 13% of

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controls. The primary end point occurred in 4.5% vs 5.6% of patients, and major bleeding occurred in 4.3% vs 3.5% of patients, although neither difference in outcomes reached statistical significance.[9] Overall, it may seem limited that the nearly 3-fold increase in both AF detection and anticoagulation use with ILRs (which are costly) did not translate into improved outcomes in individuals at exceedingly high risk of stroke.

However, these results must be interpreted cautiously because the 6-minute threshold to initiate anticoagulation stemmed from results of the ASSERT trial.[10] This trial enrolled approximately 2500 patients aged 65 years and older with hypertension but no history of AF who recently underwent dual chamber pacemaker or implantable cardioverter-defibrillator (ICD) placement. Patients were subsequently monitored for atrial tachyarrhythmia burden (episodes >6 minutes with atrial rate >190 beats per minute) and were followed-up to assess for ischemic stroke or systemic embolism.[10] By 3 months, 10.1% of patients had subclinical atrial tachyarrhythmias, which were associated with a significant 2.5-fold increased ischemic stroke or systemic embolism. However, over a longer follow-up of 3.5 years, it was the episodes that were longer than 24 hours that accounted for the greatest increased risk of stroke.[11]

The association of significant events with subclinical tachyarrhythmias in the ASSERT trial[10] does provide some evidence to suggest that treating incidentally found, subclinical arrhythmias may be important. Additional evidence could come from the ongoing ARTESIA trial,[12] a prospective, multicenter, double-blind, randomized clinical trial recruiting patients with subclinical AF detected by implantable device (pacemaker, ICD, or cardiac monitor) and risk factors for stroke. Participants are randomized to treatment with apixaban vs aspirin. If this trial demonstrates a treatment benefit with apixaban, more light will be shed on whether treating subclinical AF can reduce thromboembolic events in certain populations.

As the USPSTF notes,[4,5] there are significant data supporting improved yield with more intensive screening (and with that, the choice to initiate anticoagulation). STROKE-STOP[13] was a randomized, population-based trial of approximately 7200 participants aged 75 to 76 years in Sweden who were randomized to AF screening with a self-applied handheld ECG recorder over 2 weeks vs no intervention. After a median follow-up of 6.9 years, significantly fewer primary composite end point events occurred in the intervention group. One of the important findings was that the highest rate of ischemic stroke occurred in participants who were invited to undergo screening but chose not to participate in the trial (albeit this subset was at lower risk than those who were randomized). Although the overall results may be viewed as clear benefit from population-based AF screening, it should be noted that there was no significant difference in the individual components of the primary composite end point between the groups, including stroke and major bleeding.

Despite the caution appropriately emphasized by the USPSTF,[4,5] screening will likely increasingly occur outside of physician encounters. The Apple Heart study,[14] which enrolled approximately 420 000 patients to assess the ability of a smartwatch application to identify AF, demonstrated that mass enrollment in a clinical AF screening trial is feasible. However, to use photoplethysmography as a screening strategy, the intervention would need to be more targeted, and the accuracy of the algorithm would require continued improvement. In addition, leveraging deep learning algorithms to identify and monitor individuals at higher risk for AF may be another method to refine the population screened for AF and, perhaps, increase the yield of monitoring.

More intense screening will incur increased costs beyond monetary. These screening methods may include more frequent in-person visits, wearable monitors, and telehealth; these costs may exacerbate disparities that exist in traditional cardiovascular care. Populations already impacted by disparities in traditional cardiovascular care are likely to be similarly affected.[15]

Furthermore, the potential benefits of early AF detection should extend beyond stroke prevention. As the USPSTF notes,[4,5] attempts at disease modification through behavior and lifestyle modification are of paramount importance.[16] Patients identified with AF likely would benefit from targeted management of modifiable risk factors that contribute to AF, including obesity,

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hypertension, alcohol use, sleep apnea, smoking, and diabetes. Future studies of structured, patient-specific behavior interventions in patients with AF detected through screening may provide additional beneficial clinical outcomes.

Overall, AF affects individuals and the health care system at large in important ways. Untargeted, onetime screening with the intention to initiate thromboembolic prophylaxis in patients at increased risk for events has not been shown to produce clinical benefit compared with usual care. Indeed, practitioners are likely to encounter many incidentally discovered dysrhythmias (and ECG artifact) in patients who are asymptomatic, and how to address these will be a challenge. We need to find best means of translating evidence-based recommendations, especially recommendations that may be associated with reduced symptoms and long-term health care utilization, into language our patients can understand so that we can extend such recommendations to clinical practice. The USPSTF's new recommendation on AF screening[4,5] presents valuable opportunities for discovery, including to enhance emerging AF risk estimation techniques and build on the evolving evidence base, to improve targeted screening and measure the impact of treatment.

ARTICLE INFORMATION

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REFERENCES

1. Magnani JW, Rienstra M, Lin H, et al. Atrial fibrillation: current knowledge and future directions in epidemiology and genomics. *Circulation*. 2011;124(18):1982-1993. doi:10.1161/CIRCULATIONAHA.111.039677

2. Freedman B, Camm J, Calkins H, et al; AF-Screen Collaborators. Screening for atrial fibrillation: a report of the AF-SCREEN international collaboration. *Circulation*. 2017;135(19):1851-1867. doi:10.1161/CIRCULATIONAHA.116.026693

3. Curry SJ, Krist AH, Owens DK, et al; US Preventive Services Task Force. Screening for atrial fibrillation with electrocardiography: US Preventive Services Task Force recommendation statement. *JAMA*. 2018;320(5):478-484. doi:10.1001/jama.2018.10321

4. Kahwati LC, Asher GN, Kadro ZO, et al. Screening for atrial fibrillation: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. Published online January 25, 2022. doi:10.1001/jama.2021.21811

5. Davidson KW, Barry MJ, Magnione CM, et al; US Preventive Services Task Force. Screening for atrial fibrillation: US Preventive Services Task Force recommendation statement. *JAMA*. Published online January 25, 2022. doi:10.1001/jama.2021.23732

6. US Preventive Services Task Force. Final recommendation statement: abdominal aortic aneurysm: screening. Accessed December 10, 2021. https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/abdominal-aortic-aneurysm-screening

7. US Preventive Services Task Force. Final recommendation statement: lung cancer: screening. Accessed December 10, 2021. https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/lung-cancer-screening

8. Wright JM, January CT. Atrial fibrillation and anticoagulation: one size fits all? *Ann Intern Med*. 2018;169(8):575-576. doi:10.7326/M18-2355

9. Svendsen JH, Diederichsen SZ, Højberg S, et al. Implantable loop recorder detection of atrial fibrillation to prevent stroke (the LOOP Study): a randomised controlled trial. *Lancet*. 2021;398(10310):1507-1516. doi:10.1016/S0140-6736(21)01698-6

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10. Healey JS, Connolly SJ, Gold MR, et al; ASSERT Investigators. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med*. 2012;366(2):120-129. doi:10.1056/NEJMoa1105575

11. Van Gelder IC, Healey JS, Crijns HJGM, et al. Duration of device-detected subclinical atrial fibrillation and occurrence of stroke in ASSERT. *Eur Heart J*. 2017;38(17):1339-1344. doi:10.1093/eurheartj/ehx042

12. Lopes RD, Alings M, Connolly SJ, et al. Rationale and design of the Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation (ARTESIA) trial. *Am Heart J*. 2017;189:137-145. doi:10.1016/j.ahj.2017.04.008

13. Svennberg E, Friberg L, Frykman V, Al-Khalili F, Engdahl J, Rosenqvist M. Clinical outcomes in systematic screening for atrial fibrillation (STROKESTOP): a multicentre, parallel group, unmasked, randomised controlled trial. *Lancet*. 2021;398(10310):1498-1506. doi:10.1016/S0140-6736(21)01637-8

14. Perez MV, Mahaffey KW, Hedlin H, et al; Apple Heart Study Investigators. Large-scale assessment of a smartwatch to identify atrial fibrillation. *N Engl J Med*. 2019;381(20):1909-1917. doi:10.1056/NEJMoa1901183

15. Smith B, Magnani JW. New technologies, new disparities: the intersection of electronic health and digital health literacy. *Int J Cardiol*. 2019;292:280-282. doi:10.1016/j.ijcard.2019.05.066

16. O'Connor EA, Evans CV, Rushkin MC, Redmond N, Lin JS. Behavioral counseling to promote a healthy diet and physical activity for cardiovascular disease prevention in adults with cardiovascular risk factors: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2020;324(20):2076-2094. doi:10.1001/jama.2020.17108

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