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Population-based Screening for Atrial Fibrillation

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Abstract

Atrial fibrillation is a common and morbid arrhythmia. Stroke is a major hazard of atrial fibrillation and may be preventable with oral anticoagulation. Yet since atrial fibrillation is often asymptomatic, many individuals with atrial fibrillation may be unaware and do not receive treatment that could prevent a stroke. Screening for atrial fibrillation has gained substantial attention in recent years as several studies have demonstrated that screening is feasible. Advances in technology have enabled a variety of approaches to facilitate screening for atrial fibrillation using both medical-prescribed devices as well as consumer electronic devices capable of detecting atrial fibrillation. Yet controversy about the utility of atrial fibrillation screening remains owing to concerns about potential harms resulting from screening in the absence of randomized data demonstrating effectiveness of screening on outcomes such as stroke and bleeding. In this review we summarize current literature, present technology, population-based screening considerations, and consensus guidelines addressing the role of atrial fibrillation screening in practice.

Keywords

atrial fibrillation; screening; stroke; ECG; wearable technology; atrial flutter

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Why Screening?

The burden of atrial fibrillation

Atrial fibrillation (AF) is a common arrhythmia, estimated to affect at least 33.5 million individuals worldwide.[1] The prevalence of AF is expected to rise to nearly 12 million people in the US by 2030 and 17.9 million people in the European Union by 2060, in part due to aging populations.[2,3] The financial impact of AF on both US and European healthcare systems is substantial.[4–6]

Individuals with AF are at increased risk for morbidity and death, largely due to heart failure and ischemic stroke.[7,8] There is also increasing recognition of an association between AF and cognitive decline, which may be related in part to both overt and silent strokes.[9] Fortunately, oral anticoagulation (OAC) is highly effective for preventing strokes related to AF.[10–12] However, AF is frequently asymptomatic, and up to 5% of individuals with a diagnosis of AF present with stroke as the first clinically-evident manifestation of their arrhythmia.[13]

Rationale for screening and current recommendations

Population-based screening for AF has several potential benefits, including identification of individuals with unrecognized AF who would benefit from OAC to prevent stroke, as well as an opportunity to implement more promptly interventions known to reduce AF burden and symptoms (Figure 1).[14–16] As discussed below, however, randomized trials of AF screening have not demonstrated a reduction in stroke or other hard outcomes, although adequately powered studies have not yet reported. Furthermore, the potential benefits gained from early identification and treatment of screen-detected AF must be balanced against the potential harms and uncertainties posed by screening. First, even very specific screening tests (e.g., 12-lead ECG) applied at the population level will result in false positive diagnoses, potentially leading to excess bleeding associated with unnecessary OAC use.[17–23] Second, prolonged application of continuous forms AF monitoring increase the likelihood of detecting short episodes of AF,[24–26] which may be of uncertain clinical significance.[27–29] Given emerging evidence that AF burden is related to stroke risk, it remains unclear whether very infrequent and short AF episodes detectable only through continuous screening increase the risk of stroke sufficiently to merit OAC.[27–30] Third, not all forms of rhythm monitoring are sufficient to establish a diagnosis of AF. For example, some forms of rhythm detection may frequently lead to indeterminate results,[31] while others require confirmatory, electrocardiographic testing,[32] contributing to patient anxiety, increased costs, and further risk of false positive results.

Consistent with uncertainty surrounding the balance of benefit and harm of population-based screening for AF, consensus guidelines offer varying endorsements (summarized in Table 1). For example, the European Society of Cardiology provides a class I recommendation for performing AF screening by “pulse taking or ECG rhythm strip” in individuals aged greater than 65 years.[33] The National Heart Foundation of Australia and New Zealand provides a “strong” recommendation for “opportunistic point-of-care screening in the clinic or community” in individuals aged 65 or older by pulse palpation followed by ECG or an ECG

rhythm strip (including a handheld ECG).[34] The US Preventive Services Task Force indicates that evidence is insufficient to "assess the balance of benefits and harms" of AF screening using ECG at present.[35]

AF-SCREEN[36], an international consensus group founded to promote discussion and research about AF screening as a strategy to reduce stroke and death, as well as provide advocacy for implementation of country-specific AF screening programs, has also issued several documents summarizing evidence relevant to AF screening and providing expert consensus recommendations. The recommendations of AF-SCREEN are generally similar to those of the European Society of Cardiology, and include single-timepoint screening for all individuals aged ≥ 65 years, as well as more intensive screening (e.g., 2 weeks of twice-daily intermittent monitoring) for individuals aged ≥ 75 years or at elevated risk for stroke.[37] Additional emphases made by SCREEN-AF include the importance of linking AF screening to a treatment pathway, as well as a preference for screening using devices capable of generating an ECG waveform.[37]

Screening versus empiric treatment

As with any disease for which screening is being considered, the value of screening is diminished if the relevant treatment is sufficiently safe and effective that its administration to all at-risk individuals provides net benefit.[38] To this end, there has been substantial interest in identifying whether it is possible to identify individuals at sufficiently high risk for AF and stroke that the empiric use of OAC may be justified, such as individuals with embolic stroke of undetermined source (ESUS). Subclinical AF is observed on continuous cardiac rhythm monitoring in approximately 30% of individuals within 3 years of an stroke of undetermined etiology, implicating occult cardioembolism as a likely stroke etiology.[39] Yet two large randomized trials in patients with ESUS have raised concerns about this approach. Empiric use of OAC with rivaroxaban or dabigatran did not reduce the risk of recurrent stroke as compared to aspirin in the New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source (NAVIGATE-ESUS)[40] or Randomized, Double-Blind, Evaluation in Secondary Stroke Prevention Comparing the Efficacy and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate versus Acetylsalicylic Acid in Patients with Embolic Stroke of Undetermined Source (RE-SPECT ESUS) trials, respectively.[41] Moreover, the risk of major bleeding was increased approximately two-fold with OAC in NAVIGATE-ESUS. Apixaban for Treatment of Embolic Stroke of Undetermined Source (ATTICUS) and AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke (ARCADIA) are additional trials comparing apixaban to aspirin among patients with ESUS and are currently underway.[42,43] In contrast to empiric use, OAC treatment in individuals confirmed to have subclinical AF using continuous monitoring following stroke of unclear etiology has been shown to reduce recurrent stroke.[39] As a result, on the basis of available evidence, it appears that monitoring to document AF is likely to remain the clinical standard even in patients in whom a high suspicion for AF exists.

What has been done?

Overview of previous AF screening studies

Multiple studies have investigated the feasibility of population-based AF screening. A summary of the findings of non-randomized studies is listed in Table 2 and a summary of randomized trials is listed in Table 3. Screening has consistently been reported to lead to higher rates of AF detection. The yield of screening for identifying previously undiagnosed AF has generally ranged from about 0.1% to 5%, with a higher incidence among older individuals and with the use of continuous screening methods.[44] The test characteristics of AF screening have been reported to vary substantially by screening modality, with sensitivities ranging from 86–100% and specificities ranging from 75–98% (Table 4). Although screening studies have not demonstrated a reduction in hard outcomes such as stroke or mortality, studies adequately powered to detect such an effect have not yet reported.

Overview of AF screening modalities

There are many available methods to screen for asymptomatic AF, ranging from less expensive, intermittent methods with lower sensitivity and/or specificity[17,20,22,45] to more expensive, continuous methods which can record electrocardiographic data for weeks to years at a time (Figure 2).[46–48] Traditional modalities have included manual pulse palpation and 12-lead ECG. Newer devices include a variety of handheld, wearable and implantable technologies, including consumer-facing smartphones and watches/bands. Non-invasive oscillometric (e.g. blood pressure monitor) devices capable of detecting an irregular pulse are practical and widespread. Handheld devices (including apps integrated into smart phones) detect AF by generating a single-lead ECG as the user applies two fingers from each hand. Smart watches/bands monitor for arrhythmia using photoplethysmography, although the latest iterations have recently incorporated the ability to produce a single-lead ECG. It is important to recognize that automated interpretation of single-lead ECGs generated by handheld or wearable devices is typically performed by proprietary algorithms with varying complexity and accuracy, although all devices able to output an ECG tracing have the advantage that such tracings can later be read manually by a provider. Nevertheless, handheld or wearable single-lead ECG tracings still typically require confirmation with a traditional 12-lead ECG to ensure a proper diagnosis of AF, and substantial delays between a preliminary diagnosis of AF and a confirmatory test may reduce the effectiveness of a screening intervention. Continuous ECG-based methods (e.g. ambulatory ECG monitors, patches, and implantable cardiac monitors) are expensive, but have the greatest sensitivity for detecting AF.

While many devices have a role for the detection of AF, the most appropriate approach to deploy may ultimately depend on factors such as underlying AF and stroke risk, convenience, and costs. Clinicians, payers, and patients (who may also be consumers) are each likely to have different perspectives on optimal device selection, resulting in an array of different methods by which AF screening is likely to take place. Randomized trials and decision analytic models may help determine the most effective and efficient AF screening strategy to utilize in specific clinical contexts.

Review of previous studies by modality

Pulse palpation—Two randomized trials have investigated the efficacy of AF screening utilizing pulse palpation. Morgan and Mant[22] randomized 3,001 individuals of all ages in four primary care practices in the UK to systematic screening implemented via trained nurses performing pulse palpation along with a lead II rhythm strip, versus "opportunistic screening", defined as a reminder to document whether any pulses taken during routine clinical care were potentially suspicious for AF. In both cases, pulse palpation findings suspicious for AF were followed by a 12-lead ECG. At six months, 4.5% of individuals in the systematic screening arm had AF detected versus 1.3% of individuals in the opportunistic arm (mean difference 3.2%, 95% CI 2.0–4.4). Using any irregularity of the pulse as the positivity criterion, the sensitivity of pulse palpation was 91% and specificity was 74%. An important limitation of this study was that individuals with prevalent AF were not excluded, and 82% of individuals with screen-detected AF had a previous diagnosis of AF present in their medical record. This not only enriched the risk of AF beyond what might be expected in a screening population, but also introduced the potential for ascertainment bias.

The Screening for Atrial Fibrillation with Electrocardiography (SAFE) trial[49] was a large, cluster-randomized clinical trial reported in 2007 investigating screening for AF using pulse palpation in 50 primary care centers in the United Kingdom. SAFE randomized 14,802 individuals aged ≥65 years to a) one-time screening with 12-lead ECG, b) one-time pulse palpation with a 12-lead ECG if the pulse felt irregular, and c) no screening. After 12 months, AF was detected in 1.63% of individuals in the intervention practices versus 1.04% in control practices (mean difference 0.59%, 95% CI 0.20–0.98). Rates of AF detection were nearly identical with 12-lead ECG screening (1.64%) versus pulse palpation with follow up 12-lead ECG (1.62%), despite the fact that 2,357 ECGs were performed in the former group versus only 238 in the latter. Economic analyses based on the results of SAFE have therefore suggested superior cost-effectiveness when pulse palpation is performed prior to 12-lead ECG.[50] Of note, it is largely on the basis of the SAFE study that the European Society of Cardiology guidelines recommend screening with either 12-lead ECG or pulse palpation followed by 12-lead ECG if abnormal in individuals aged >65 years.[51]

Oscillometric devices—There have been several non-randomized studies investigating the efficacy of devices that leverage oscillometric technology (i.e., blood pressure cuff) to detect AF. In a Canadian study by Quinn et al.[52], individuals aged ≥ 65 underwent AF screening using pulse palpation, single-lead ECG, or oscillometric device deployed within 22 primary care clinics. Individuals with a positive result on 1 or more tests underwent 12-lead ECG with or without 24-hour Holter monitor. Out of 2,052 participants who underwent all 3 screening tests, 56 had confirmed AF (prevalence of screen-detected AF 2.7%), of which 12 (0.6%) represented a new diagnosis of AF. Oscillometric screening demonstrated superior specificity when compared to pulse palpation, with a positive predictive value of 53.4% (95% CI 42.0–64.9) for AF. Notably, screening increased the proportion of AF patients receiving adequate anticoagulation (defined as taking a direct-acting OAC or warfarin with time in the therapeutic range > 65%) from 63% to 82%.

In a second study by Kearley et al. in the United Kingdom[53], 1,000 ambulatory patients aged ≥ 75 in 6 general practices underwent AF screening with an oscillometric device or single-lead ECG with 12-lead ECG used as the reference standard. Of 1,000 individuals screened, 79 (7.9%) individuals had AF detected on 12-lead ECG, of which 11 (1.4% of the 889 individuals without known AF) represented a new AF diagnosis. The osillometric device had a sensitivity of 94.9% (95% CI 87.5–98.6) and a specificity of 89.7% (95% CI 87.5–91.6) for AF.

Chan et al. also assessed AF screening using an oscillometric device within a sample of 5,969 primary care patients in Hong Kong using single-lead ECG interpreted by cardiologists followed by confirmatory 12-lead ECG as the reference standard.[32] Individuals enrolled were age ≥ 65 or had a diagnosis of hypertension or diabetes, and did not have prevalent AF. Of the 5,969 individuals screened, AF was diagnosed and confirmed by 12-lead ECG in 72 patients (1.21%). The oscillometric device demonstrated sensitivity of 80.6% (95% CI 69.5–88.9) and specificity of 98.7% (95% CI 98.3–98.9) for AF.

12-lead ECG—Several non-randomized studies have investigated the feasibility of traditional 12-lead ECG for AF screening. In the SAFE study described above, systematic deployment of 12-lead ECG led to a 0.60% absolute increase in AF diagnosis when compared to no screening.[49] More recently, in the STROKESTOP study[54], Svennberg et al. invited half of the population in two regions of Sweden aged 75–76 years to AF screening with 12-lead ECG followed by single-lead ECG monitoring for up to 14 days. The initial 12-lead ECG component of the screening intervention led to a new diagnosis of AF in 37 individuals (0.5% of the screened population). In a second Swedish study[55], Engdahl et al. invited all inhabitants aged 75–76 years in a large municipality to a similar stepwise screening program with 12-lead ECG followed by intermittent single-lead ECG in selected individuals. The initial 12-lead component of the screening program resulted in a new diagnosis of AF in 10 individuals (1.2% of the screened population).

Patch Monitor—The mSToPS trial[48] randomized 1,659 individuals to either immediate or delayed (after 4 months) AF screening with a single-lead patch monitor for up to 28 days. Eligibility for the study included age ≥ 75 years, male aged ≥ 55 years with at least 1 stroke risk factor, and female aged ≥ 65 years with at least 1 stroke risk factor. At 4 months, new AF was identified in 3.9% of the immediate screening group versus 0.9% in the delayed group (absolute difference 3.0%, 95% CI 1.8–4.1). At 1 year, new AF was identified at a rate of 6.7% per 100 person-years in individuals screened versus 2.6% per 100 person-years in matched controls who did not undergo any screening. Results of an observational comparison between the active and delayed screening arms with a matched control group on the incidence of stroke and other outcomes have not yet been reported.

The ongoing reducinG Stroke by Screening for UndiAgnosed atRial Fibrillation in Elderly inDividuals Study (GUARD-AF, ClinicalTrials.gov NCT4126486)[56] is a randomized trial of AF screening using the Zio XT (iRhythm, San Francisco, CA) patch monitor deployed within primary care practices. GUARD-AF aims to enroll 52,000 individuals aged ≥ 70 years and is designed to detect a potential reduction in incident stroke rates with AF screening.

Single-lead handheld ECG—There has been substantial recent interest in screening for AF using handheld devices with the ability to produce single-lead ECG waveforms. In the same STROKESTOP study by Svennberg et al. using 12-lead ECGs[54], the addition of up to 14 days of monitoring with a single-lead handheld ECG increased the rate of new AF detection from 0.5% to 3.0% (95% CI 2.7–3.5). In the Swedish stepwise screening study conducted by Engdahl et al.[55], two weeks of intermittent single-lead ECG recording led to a new diagnosis of AF in 7.4% (95% CI 5.2–10.4). In the Netherlands, Kaasenbrood et al.[57] performed pragmatic screening of individuals obtaining the influenza vaccine within 10 primary care practices. Using the MyDiagnostick handheld ECG device, 3,269 individuals (90.4% above age 60 due to Dutch influenza vaccine guidelines) were screened in a single day, with 37 (1.1%) of new AF cases detected. The majority of individuals diagnosed with new AF (78.4%) merited OAC based on an elevated CHA_2DS_2-VASc[10] stroke risk score.

Several studies have investigated deployment of AF screening in the pharmacy setting. In the Screening Education and Recognition in Community pHarmacies of Atrial Fibrillation (SEARCH-AF) study[58], iPhone-based single-lead ECG screening was deployed in 10 pharmacies in Sydney, Australia. Screening of 1,000 individuals resulted in newly identified AF in 15 (1.5%, 95% CI 0.8–2.5). Of these, 10 (1.0%) had no previous history of AF, and 9 were ultimately prescribed OAC for stroke prevention. Retrospective application of an automated AF detection algorithm to raw waveforms acquired from the single-lead ECG resulted in test sensitivity of 98.5% (95% CI 92–100) and specificity of 91.4% (95% CI 89–93) compared to cardiologist review. The Program for the Identification of “Actionable” Atrial Fibrillation in the Pharmacy Setting (PIAAF-Pharmacy) study screened individuals aged ≥ 65 years in 30 Canadian pharmacies with single-lead handheld ECG. Out of 1,145 individuals who underwent single time-point screening, a new diagnosis of AF was made in 24 individuals (2.4%, 95% CI 1.6–3.4).

Both SEARCH-AF and the STROKESTOP study performed basic cost-effectiveness analyses utilizing estimated efficacy and costs. In SEARCH-AF, screening was estimated to be cost-effective for men and women aged 65–84 years, with an incremental cost-effectiveness ratio of $4,066 per quality-adjusted life year saved. In STROKESTOP, deployment of the studied screening program was estimated to incur a cost of €4,614 ($5,039) per quality-adjusted life year saved. Although both of these estimates suggest that the cost-effectiveness of AF screening is favorable, both models depend on a reasonably high proportion of screen-positive patients receiving and persisting on OAC therapy.

Chan et al. have reported two non-randomized studies of AF screening in Chinese populations using handheld single-lead ECGs. In the first study, 13,122 individuals from Hong Kong were invited to participate in the screening intervention.[45] The overall prevalence of detected AF was 1.8% (95% CI 1.6–2.0). Of these, 101 individuals (0.8% of the screened population) were found to have previously unknown AF. In a second study of 5,969 individuals in a primary care setting in Hong Kong, AF was diagnosed in 72 patients (1.21%) and confirmed with a 12-lead ECG.[32]

Recently, a large randomized trial of single-lead handheld ECG screening has been reported, REHEARSE-AF.[59] Using the AliveCor Kardia monitor linked to a WiFi-enabled iPod, 1,001

individuals aged ≥65 years who were free of prevalent AF with a CHA_2DS_2-VASc score ≥2 were randomized to screening or routine care. Screened participants were instructed to acquire single-lead ECGs at home twice weekly over 12 months (with optional additional recordings for symptoms). At 12 months, twice-weekly ECGs were recorded by all participants in 39 of 52 study weeks, with at least one weekly ECG recorded by all participants in 48 of 52 weeks and 60,440 recordings taken in total. AF was diagnosed in 19 (3.8%) of individuals in the screening intervention arm versus 5 (1.0%) in the no screening arm (hazard ratio for AF diagnosis 3.9, 95% CI 1.4–10.4). There was no statistically significant difference in rates of ischemic stroke or transient ischemic attack in individuals randomized to screening versus no screening (4 vs. 8, hazard ratio 0.51, 95% CI 0.15–1.7), respectively. In a basic cost analysis, the overall cost of intervention was reported at $204,830, with an estimated screening-related cost per AF diagnosis of $10,780.

Photoplethysmography-based devices—The latest AF screening modality to be deployed are devices (e.g., smart-watch, band, smart phone) utilizing photoplethysmography (PPG) to detect peripheral pulse irregularity. One of the largest assessments of a wearable PPG-enabled device for AF screening, the Apple Heart Study, was recently reported.[47] The Apple Heart Study was a single-arm non-randomized screening intervention using a PPG-enabled Apple Watch linked to an iPhone app. Consumer volunteers who owned an Apple Watch and a compatible iPhone were invited to participate and download the Heart Study app if they reported no history of AF or use of an anticoagulant prior to enrollment. Detection of 5 of 6 irregular PPG-derived tachograms within a 48-hour period triggered a notification via the Heart Study app, notifying participants to contact a telemedicine physician for a consultation. Eligible individuals were then mailed a 7-day ECG patch monitor for confirmation. Of 419,297 participants, a pulse notification was triggered in 2,161 (0.52%) over 9 months. Patch monitors were sent to 658 of these participants, of which 450 were worn, returned, and considered analyzable. New AF was confirmed in 153 (34%) of these 450 individuals, or 0.036% of the overall study sample. Among 86 participants who received a pulse notification while wearing the ECG patch, 72 had demonstrable AF simultaneously on the patch, corresponding to a positive predictive value of 84% for the pulse notification. The planned HEARTLINE study (NCT04276441) will assess the efficacy of the Apple Watch Series 4 (capable of generating a single-lead ECG) to diagnose AF, encourage adherence to OAC therapy, and potentially prevent AF-related stroke.

A second PPG-based screening intervention was recently reported in the Huawei Heart Study based in China.[60] Consumers aged ≥18 years with an eligible Huawei phone running an Android operating system who owned a PPG-enabled device (smart watch or band) were invited to participate and download a mobile health app. Periodic PPG-based measurements were taken every 10 minutes, with a resulting 60 seconds of continuous data collection. Individuals could also trigger active measurements voluntarily. An alert for “suspected AF” would be initiated based on a proprietary automated PPG-based algorithm, after which individuals underwent confirmatory testing arranged either remotely or through networked hospitals. Over six months, 187,912 individuals underwent screening and 424 (0.23% of those screened) received an alert for “suspected AF.” Of these, 262 (61.8%) had follow-up

evaluations with a medical history, physical exam, and either ECG or 24-hour Holter monitor. Of the 262 with full assessments, 227 (87.0%) were confirmed as having AF. With confirmed AF using ECG or 24-hour Holter monitor as the gold standard, the PPG-based algorithm was estimated to have a PPV of 91.6% (95% CI 91.5–91.8).

An additional study, the Fitbit Heart Study[61], has recently launched and aims to validate a distinct PPG algorithm.

Future

AF screening will continue to grow in clinical use, as a result of current guidelines and endorsements based primarily on the ability of existing devices to accurately detect AF. The presence of affordable, consumer-facing devices coupled with a strong desire to avoid stroke will also continue to drive the uptake of AF screening, independent of the guideline process. The lack of benefit from empiric anticoagulation in several randomized trials in populations with a high prevalence of undiagnosed AF (e.g. post embolic stroke of undetermined source) leaves screening for AF as the current clinical approach.

Despite enthusiasm for AF screening, there are key unresolved issues that must be answered. These include which populations to screen, with what device, using what screening methodology, for how long to screen, and what duration or burden of AF is sufficient to justify initiation of OAC. Organizations such as the USPSTF are unlikely to endorse wide-spread, population-based AF screening among asymptomatic individuals until randomized trial data demonstrate a reduction in stroke with AF screening. Fortunately, there are now numerous randomized trials of AF screening which are either underway, or soon to start (Table 3) which are designed to be adequately powered to address many of these questions. The previously mentioned AF-SCREEN consensus group is also planning to perform individual-patient data meta-analysis of such trials. This will allow meta-regression, to help understand if there are any aspects of specific AF screening programs (e.g. setting, population, etc.) that lend themselves to a cost-effective reduction in stroke.

Another important consideration is the next steps following a new diagnosis of AF obtained via screening. As progressively more AF is detected using consumer devices, there may be an opportunity to leverage these very same devices to facilitate engagement in interventions known to reduce AF burden and symptoms, such as targeted weight loss[14], alcohol cessation[15], blood pressure control[62], and sleep apnea management.[63] Illustrating this principle, the mAFA II trial, which included a subset of individuals diagnosed with AF via screening with single-lead handheld ECG as part of the Huawei Heart Study, has recently reported a 4.1% absolute reduction in the primary endpoint of ischemic stroke, systemic thromboembolism, death, and rehospitalization (driven by a 3.3% reduction in rehospitalization) after randomization to a smartphone-based integrated care delivery app.[16]

There is also emerging interest in whether the efficiency of AF screening can be maximized by targeting individuals at highest risk for incident AF. Indeed, clinical risk factors,[64,65] biomarkers,[66] genetic predisposition,[67] cardiac structural features,[68,69] and electrocardiographic artificial intelligence algorithms[70] have all been reported to serve as

promising risk markers for AF which may facilitate screening. Many groups are also examining whether the combination of AF screening with other public health initiatives (e.g. blood pressure screening, vaccination, etc.) enhances screening acceptability to individuals and maximizes cost-effectiveness. The benefits of population-based AF screening will become much better understood over the next 5 years. It is plausible that multiple methods of screening for AF, rather than a single approach, will be considered acceptable in the future.

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Abbreviations

AF	Atrial fibrillation
OAC	oral anticoagulation
ESUS	embolic stroke of undetermined source
NAVIGATE-ESUS	New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source
RE-SPECT ESUS	Randomized, Double-Blind, Evaluation in Secondary Stroke Prevention Comparing the Efficacy and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate versus Acetylsalicylic Acid in Patients with Embolic Stroke of Undetermined Source
ATTICUS	Apixaban for Treatment of Embolic Stroke of Undetermined Source
ARCADIA	AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke
SAFE	Screening for Atrial Fibrillation with Electrocardiography
GUARD-AF	reducinG Stroke by Screening for UndiAgnosed atRial Fibrillation in Elderly inDividuals
SEARCH-AF	Screening Education and Recognition in Community pHarmacies of Atrial Fibrillation
PIAAF	Program for the Identification of “Actionable” Atrial Fibrillation
PPG	photoplethysmography

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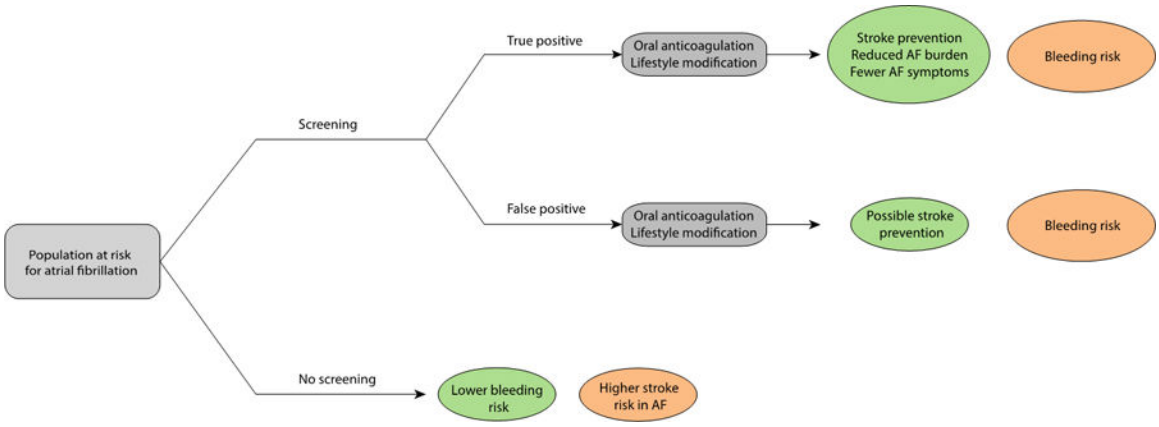

Figure 1.

Rationale, risks, and benefits of atrial fibrillation screening.

The rationale for atrial fibrillation screening is depicted, as well as the relevant benefits (green) and risks (orange) expected with each approach. Individuals with undiagnosed incident AF are at risk for developing cardioembolic stroke prior to initiation of risk-based anticoagulation. Screening may lead to earlier diagnosis of AF, initiation of risk-based anticoagulation to prevent strokes, and an opportunity to institute risk factor modification strategies (e.g., weight loss, alcohol cessation, blood pressure control, sleep apnea management) to reduce AF symptoms and burden.[14,15,62,63] For true positives (individuals with AF correctly identified as having AF using screening), the benefits may outweigh the risk of bleeding conferred by anticoagulation. For false positives (individuals without AF incorrectly identified as having AF using screening), the risk of bleeding likely outweighs any potential benefit of anticoagulation on non-AF related stroke. Without screening, fewer cases of otherwise undiagnosed AF will be identified, leading to lower overall bleeding risk from a lower rate of anticoagulation, but also more strokes resulting from unrecognized AF.

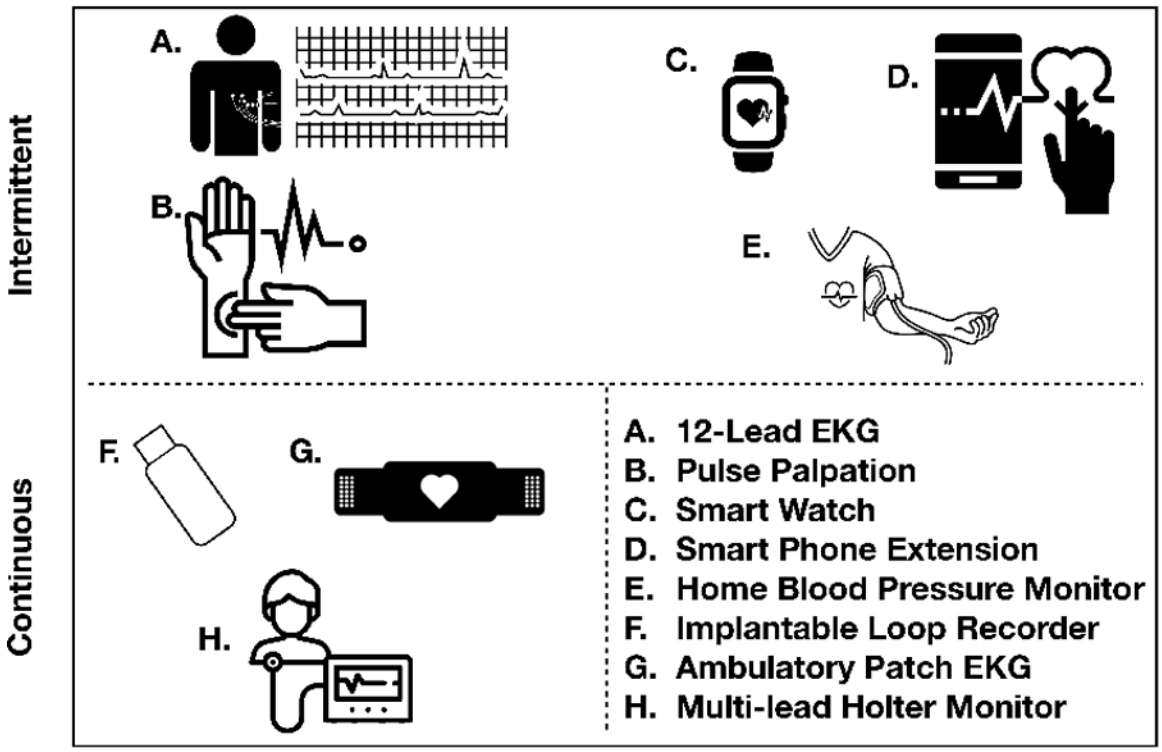

Figure 2.

Overview of atrial fibrillation screening modalities Depicted is a summary of established modalities for atrial fibrillation screening.

Modalities in the top row (A-E) detect atrial fibrillation using intermittent assessment of cardiac rhythm, while modalities in the bottom row (F-H) detect atrial fibrillation through continuous monitoring.

Table 1.

Summary of guideline recommendations and consensus statements pertaining to AF screening

Society	Year	Recommendation	Class / strength of recommendation	Level / quality of evidence
European Society of Cardiology[33]	2016	Opportunistic screening for AF is recommended by pulse taking or ECG rhythm strip in patients >65 years of age	I	B
		Systematic ECG screening may be considered to detect AF in patients aged 75 years or older, or those at high stroke risk	IIb	B
National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand[34]	2018	Opportunistic point-of-care screening in the clinic or community should be conducted in people aged 65 years or more	Strong	Moderate
United States Preventive Services Task Force[35]	2018	The current evidence is insufficient to assess the balance of benefits and harms of screening for AF with electrocardiography	I	-
European Heart Rhythm Association (endorsed by Heart Rhythm Society, Asia Pacific Heart Rhythm Society, and Sociedad Latinoamericana de Estiulacion Cardiaca y Electrofisiologia)[71]	2017	Opportunistic screening for AF is recommended by ESC guidelines in persons aged 65 years or older	Recommended	-
		Systematic ECG screening may be considered to detect AF in patients aged 75 years or older, or those at high stroke risk	Recommended	-
		ECG confirmation of AF is needed before considering the patient for anticoagulation therapy	Recommended	-
		Repeated recordings can be considered to document AF in selected asymptomatic patients	May be used	-
		When performed in high risk populations, screening for AF is advised because of its cost-effectiveness	May be used	-

Table 2.

Summary of non-randomized studies of atrial fibrillation screening

Author/study	Year	Country	Setting	Screened age (years)	N	Modality/approach	Screening period	New atrial fibrillation detection rate*
Wheeldon et al.[72]	1998	United Kingdom	Primary care	≥ 65	1,422	12-lead ECG	One-time	5.4%
Engdahl et al.[55]	2013	Sweden	Community invitation	75–76	848	12-lead ECG, then 2-week single-lead handheld ECG twice daily	2 weeks	1.0% (initial assessment) 3.5% (2 weeks)
Lowres et al. (SEARCH-AF)[58]	2014	Australia	Pharmacy	≥ 65	1,000	Single-lead handheld ECG	One-time	1.5%
Kearley et al.[53]	2014	United Kingdom	Primary care	≥ 75	1,000	Single-lead handheld ECG, blood pressure monitor	One-time	1.4%
Svennberg et al. (STROKESTOP)[54]	2015	Sweden	Community invitation	75–76	7,173	12-lead ECG, then 2-week single-lead handheld ECG twice daily	2 weeks	0.5% (initial assessment) 3.0% (2 weeks)
Kaassenbrood et al.[57]	2016	Netherlands	Influenza vaccination	≥ 60	3,269	Single-lead handheld ECG	One-time	1.1%
Chan et al.[73]	2016	Hong Kong	Community invitation	≥ 18	13,122	Single-lead handheld ECG	One-time	0.8%
Sandhu et al.	2016	Canada	Pharmacy	≥ 65	1,145	Single-lead handheld ECG	One-time	2.
Chan et al.[32]	2017	Hong Kong	Primary care	≥ 65	5,969	Single-lead handheld ECG, blood pressure monitor	One-time	1.2%
Quinn et al.[52]	2018	Canada	Primary care	≥ 65	2,171	Pulse palpation, single-lead handheld ECG, blood pressure monitor	One-time	0.6%
Perez et al.[47]	2019	United States	Consumer volunteers	≥ 22	419,297	PPG-based smart-watch followed by ECG patch in subset	9 months	0.52%† 0.036% (confirmed AF)
Guo et al. (Huawei Heart Study)[60]	2019	China	Consumer volunteers	≥ 18	187,912	PPG-based smart-watch or band followed by 12-lead ECG in subset	2 weeks to 6 months	0.23%† 0.12% (confirmed AF)

*at initial assessment unless otherwise specified

†abnormal pulse notification only

Table 3.

Summary of randomized trials of atrial fibrillation screening

Author/study	Year	Country	Setting	Screened age (years)	N	Modality/approach	Screening period	New atrial fibrillation detection rate
Morgan and Mant.[22]	2002	United Kingdom	Primary care	All	Systematic (N=1,499)	Pulse assessment and lead II rhythm strip	6 months	0.8%
					Opportunistic (N=1,502)	Clinical pulse assessment with discretionary 12-lead ECG if abnormal	6 months	0.5%
Fitzmaurice et al. (SAFE)[49]	2007	United Kingdom	Primary care	≥ 65	Systematic (N=4,933)	Pulse assessment and 12-lead ECG	One-time	1.62%
					Opportunistic (N=4,933)	Pulse assessment and 12-lead ECG *if abnormal*	One-time	1.64%
					No screening (N=4,936)	-	-	1.04%
Halcox et al. (REHEARSE-AF)[59]	2017	United Kingdom	Primary care or research visits	> 65	Screening (N=501)	Single-lead handheld ECG twice weekly	12 months	3.7%
					No screening (N=500)	-	-	1.0%
Steinhubl et al. (mSToPS)[48]	2018	United States	Health plan enrollees	≥ 75, ≥ 55 (male with 1 AF/stroke risk factor), ≥ 65 (female with 1 AF/ stroke risk factor)	Immediate screening (N=1,366)	Single-lead patch monitor for up to 14 days (screened period)	4 months	3.9%
					Delayed screening (N=1,293)	Single-lead patch monitor for up to 14 days (unscreened period)	4 months	0.9%

Table 4.

Ongoing studies of AF screening

Study	Country	Status	N	Modality	Approach	Endpoint
DANCAVAS[74]	Denmark	Nearly complete	35,000	3-lead ECG	One-time	All-cause mortality
STROKESTOP II[66]	Sweden	Nearly complete	8,000	Zenicor single-lead ECG	Twice daily for 14 days	New-onset AF Initiation of OAC
SCREEN-AF[75]	Canada	Recently completed	856	Zio patch monitor, WatchBP oscillometric device	2 weeks at start and at 3 months	New-onset AF
AF-CATCH[76]	China	Follow-up	7,641	AliveCor single-lead ECG	1x/yr vs. 4x/yr vs. 1x/wk in 1st month	New-onset AF
MonDAFIS[77]	Germany	Follow-up	3,470	Mobile telemetry	Post-stroke, up to 7 days	Oral anticoagulation
D2AF[78]	Netherlands	Ongoing	19,200	MyDiagnostick single-lead ECG, WatchBP oscillometric device	One-time	New-onset AF
LOOP[79]	Denmark	Ongoing	6,000	Implantable loop recorder	4 years continuous	Stroke or systemic embolism
mSToPS[48]	United States	Ongoing	6,000	Zio patch monitor	2–4 weeks	Stroke, systemic embolism, myocardial infarction, death
VITAL-AF[80]	United States	Ongoing	35,000	AliveCor single-lead ECG	At each encounter	New-onset AF
GUARD-AF[56]	United States	Ongoing	52,000	Zio patch monitor	2 weeks	Stroke Major bleeding
London Pharmacy Study[81]	United Kingdom	Starting soon	600	Pulse palpation, AliveCor single-lead ECG	One-time	Test accuracy of screening modalities
SAFER[82]	United Kingdom	Ongoing	120,000	Zenicor single-lead ECG	Twice daily for 14 days	Stroke
Fitbit Heart Study[61]	United States	Ongoing	100,000	Wrist-based PPG	Wearable PPG-based algorithm followed by ECG patch	New-onset AF

Table 5.

Summary of test characteristics of selected AF screening modalities

Modality	Sensitivity (reported range)	Specificity (reported range)	References
Pulse palpation	91.6 (16.0–100)	78.8 (65.0–91.0)	17,20,22,50
12-lead ECG	92.7 (66.0–100)	97.4 (85.0–98.0)	18,50
Blood pressure cuff	95.5 (69.5–98.6)	91.9 (86.7–98.9)	32,50,53
Single-lead ECG	96.1 (36.8–98.0)	94.0 (91.4–100)	21,50,83
Patch monitor	100 *	96.6 *	84
Photoplethysmography	92.9 (77.0–100.0)	97.7 (86.7–99.7)	47,50,60,73

* Uncertainty not reported