Circulation

FRONTIERS

Research Priorities in Atrial Fibrillation Screening

A Report From a National Heart, Lung, and Blood Institute Virtual Workshop

ABSTRACT: Clinically recognized atrial fibrillation (AF) is associated with higher risk of complications, including ischemic stroke, cognitive decline, heart failure, myocardial infarction, and death. It is increasingly recognized that AF frequently is undetected until complications such as stroke or heart failure occur. Hence, the public and clinicians have an intense interest in detecting AF earlier. However, the most appropriate strategies to detect undiagnosed AF (sometimes referred to as subclinical AF) and the prognostic and therapeutic implications of AF detected by screening are uncertain. Our report summarizes the National Heart, Lung, and Blood Institute's virtual workshop focused on identifying key research priorities related to AF screening. Global experts reviewed major knowledge gaps and identified critical research priorities in the following areas: (1) role of opportunistic screening; (2) AF as a risk factor, risk marker, or both; (3) relationship between AF burden detected with long-term monitoring and outcomes/treatments; (4) designs of potential randomized trials of systematic AF screening with clinically relevant outcomes; and (5) role of AF screening after ischemic stroke. Our report aims to inform and catalyze AF screening research that will advance innovative, resource-efficient, and clinically relevant studies in diverse populations to improve the diagnosis, management, and prognosis of patients with undiagnosed AF.

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With the aging of the population and improved survival with cardiovascular disease, the age-adjusted incidence and prevalence[1] and lifetime risk[2] of atrial fibrillation (AF) are increasing in the United States and globally.[3] The epidemic of AF has been accompanied by increased awareness of its complications, including ischemic stroke, cognitive impairment, dementia, heart failure, myocardial infarction, arterial and venous thromboembolism, chronic kidney disease, diminished quality of life, increased health care costs, and premature death.[3]

In 2009, the National Heart, Lung, and Blood Institute (NHLBI) identified research opportunities for the prevention of AF that were based on the proceedings of an NHLBI expert workshop.[4] A decade later, the NHLBI initiated a series of webinars bringing together international AF leaders to characterize ongoing research gaps and new opportunities to inform and accelerate future AF research. The novel webinar format was pursued by NHLBI to capture the expertise of global AF leaders in a resource-effective and timely fashion. The 2 workshops focused on AF ablation[5] and the bidirectional relations between AF and heart failure.[6] This article represents the

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outcome of the third virtual workshop, held December 6, 2019, which focused on AF screening.

Using commercial and Medicare administrative claims databases, experts estimate that ≈4.6 million Americans have diagnosed AF, whereas ≈700 000 (13%) have undiagnosed AF.[7] However, AF often is unrecognized clinically until the onset of complications. Simultaneously, AF is increasingly being detected by consumer-owned devices, with uncertain clinical implications. Hence, patients, clinicians, researchers, health systems and organizations, private and public payers, and governmental agencies have intense interest in delineating the optimal role of and approach to screening for AF. Numerous technologies can be used to screen individuals for AF, including the gold standard ECG, novel noncontact technologies,[8] noninvasive devices that detect pulse irregularity at a single time point, wearable devices such as smartwatches and patches, and implanted devices that monitor electrocardiographic rhythm long term.[9] The underlying premise of AF screening is that early detection will prompt management changes to potentially prevent progression and complications of AF.

There are many unanswered questions about the role of AF screening, uncertainty about the therapeutic implications of screen-detected AF, and concerns that AF screening may engender unwarranted testing, treatments, costs, and complications. The workshop covered the following topics related to AF screening: (1) role of opportunistic AF screening; (2) AF as a risk factor, risk marker, or both; (3) relations between AF burden detected with long-term monitoring and treatments/outcomes; (4) designs of potential randomized trials of systematic AF screening with clinically relevant outcomes; and (5) role of AF screening after ischemic stroke. The individual topic frameworks and recorded webinar will be posted on the NHLBI website simultaneously with the publication of this report. This document seeks to identify AF screening research opportunities that will be impactful, innovative, resource efficient, and clinically relevant with the ultimate goal of improving the detection, management, and prognosis of patients with undiagnosed AF.

OPPORTUNISTIC SINGLE-TIME-POINT SCREENING FOR AF

Background

Incidentally detected AF and opportunistic single-time-point screening (OppSTS) occur in usual clinical practice during in-person clinic visits made for reasons other than screening for AF. The distinction between incidentally detected AF and OppSTS is that OppSTS occurs when primary care providers are encouraged to systematically screen for AF during routine consultations by examining pulse palpation, auscultation, or blood pressure checks in patients at heightened risk for AF (eg, patients ≥65 years of age); if pulse irregularity is detected, a follow-up ECG is obtained to confirm AF.[10,11] OppSTS was not considered screening by the US Preventive Services Task Force, which regarded OppSTS as prompted pulse taking.[12] OppSTS has been shown to be feasible in selected practice settings, may be cost-effective, and is recommended by a variety of professional societies and organizations (Figure 1).[9,13–15] Systematic screening occurs when a target population (individuals ≥65 years of age or with heart failure, etc) is requested to undergo screening for AF, which may involve single or intermittent testing or continuous recordings of variable duration. In 2018, the US Preventive Services Task Force concluded that current evidence was insufficient to recommend routine systematic electrocardiographic screening for AF and noted the need for additional randomized, controlled trials (RCTs) evaluating the benefits and harms of systematic AF screening compared with usual care.[12] Hence, an understanding of OppSTS is essential as a potential comparator for pragmatic RCTs of systematic screening.

The yield of OppSTS is highly variable, depending on age, multiple demographic and clinical factors, most of which are related to underlying risk of AF, and the OppSTS strategy and screening modality (Figure 1). OppSTS detects 1.4% of patients with previously unrecognized AF if the age criterion of ≥65 years is used, with higher results in men than in women (regardless of detection method, setting, or region).[16] In a meta-analysis of 19 single-time-point screening studies from around the world with electrocardiographic verification of the AF diagnosis, the number needed to screen to detect 1 person ≥65 years of age with a Class 1 recommendation for anticoagulation (throughout the document, anticoagulation refers to oral forms) was 83.[16]

Despite the higher incidence and prevalence of clinically detected AF in individuals of European ancestry,[3] a recent multiethnic systematic screening study (mean age, 74 years; 51% women) reported that AF detected by electrocardiographic patch, which screened continuously for 14 days, was similar across race/ethnic groups. AF detection was 7.1% in White individuals, 6.4% in Black individuals, 6.9% in Hispanic individuals, and 5.2% in Chinese individuals (versus White individuals, all $P>0.50$).[17] The rates were considerably higher than age- and sex-adjusted rates reported from a single-time-point AF screening meta-analysis of individuals ≥65 years of age (≥1.44%) and <65 years of age (0.41%), presumably because of the longer screening duration and higher screening intensity.[16] The similar detection rates with systematic AF screening provide support for the hypothesis that racial variation in clinical AF partially reflects ascertainment bias and motivates the critical need to ensure that screening studies include diverse patient populations. The call for greater

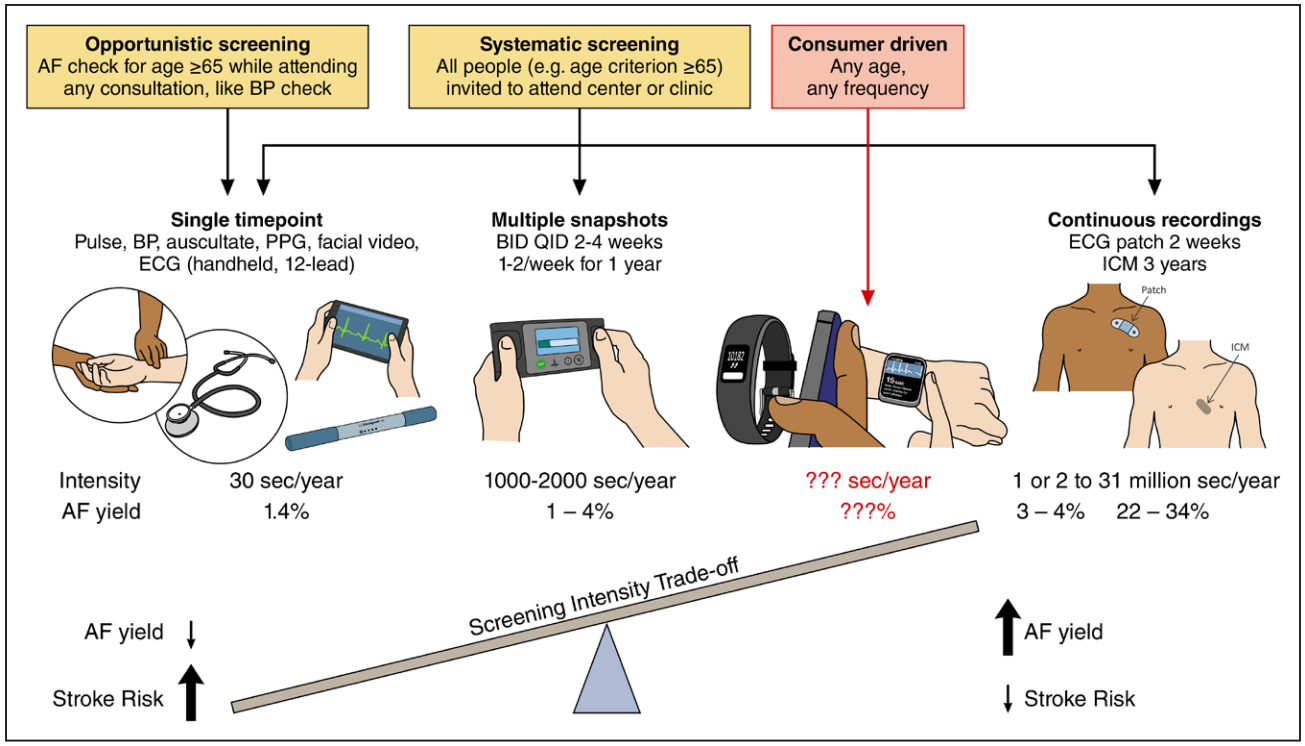

Figure 1. Comparison of opportunistic single-time-point screening with systematic and consumer-led screening.
Tradeoffs between screening intensity/atrial fibrillation (AF) yield and stroke risk of screen-detected AF along the screening intensity continuum are illustrated. BID indicates twice daily; BP, blood pressure; ICM, intracardiac monitor; PPG, Photoplethysmogram; and QID, 4 times a day.

inclusion of ethnic/racial minorities in AF patients is further supported by a study reporting the substantial underrepresentation and underreporting of racial and ethnic minorities in the clinical studies cited in current guidelines for AF.[18]

It has not been definitively proven that AF detected by OppSTS carries a risk of thromboembolism comparable to that of clinically recognized AF. However, given strong evidence from RCTs for net benefit of anticoagulation in patients with clinically recognized AF and other stroke risk factors, a placebo-controlled RCT of anticoagulation in OppSTS-detected AF may be challenging to perform. Thus, the prognosis of AF detected incidentally during a clinical encounter has been studied as a surrogate for OppSTS-detected AF. The prognosis of incidentally detected asymptomatic AF appears no different from or may be even worse than that of clinically detected AF with symptoms,[19] and the risk reduction observed with anticoagulation appears to be similar.[20] These data underlie the viewpoint supporting OppSTS now.[11] However, this viewpoint is tempered by several factors, including recognition that (1) the likelihood of detecting AF with OppSTS is heterogeneous; (2) those with AF detected have variable risk of stroke and other outcomes; (3) the accuracy of OppSTS varies by screening strategy and modality; (4) false-positive screening tests may carry particular risks of economic, medical (including bleeding), and quality of life consequences; and (5) strong evidence for the role of treatment such as routinely recommended anticoagulation in improving outcomes in screen-detected AF is lacking.

Knowledge Gaps

Randomized trials of OppSTS versus no screening to prevent stroke or death are lacking, and it is uncertain whether the prognosis of OppSTS-detected AF and the prognosis of clinically detected AF are the same. These questions can be answered by screening studies with appropriate inclusion criteria and enough follow-up time to ascertain end points for which clinical management may change if AF is detected (Figure 2). RCTs would be required to demonstrate that OppSTS has a net benefit compared with usual care. However, OppSTS is already part of routine high-quality clinical care in many settings, and the large sample size required and study expense would make enrollment in stand-alone trials of OppSTS challenging. Alternative approaches would be to direct resources toward systematic screening studies comparing greater screening intensity with usual OppSTS.[21] OppSTS studies also could be designed as pragmatic trials involving integrated health care delivery systems using cluster designs and electronic health record tools for cost-efficient outcome assessments.

Randomized trials of OppSTS might target individuals eligible for guideline-directed anticoagulant therapy to prevent stroke and death.[15] Given the paucity of screening data in racially/ethnically diverse individuals,

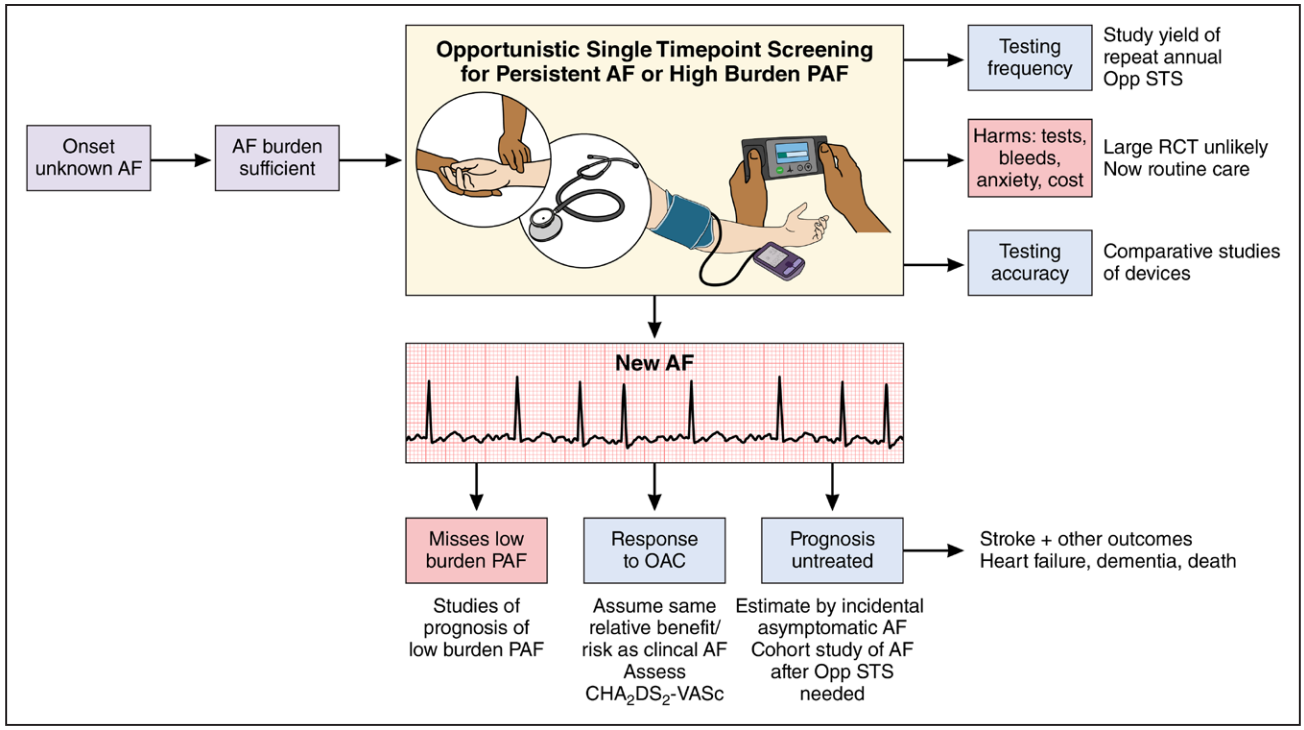

Figure 2. Opportunistic single time point screening for atrial fibrillation (AF).
Questions remain about screening test accuracy by methodology, how often to screen, harms from screening, and whether treating screen-detected AF has the same benefits as clinically detected AF. OAC indicates oral anticoagulant; Opp STS, opportunistic single-time-point screening; PAF, paroxysmal atrial fibrillation; and RCT, randomized, controlled trial.

it will be essential to ensure that screening studies include adequate numbers of individuals of non-European ancestry.

There is insufficient information on the relation of detection method (eg, manually checked pulse, pulse-based technologies, single-lead, multiple limb–lead ECG, or noncontact) to accuracy and prognosis. An additional area of uncertainty is the balance between screening-related benefits and potential adverse outcomes that may ensue from false-positive screening tests, including additional tests, additional procedures, and treatment-related complications (eg, bleeding and worse quality of life).

Other knowledge gaps relate to how the type of AF detected may affect outcomes. For instance, it is uncertain how stroke risk varies with the proportion of cases of AF detected by OppSTS that is persistent or the degree of AF burden in those with paroxysmal AF. In addition, the incremental annual detection rate of OppSTS in those previously undiagnosed with AF is unknown. Stratification by AF type in pertinent studies is needed to inform requirements for repeated OppSTS (until AF detection) versus more intensive screening strategies.

Research Opportunities

1. Examine the outcomes of OppSTS-detected AF in ethnically/racially diverse studies such as pragmatic trials or prospective cohort studies comparing carefully matched OppSTS-detected AF with clinically detected AF to generate knowledge about their relative prognoses.
2. Determine the proportion of OppSTS-detected AF that is persistent by conducting observational and administrative studies that examine extended monitoring and follow-up.
3. Study the impact of detection-method accuracy (including newer technologies) on beneficial health outcomes versus additional unnecessary tests and procedures and diminished quality of life. This research could include prospective comparative studies, pragmatic trials, and RCTs of different devices and screening strategies with stroke, mortality, and other clinically relevant end points in diverse populations.

AF: RISK FACTOR, RISK MARKER, OR BOTH?

Background

AF is a potent risk factor for cardioembolic stroke, mechanistically linked through reduced left atrial flow velocities and formation of thrombus, primarily in the left atrial appendage.[22] A higher burden of AF has been associated with increased ischemic stroke risk,[23–25] supporting a causal link between altered atrial hemodynamics induced by AF and thromboembolic risk. The AF burden–stroke

association, however, relies on secondary analyses that may be confounded by differences in the clinical risk profile of individuals with low versus high AF burden. Studies are ongoing to clarify whether treating AF early with rhythm control or upstream therapies prevents major adverse cardiovascular events, which would potentially enhance the justification to research AF screening strategies in individuals at intermediate or high estimated risk.[26]

Alternatively, AF may serve as a risk marker of stroke. Stroke risk factors overlap significantly with factors predicting the development of AF.[27,28] Lower left atrial flow velocities and stasis are related to stroke risk, as evaluated by the CHA_2DS_2-VASc score,[29] implying an interaction between risk and atrial hemodynamics. Moreover, current approaches to restore sinus rhythm do not eliminate stroke risk despite causing significant reductions in AF burden,[30] consistent with evidence that anticoagulation is also effective in preventing ischemic stroke in high-risk patients in sinus rhythm and without a history of AF.[31] Conversely, despite having a major impact on left atrial hemodynamics, AF does not increase stroke risk to a level that warrants anticoagulation in young patients with low CHA_2DS_2-VASc score.[32] In addition, stroke risk predicted with the CHA_2DS_2VASc score is modulated by AF burden, with low risk upgraded by high AF burden and vice versa in some studies,[24] whereas other studies have reported that greater AF burden is linked to higher stroke and transient ischemic attack (TIA) risk independently of predicted risk using the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation Study) or CHA_2DS_2-VASc score.[33]

Mortality is higher in patients with stroke with AF than in individuals who have either AF or stroke, regardless of whether AF precedes or follows the stroke, suggesting a common pathway for both conditions.[34] Together with recent data showing that thromboembolic events may occur remotely from AF episodes,[34,35] these findings indicate that long-term exposure to the environmental and genetic risk factors that promote AF also may independently promote thromboembolic events.

A similar paradigm applies to other end points. For instance, heart failure is both a cause and a complication of AF.[36] Whereas restoration of sinus rhythm has been found to be beneficial in selected patients with heart failure with AF,[37] left ventricular energetics and perfusion are impaired even in patients with so-called lone AF and do not fully recover after successful ablation.[38] Similarly, a meta-analysis reported that AF was associated with increased risk of myocardial infarction (relative risk, 1.54 [95% CI, 1.28–1.85]),[39] and conversely, myocardial infarction is included in risk prediction models for AF (hazard ratio, 1.64 [95% CI, 1.38–1.96]).[28]

Knowledge Gaps

Taking the existing evidence into consideration, it would seem logical to monitor heart rhythm periodically in individuals at high risk for AF and, more specifically, in those individuals who would be expected to benefit most from anticoagulation and aggressive risk factor management if AF were diagnosed. An alternative approach would be to combine major adverse cardiovascular events (eg, stroke, heart failure) risk stratification with the probability of incident AF using ECG, imaging, blood biomarkers, and genetic/genomic markers (Figure 3). Management (eg, anticoagulation) decisions might be based on more precise risk assessment of both conditions rather than AF detection alone. The former approach is supported by data indicating, for example, a significant association between left atrial dilatation and the probability of detecting AF with implantable devices[40] and the predictive value of these and other parameters (eg, NT-proBNP [N-terminal pro-B-type natriuretic peptide] and left atrial function[41]) for stroke risk. These strategies, however, have not been systematically tested, nor has their respective cost-effectiveness been compared.

More sophisticated atrial and ventricular phenotyping could play an important role not only in refining stroke risk but also in risk stratification for predicting the development of heart failure and other outcomes in the presence of AF. Such modalities might include the detection of diffuse fibrosis (eg, by T1 mapping cardiovascular magnetic resonance imaging), the evaluation of myocardial metabolism and energetics (eg, by 31P magnetic resonance spectroscopy or hyperpolarized carbon-13 cardiovascular magnetic resonance imaging),[38,42] or the assessment of local inflammation by computed tomography.[43] In individuals in sinus rhythm, identification of early myocardial markers for risk of stroke and other AF-related complications such as heart failure may aid the selection of patients who would benefit from more intensive AF screening and potentially preventive therapies. A deeper knowledge of the myocardial and systemic substrates of AF may stimulate RCTs of new or repurposed agents.[44]

An emerging area of AF screening research involves artificial intelligence (AI) algorithms of electronic health records, electrocardiographic signals, imaging data (eg, echocardiographic, cardiovascular magnetic resonance), noncontact facial monitoring,[8] and biomarker/genomic data. A recent large-scale, but single-center, retrospective study demonstrated the feasibility of an AI-based electrocardiographic algorithm for detecting the likelihood of previous AF (by ECG) on the basis of sinus rhythm ECGs.[45] Machine learning could potentially enhance identification of future AF risk and associated complications.[46–48] For example, an AI model incorporating time-dependent serial prothrombin international normalized ratio times in the first 30 days of enrollment in the GARFIELD-AF registry (Global Anticoagulant Registry in the Field–Atrial Fibrillation) has been reported to predict major bleeding, stroke/systemic embolism, and

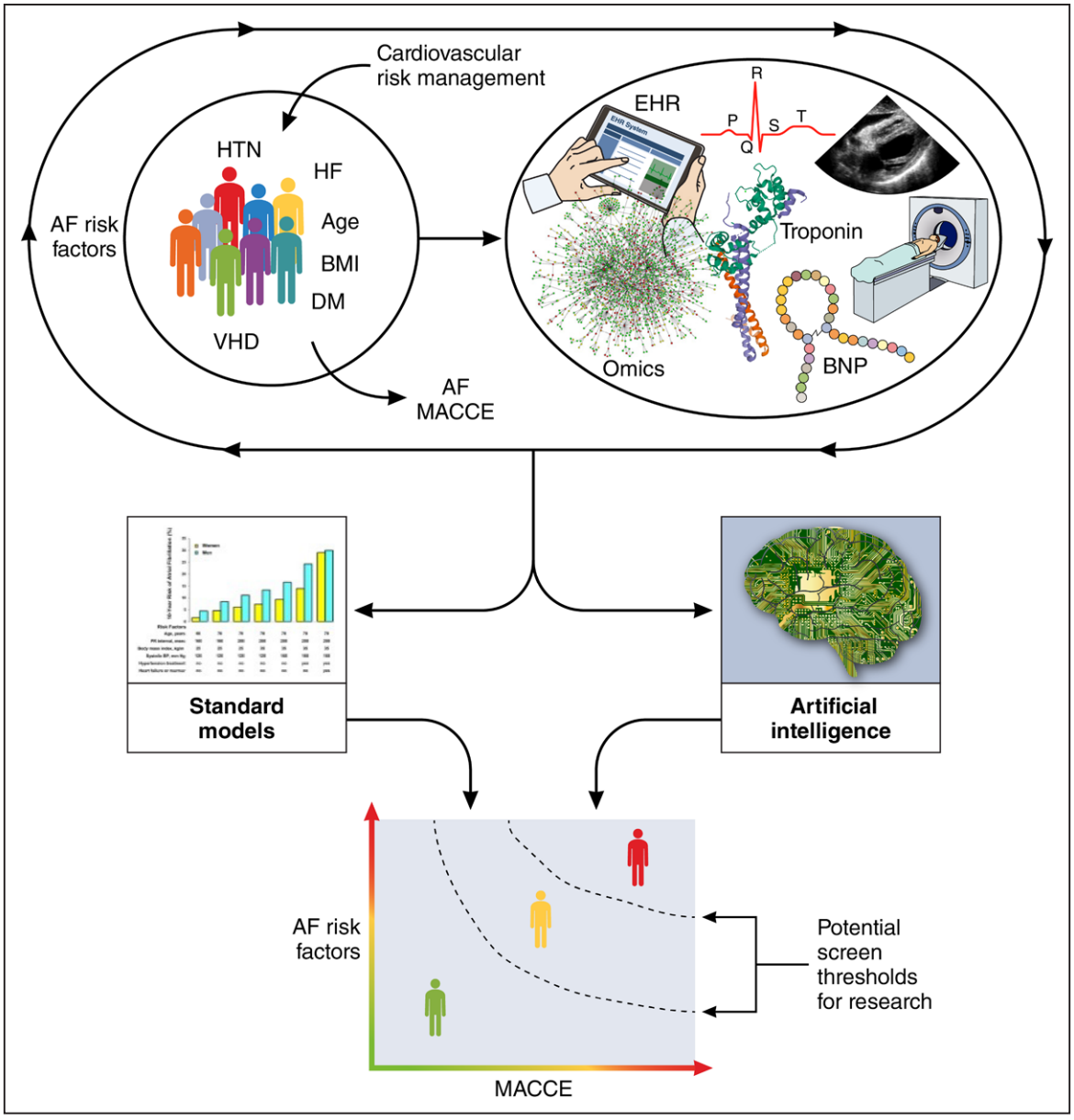

Figure 3. Both atrial fibrillation (AF) risk factors (left, some examples given) and health data, including sophisticated imaging and biomarker data, may distinguish individuals at low (green), intermediate (yellow), and high (red) risk, in terms of both incident (or recurrent) AF and major adverse cardiovascular and cerebrovascular events and conditions (MACCEs).

Both retrospective and prospective studies should compare risk prediction by standard models and artificial intelligence, taking the elements within upper main ellipse into account, including response to risk management, incident AF, and MACCEs. The strategy for prioritization of research would focus most efficiently on people with high risk of AF and MACCEs (upper potential screen threshold for research). BMI indicates body mass index; BNP, brain natriuretic peptide; DM, diabetes; EHR, electronic health record; HF, heart failure; HTN, hypertension; and VHD, valvular heart disease.

death more effectively than time in therapeutic international normalized ratio range.[49] However, many AI studies to date are not transparent, have not been externally validated,[50] and are susceptible to bias.[51,52] In addition, the advantage of AI algorithms over standard risk prediction models[47] and their implications for clinical decision making, including intensification of screening for AF or treatment decisions, remain uncertain. Furthermore, AI-derived noncontact monitoring raises potential privacy concerns. However, if validated and guided by equity and integrity, AI may advance AF screening research and improve the precision of AF care.

Research Opportunities

1. Use large-scale longitudinal studies to generate data on systemic and myocardial (especially atrial myopathy) substrates of AF using ECG, echocardiography, cardiovascular magnetic resonance, computed tomography, and biomarkers (traditional, genetic, and omic) to demonstrate whether estimated risk of AF and AF-related complications (eg, major adverse cardiovascular and cerebrovascular events and conditions such as stroke, heart failure, and dementia) can be refined. Such data

will assist in prioritizing research in screening individuals with undiagnosed AF and research to discover novel therapeutic targets.

2. Investigate and validate AI algorithms and standard risk prediction models of cross-sectional and longitudinal data, including electronic health record, electrocardiographic, biomarker, genetic/omic, and imaging data, while adhering to privacy protections, transparency, diversity, equity, and inclusiveness. Priorities for research would test whether implementing or intensifying AF screening and predicting which patients with screen-detected AF will develop complications will result in net clinical benefit.

BURDEN OF AF AND DETECTION OF AF WITH DIFFERENT TECHNOLOGIES

Background

In AF, stroke risk stratification schema such as $CHADS_2$, CHA_2DS_2-VASc, Framingham, and ATRIA were developed from populations of patients with clinically diagnosed AF without respect to AF burden (defined as total density or percent of time in AF) or duration. Over the past decade, there have been dramatic advances in diagnostic monitoring and detection of AF across a variety of implantable, noninvasive, and consumer-facing wearable devices, which have enabled near-continuous detection of short, often subclinical, arrhythmia episodes.[53,54] Population screening also has been proposed with these devices.[9]

In patients with cardiac implantable electronic devices (CIEDs), observational data have shown that atrial high-rate episodes (AHREs) as short as 6 minutes are associated with incident clinical AF and incident ischemic stroke.[55] There is, however, a risk gradient because higher risk of stroke is associated with longer AHREs, especially those ≥24 hours.[23] Studies from implantable and noninvasive devices have shown a stroke-risk gradient based on AF burden, AF duration, and cardiovascular risk factors.[24,33] However, earlier studies also have reported temporal dissociation between AF episodes and ischemic stroke events,[34,35] albeit a higher stroke risk in the 5 days after AF occurrence.[35] Temporal discontinuity data suggest that AF may be a marker of thrombogenic substrate and vascular risk, even during prolonged periods of sinus rhythm.

The accuracy of consumer devices used for the detection of AF also is uncertain. For instance, a recent meta-analysis of 10 studies noted that smartphone camera applications to detect AF had reasonably high sensitivity (94.2%), specificity (95.8%), and negative predictive value (99.8%). However, the authors reported that the included studies had methodological limitations and modest positive predictive values (20.5%-39.2%), even when restricted to individuals ≥65 years with hypertension.[56] The authors concluded that, in asymptomatic individuals, the false-positive AF results exceeded the true-positive AF results.

The absence of RCT data anchored on AF burden thresholds that should prompt anticoagulation has led to large evidence gaps and substantial treatment variation related to anticoagulation.[57,58] RCTs are ongoing for CIEDs[59–61] and implantable loop recorders in higher-risk individuals ≥70 years of age (Danish LOOP [Atrial Fibrillation Detected by Continuous Loop Monitoring]; NCT02036450).[62] Nevertheless, evidence gaps are likely to remain for atrial arrhythmias detected from a range of medical and consumer-grade devices.[63]

Knowledge Gaps

It is unknown whether the pathophysiology of stroke in patients with clinically diagnosed AF and that of subclinical AF (SCAF) or device-detected AHREs are the same and whether anticoagulation reduces stroke risk in patients with CIED-detected AHREs/SCAF (Table 1). It is unknown whether AF burden or the longest episode of AF better predicts AF-related complications. In addition, research is needed to establish the optimal thresholds for AHREs/SCAF burden and duration that merit anticoagulation and how such thresholds should vary depending on the extent of coexisting clinical stroke risk factors, other comorbidities, and bleeding risk.

The optimal frequency, intensity, and type of AF monitoring are not established. It is unknown which device is most cost-effective to screen for AF in different patient groups and whether clinical and cost-effective AF screening can be achieved with intermittent electrocardiographic (single- and 12-lead) snapshots. It is also undetermined how data from pacemakers, implantable cardioverter-defibrillators, implantable loop recorders, wearable devices, and noncontact approaches calibrate with each other for AF burden and risk of outcomes.

A major unanswered question is the balance between potential benefits and risks of consumer-driven screening. Consumers have increasing access to commercial devices that have the potential to diagnose AF early, offering the hope that AF progression and complications can be prevented. However, evidence is lacking in several areas, including which segments of the population to target for screening, whether early detection of AF prevents progression and complications, and what strategies could prevent AF progression and complications such as neurohormonal modulators, anti-inflammatory medications, antifibrosis therapies, and aggressive risk factor management.

In addition, there are major concerns about unintended consequences of consumer-driven screening. For instance, will individuals with previous paroxysmal AF be falsely reassured by the absence of detected AF

Table 1. AF Burden Measurement in Diagnostic Devices, Clinical Evidence Based on AF Duration, and Knowledge Gaps and Opportunities

Device	Context of AF identification	AF burden measurement	Duration of detected atrial arrhythmias	Expected incremental increase in risk of stroke	Type of evidence for benefit of oral anticoagulation
Insertable cardiac monitor	Continuous, programmable; device-detected AF	Yes	AT without AF	Lower	No data
Implantable pacemaker or defibrillator	Continuous, programmable; device-detected AF	Yes	Very short (<6 min)		No data
Patch-based ambulatory electrocardiographic monitor	5-14 d continuous	Yes	Subclinical Short (6 min–24 h)		Observational data; ARTESIA and NOAH-AFNet trials ongoing
Pulse and ECG-capable smartwatch	Opportunistic pulse checking; user-prompted ECG rhythm strip	No	Clinical Paroxysmal		Randomized trials
Portable smartphone-connected single or multichannel ECG	User-prompted ECG rhythm strip	No	Clinical Persistent (weeks/months)		Randomized trials
12-Lead ECG or telemetry rhythm strip	Clinical presentation	No	Clinical Permanent (months/years)	Higher	Randomized trials

AF indicates atrial fibrillation; ARTESIA, Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation; AT, atrial tachycardia; and NOAH-AFNet, Non-Vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes Trial.

if devices are used intermittently? There are uncertainties about the potential for complications from treatment of falsely diagnosed AF or AF not destined to cause harm such as increased patient anxiety, downstream testing/treatment financial costs, and anticoagulation or rhythm control–related complications.[12] There are also nontrivial health system concerns such as unintended exacerbation of health care disparities and increased frontline clinician stress from managing growing volumes of consumer-detected findings in the absence of evidence-based algorithms for follow-up testing and treatment, creating uncertainty and potential liability.

Research Opportunities

1. Investigate whether the pathophysiology of ischemic stroke in patients with clinically diagnosed AF is the same as that in individuals with device-detected AHREs/SCAF using various study designs (eg, registry, observational cohort), and test whether anticoagulation reduces the risk of stroke in patients with AF detected by implanted monitors, wearables, and consumer devices (RCTs).
2. With technologies that can screen heart rhythms for longer periods of time and detect shorter episodes of arrhythmia, assess the optimal AF burden or AF episode duration threshold for prompting specific treatments, including anticoagulation and risk factor treatment and lifestyle modification. Study how such thresholds should be modified in the setting of specific comorbidities (using data from RCTs, registries, post hoc analyses from RCTs) or screening device type used (eg, noninvasive wearables, implantable loop recorders, CIEDs).
3. Rigorously study the patient-, clinician-, and health system–level consequences of patient-initiated screening with consumer devices to develop and assess implementation algorithms for downstream testing and management (implementation science, registries, electronic health record data analyses, and RCTs) and to eliminate health care disparities related to screening.

RANDOMIZED STUDY OF SYSTEMATIC AF SCREENING WITH CLINICALLY RELEVANT OUTCOMES

Background

The creation of population-based AF screening programs to prevent stroke is attractive because such programs fulfill most of the Wilson-Junger criteria for successful screening programs.[64] AF is prevalent, is clearly associated with stroke[65] and other adverse outcomes,[66] can be identified in a preclinical phase, and can be treated with anticoagulation, which is highly effective at preventing ischemic stroke.[67] However, prevention-oriented organizations have not uniformly endorsed AF screening,[12,68] given the lack of RCT evidence that AF screening prevents stroke and concern that false positives will lead to higher costs, downstream testing, and bleeding. Nevertheless, direct-to-consumer AF detection devices are becoming more widely used.[69,70]

Numerous studies have documented that a variety of technologies can detect AF in different populations;[71–73] however, extrapolation to the impact of AF detection

on stroke[21] and other adverse outcomes has not compelled the introduction of population-based screening.[12] Several large trials are underway (Table I in the Data Supplement). It is also recognized that a single screening strategy is unlikely to be suitable for every patient population, health care setting, or country.

Whereas the vast majority of AF-screening efforts have focused on AF detection to prevent stroke, the most common outcomes after AF are death and heart failure.[74] As mentioned, AF predisposes to a wide array of other outcomes,[66] including cognitive decline,[75] dementia,[76] chronic and end-stage kidney disease,[77] extracranial systemic emboli,[78] venous thromboembolism,[79] myocardial infarction,[39] heart failure,[39,77] sudden death,[77] lower quality of life,[80] physical disability,[81] higher health care costs,[82] hospitalizations,[83] and all-cause mortality.[77] Hence, there is a need to examine other end points in AF screening studies, particularly cardiovascular, cognitive, health system, and mortality outcomes. Similarly, there is a need to develop an evidence base of effective strategies to prevent nonstroke complications of AF.

Knowledge Gaps

It is unclear whether population-based AF screening programs can prevent stroke and do so cost-effectively (Figure 4). It is also uncertain whether asymptomatic individuals with AF incidentally identified by implanted, wearable, or direct-to-consumer devices benefit from anticoagulation. Several knowledge gaps must be addressed before RCTs can attempt to answer these questions. For example, what population is optimal for AF screening? Both the prevalence of AF and the risk of stroke increase with advancing age; thus, screening older populations (eg, ≥65 or ≥75 years) may be most resource effective. AF and stroke risks increase further in individuals with additional clinical risk factors or biomarkers; whether such factors should be considered in the selection of patients for screening should be examined. The best screening method also is uncertain. Single-time-point, reusable devices are inexpensive and may be cost-effective, particularly because they detect mostly persistent AF, which has a higher stroke risk. However, long-term ambulatory electrocardiographic monitoring is more sensitive and could also be cost-effective if its cost decreases. Algorithms to minimize false positives also will be essential. In addition, one must define the threshold of AF burden that is associated with stroke risk, particularly given the long-term monitoring capabilities of consumer devices. Finally, one must demonstrate that screen-detected AF leads to initiation of therapies that result in a reduction of stroke and other outcomes.

Several RCTs of AF screening are now ongoing or in development, totaling >300 000 patients (see Table I in the Data Supplement for examples of completed and ongoing studies). Given the mathematical and logistical challenges of translating AF detection into stroke prevention, the AF screening community and public will require RCT data to understand what components of screening strategies work best and to define which strategies work best in specific patients, settings, and countries. Ideally, data will be meta-analyzed across studies to enhance the ability to define subgroups of patients with AF who are most likely to benefit from screening.

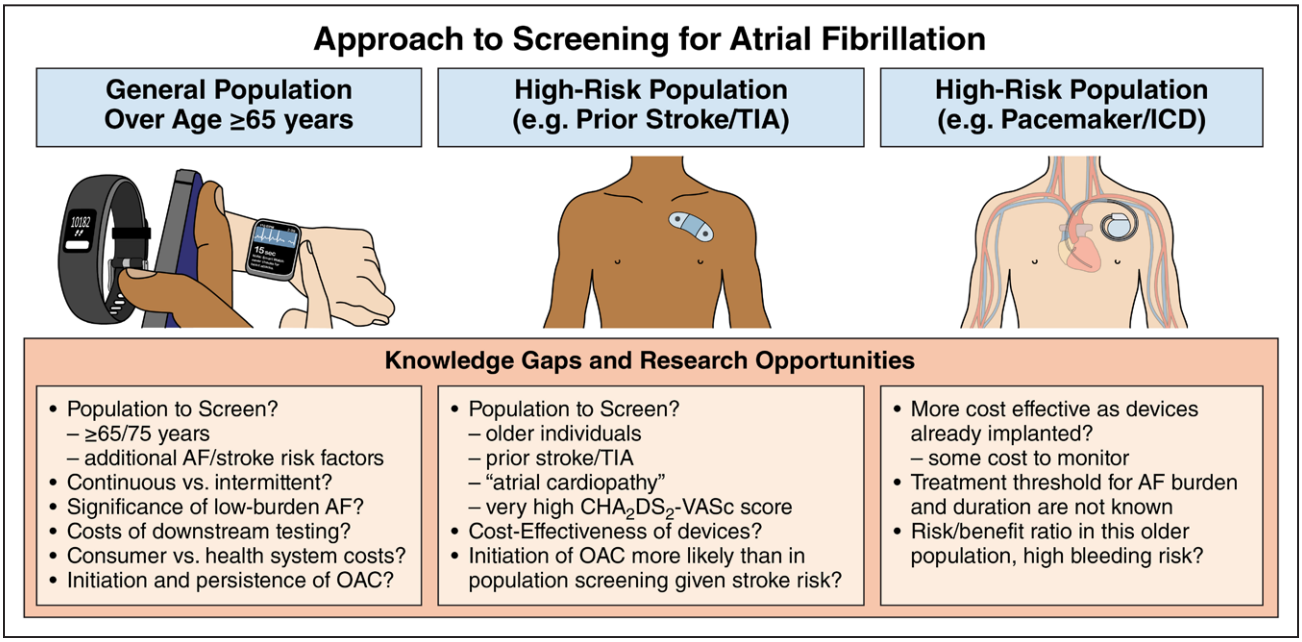

Figure 4. Knowledge gaps and research opportunities to be addressed in randomized trials of screening for atrial fibrillation (AF).
ICD indicates implantable cardioverter-defibrillator; OAC, oral anticoagulant; and TIA, transient ischemic attack.

Research Opportunities

1. Conduct large RCTs of AF screening strategies in diverse (eg, age, sex, race/ethnicity, urban/rural) at-risk populations of individuals to prevent stroke and other AF-associated outcomes, including major adverse cardiovascular events (heart failure, myocardial infarction, arterial and venous thromboembolism, sudden death), cognitive impairment/dementia, chronic kidney disease progression, health system resource use, and all-cause death, as well as downstream complications (eg, bleeding) and health system and process outcomes (eg, hospitalizations, time required to interpret screening tests, and follow-up testing).
2. Perform patient-level meta-analysis and meta-regression of similar RCTs from different health systems and countries examining stroke and other outcomes related to AF screening strategies, and identify specific subgroups of patients most likely to benefit from screening.
3. Assess health system and economic analyses of various population-based screening strategies through administrative and clinical databases.

POSTSTROKE SCREENING FOR AF

Background

This section focuses on poststroke screening for AF. A subsequent NHLBI workshop report addresses research priorities for risk stratification and stroke prevention in individuals with AF.

Previously undiagnosed clinical AF is frequently identified after acute stroke or TIA.[84] Up to 25% of patients with cryptogenic stroke may have AF detected, depending on patient characteristics, stroke type, and intensity of AF monitoring.[85] Intensive search for AF in the poststroke setting often reveals SCAF consisting of very short episodes[86] with unclear thromboembolic potential. Poststroke AF in a given patient may represent (1) preexisting AF that led to stroke, (2) new-onset AF that occurred because of the stroke itself,[87] (3) lagging thrombogenic atrial myopathy marker that led to stroke,[88] or (4) an incidental finding in a population with significant cardiovascular/stroke risk factors.[89] Regardless, in current practice, poststroke AF diagnosis usually changes treatment with initiation of long-term anticoagulation.[90] The detection of AF poststroke is important because recent RCTs do not support routine anticoagulation for secondary stroke prevention in the absence of known AF.[91,92]

Whereas electrocardiographic monitoring during hospitalization for stroke is common, more prolonged monitoring for poststroke AF, which significantly increases the yield of AF detection over 72 hours[93,94] or beyond, is not widely implemented. To be resource efficient, intensive AF monitoring requires a refined patient population. Demographics, classic cardiovascular risk factor burden, stroke characteristics, signs of atrial myopathy[95] (including ECG, structural, hemodynamic changes, biomarkers),[96–98] and AF genetic risk scores[99] may guide patient selection for monitoring beyond 72 hours.

Knowledge Gaps

Optimal methods for poststroke AF monitoring have yet to be defined (Figure 5). It is unknown whether anticoagulation driven by different AF monitoring strategies or other markers of atrial myopathy besides AF improves event-free survival (recurrent stroke/TIA/systemic embolism and dementia) and mortality.

The underlying pathophysiological mechanisms linking AF and stroke are also incompletely understood. Experimental and model systems to explore causal pathways and to define AF subtypes according to their pathological relation to stroke (ie, causal, bystander, AF induced by stroke, marker of atrial myopathy) are largely missing.

There is a lack of in-depth phenotyping of stroke cohorts with ECG and improved noninvasive imaging for the atrial-ventricular-vascular axis. Existing and new information from biomarkers, genetics, and other omics (eg, epigenomic, transcriptomic, proteomic, metabolomic, and microbiome) in relation to atrial myopathy as it applies to stroke has not been leveraged sufficiently. Clinical factors, stroke features, biomarkers, imaging variables, genetics, and omics to refine selection of poststroke patients/patients with TIA for more intensified AF screening also have not been sufficiently characterized.

From a clinical perspective, integrated care concepts[100] after stroke for internal medicine/cardiology workup during the index stroke hospitalization and after discharge in patients at high risk for AF to improve quality of life, cost, and outcomes are missing.

Research Opportunities

1. Existing and new deeply phenotyped, diverse (age/sex/race/ethnicity/urban versus rural/region) cohorts should be examined to better characterize patients with AF after ischemic stroke to develop and validate poststroke incident AF prediction tools examining combinations of patient characteristics, stroke features, electrocardiographic, imaging, laboratory, omics, and genetic markers. In particular, the role of atrial myopathy (with or without ventricular remodeling and hemodynamic changes) in stroke risk and selection of

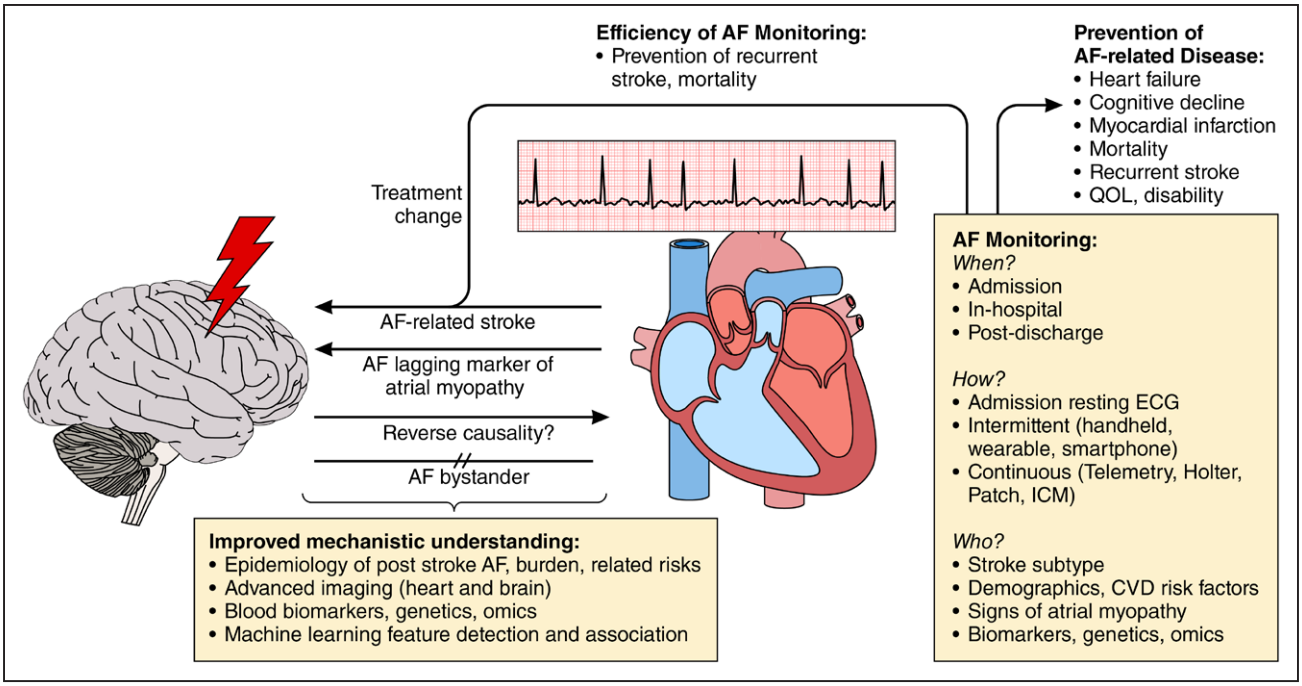

Figure 5. Questions to address in screening for atrial fibrillation (AF) in individuals who experience a new ischemic stroke in the absence of previously recognized AF.

It will be important to identify when, how, and whom to monitor after stroke. CVD indicates cardiovascular disease; ICM, intracardiac monitor; and QOL, quality of life.

patients for intensified poststroke AF monitoring requires investigation.

2. Observational and randomized studies of diverse populations should generate evidence on the effectiveness of post–ischemic stroke AF monitoring strategies and assessment and treatment of atrial myopathy independently of clinical AF diagnosis for improved outcomes, including stroke recurrence, heart failure, cognitive impairment, quality of life, disability, and mortality.
3. Optimal monitoring strategies after ischemic stroke need to be defined. Advances require investigations of the pathway to AF diagnosis (currently based on electrocardiographic tracing), implementation science to determine how to integrate optimal diagnostic methods in daily workflow in diverse populations, and study of shared decision making so that patients are engaged with the chosen approach. Besides classic monitoring techniques, external and implantable loop recorders and increasingly available wearables need to be investigated systematically and against gold standard approaches.

CONCLUSIONS

Increasing awareness of the prevalence of undiagnosed AF, coupled with recognition that AF often is first diagnosed with the onset of complications, has stimulated enthusiasm for AF screening and an increase in the number of consumer products potentially capable of diagnosing AF. However, there is a lack of robust evidence to determine the most appropriate patients to target for screening, which screening strategies and technologies to use in what context, and what additional testing and treatments to pursue with screen-detected AF.

Several themes emerged from the workshop to advance the field of AF screening. To develop a compelling evidence base, it is essential to generate and share data across studies (enabling pooled analyses and meta-analyses) and to pursue study designs including basic/mechanistic, administrative, health care/electronic medical records, registries, cohorts, pragmatic trials, and RCTs. Studies of AF screening need to examine AF burden, duration, and pattern in relation to multiple outcomes (eg, cardiac, brain, kidney, quality of life, costs, all-cause death), in addition to stroke and TIA. The role of AF screening needs to be investigated in various patient subgroups (eg, age, sex, race/ethnicity, urban/rural, and comorbidities), practice settings, and countries but will be most resource effective if focused on individuals for whom therapy may change if AF is diagnosed. Given the underrepresentation and underreporting of racial and ethnic minorities in AF studies,[18] it will be particularly important to ensure their adequate representation in AF screening studies. In particular, it will be vital to determine how AF prognosis and treatment vary by AF detection method (eg, incidental, noncontact/nonelectrocardiographic screening, routine electrocardiographic screening, consumer devices, extended clinical electrocardiographic monitoring, and

Table 2. Prioritized Research Opportunities for AF Screening

OppSTS for AF
Examine the outcomes of OppSTS-detected AF in ethnically/racially diverse studies such as pragmatic trials or prospective cohort studies comparing carefully matched OppSTS-detected AF with clinically detected AF to generate knowledge about their relative prognoses.
Determine the proportion of OppSTS-detected AF that is persistent by conducting observational and administrative studies that examine extended monitoring and follow-up.
Study the impact of detection method accuracy (including newer technologies) on beneficial health outcomes vs additional unnecessary tests and procedures and diminished quality of life. This research could include prospective comparative studies, pragmatic trials, and RCTs of different devices and screening strategies with stroke, mortality, and other clinically relevant end points in diverse populations.
AF: risk factor, risk marker, or both?
Use large-scale longitudinal studies to generate data on systemic and myocardial (especially atrial myopathy) substrates of AF using ECG, echocardiography, CMR, computed tomography, and biomarkers (traditional, genetic, and omic) to demonstrate whether estimated risk of AF and AF-related complications (eg, major adverse cardiovascular and cerebrovascular events and conditions such as stroke, heart failure, and dementia) can be refined. Such data will assist in prioritizing research in screening individuals with undiagnosed AF and research to discover novel therapeutic targets.
Investigate and validate AI algorithms and standard risk prediction models of cross-sectional and longitudinal data, including electronic health record, ECG, biomarker, genetic/omic, and imaging data, while adhering to privacy protections, transparency, diversity, equity, and inclusiveness. Priorities for research would test whether implementing or intensifying AF screening and predicting which patients with screen-detected AF will develop complications will result in net clinical benefit.
Burden of AF and detection of AF with different technologies
Investigate whether the pathophysiology of ischemic stroke in patients with clinically diagnosed AF is the same as that in individuals with device-detected AHREs/SCAF using various study designs (eg, registry, observational cohort) and test whether anticoagulation reduces the risk of stroke in patients with AF detected by implanted monitors, wearables, and consumer devices (RCT).
With technologies that can screen heart rhythms for longer periods of time and detect shorter episodes of arrhythmia, assess the optimal AF burden or AF episode duration threshold for prompting specific treatments, including anticoagulation and risk factor treatment and lifestyle modification. Study how such thresholds should be modified in the setting of specific comorbidities (using data from RCT, registries, post hoc analyses from RCTs) or screening device type used (eg, noninvasive wearables, implantable loop recorder, CIED).
Rigorously study the patient, clinician, and health system-level consequences of patient-initiated screening with consumer devices to develop and assess implementation algorithms for downstream testing and management (implementation science, registries, electronic health record data analyses, and RCTs) and to eliminate health care disparities related to screening.
Randomized study of systematic AF screening with clinically relevant outcomes
Conduct large RCTs of AF screening strategies in diverse (eg, age, sex, race/ethnicity, urban/rural) at-risk populations of individuals to prevent stroke and other AF-associated outcomes, including major adverse cardiovascular events (heart failure, myocardial infarction, arterial and venous thromboembolism, sudden death), cognitive impairment/dementia, chronic kidney disease progression, health system resource use, bleeding, and all-cause death, as well as downstream complications (eg, bleeding) and health system and process outcomes (eg, hospitalizations, time required to interpret screening tests, and follow-up testing).
Perform patient-level meta-analysis and meta-regression of similar RCTs from different health systems and countries examining stroke and other outcomes related to AF screening strategies and identify specific subgroups of patients most likely to benefit from screening.
Assess health system and economic analyses of various population-based screening strategies through administrative and clinical databases.
Poststroke screening for AF
Existing and new deeply phenotyped, diverse (age/sex/race/ethnicity/urban vs rural/region) cohorts should be examined to better characterize patients with AF after ischemic stroke to develop and validate poststroke incident AF prediction tools examining combinations of patient characteristics, stroke features, ECG, imaging, laboratory, omics, and genetic markers. In particular, the role of atrial myopathy (with/without ventricular remodeling and hemodynamic changes) in stroke risk and selection of patients for intensified poststroke AF monitoring requires investigation.
Observational and randomized studies of diverse populations should generate evidence of the effectiveness of postischemic stroke AF monitoring strategies and assessment and treatment of atrial myopathy independently of clinical AF diagnosis for improved outcomes, including stroke recurrence, heart failure, cognitive impairment, quality of life, disability, and mortality.
Optimal monitoring strategies after ischemic stroke need to be defined. Advances require investigations of the pathway to AF diagnosis (currently based on electrocardiographic tracing), implementation science to determine how to integrate optimal diagnostic methods in daily workflow in diverse populations, and study of shared decision making so that patients are engaged with the chosen approach. Besides classic monitoring techniques, external and implantable loop recorders and increasingly available wearables need to be investigated systematically and against gold standard approaches.

AF indicates atrial fibrillation; AHRE, atrial high-rate episode; AI, artificial intelligence; CIED, cardiac implantable electronic device; CMR, cardiac magnetic resonance; OppSTS, opportunistic single-time-point screening; RCT, randomized controlled trial; and SCAF, subclinical atrial fibrillation.

CIED), patient characteristics (eg, age, sex, race/ethnicity, and comorbidities), and AF risk markers (eg, atrial myopathy, electrocardiographic, imaging, biomarkers, omics, and genetic factors). Although AI algorithms hold great promise for refining patient selection for AF screening and prediction of outcomes in screen-detected AF, much more needs to be done to ensure that such algorithms are transparent, accurate, unbiased, and validated and improve patient care in diverse patient populations. Finally, close attention will need to be paid to both the potential benefits and adverse outcomes of AF screening strategies on the patient (eg, anxiety, testing, treatment complications) and the health system (eg, disparities, costs, and clinician liability and fatigue) before widespread screening is recommended. The research gaps and opportunities outlined in the workshop

(Table 2) will, we hope, accelerate AF screening research to improve the diagnosis, management, and prognosis of patients with undiagnosed AF.

ARTICLE INFORMATION

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Supplemental Materials

Data Supplement Table I
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