

Screening for Atrial Fibrillation - A Report of the AF-SCREEN International Collaboration

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SCREENING FOR ATRIAL FIBRILLATION: A REPORT OF THE AF-SCREEN INTERNATIONAL COLLABORATION

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Abstract

Background: Approximately 10% of ischemic strokes are associated with atrial fibrillation (AF) first diagnosed at the time of stroke. Detecting asymptomatic AF would provide an opportunity to prevent these strokes by instituting appropriate thrombo-prophylaxis. The AF-SCREEN international collaboration was formed in September 2015, to promote discussion and research about AF screening as a strategy to reduce stroke and death, and to provide advocacy for implementation of country-specific AF screening programs.

Methods: During 2016, 60 expert members of AF-SCREEN, including physicians, nurses, allied health professionals, health economists, and patient advocates were invited to prepare sections of a draft document. In August 2016, 51 members met in Rome to consider the draft document, and redraft the key recommendations arising from the document using a Delphi process. All members were subsequently able to vote on the recommendations online, with a majority of 85% used for adoption.

Results: Seven key recommendations were adopted. These recommendations emphasize that screen-detected AF found at a single-timepoint or by intermittent ECG recordings over 2 weeks is not a benign condition. Regarding methods of mass screening, handheld ECG devices have the advantage of providing a verifiable ECG trace and are preferred. Recommendations are provided for screening specified patient groups, but it is recognized that the setting should be country-specific.

Conclusions: These new recommendations have incorporated current knowledge and provide a strong case for AF screening, while recognizing that large randomized outcomes studies would be helpful to strengthen the evidence.

AF-SCREEN: establishment and goals

AF-SCREEN international collaboration was founded in September 2015 and includes over 100 physicians, nurses, allied health professionals, epidemiologists, health economists and patient group representatives from 31 countries. The collaboration seeks to promote discussion and research about screening for unknown or under-treated atrial fibrillation (AF) to reduce stroke and death, and to provide advocacy for implementation of country-specific AF screening programs (www.af-screen-intcollab.org, accessed Sept 9 2016).

Although many with AF develop symptoms leading to appropriate diagnosis and management, the first manifestation may be a debilitating stroke or death. Finding AF before symptoms are manifested could lead to initiation of appropriate therapy including oral anticoagulants (OACs), which are very effective in reducing stroke and death in those with elevated risk profile; and potentially to “upstream” risk-factor modifications to reduce complications from AF progression.

The past decade has witnessed a surge in the number and sophistication of diagnostic tools, ranging from inexpensive devices which detect persistent or paroxysmal AF, to devices capable of long-term continuous characterization of brief, asymptomatic AF. Those participating in the AF-SCREEN collaboration recognize a unique and timely opportunity to re-examine the approaches and rationale for AF diagnosis at an early asymptomatic stage.

AF-SCREEN Recommendations

The document content and structure were agreed by members, and individual sections with draft recommendations written by small groups with content expertise. A Delphi process involved the steering committee voting on recommendations selected for discussion/secret voting at the AF-SCREEN meeting. Following voting at the meeting, recommendations were workshopped, and 7 selected for on-line voting by all members. All received >85% agreement (Panel).

Panel 1

AF-SCREEN recommendations

1. Screen-detected AF as found on single timepoint screening, or intermittent 30 second recordings over 2 weeks, is not a benign condition, and with additional stroke risk factors, carries sufficient risk of stroke to justify consideration of screening and therapy to prevent

stroke. *105 votes, 98% agreed*

2. Single timepoint screening of people aged 65 or over in the clinic or community is recommended, based on yield of screening and cost-effectiveness. *104 votes, 93% agreed*
3. As a further step after single timepoint screening, two weeks of twice-daily intermittent handheld ECG recording should be considered for screening for AF in people aged 75 or over, or in younger age groups at high risk of AF or stroke. *104 votes, 86% agreed*
4. Long-term continuous rhythm monitoring using either external or implanted devices or extended intermittent patient-activated recordings is recommended for individuals with recent embolic stroke of undetermined source (ESUS). *104 votes, 92% agreed*
5. The setting for AF screening needs to be individualized according to country-specific and health care system-specific requirements and resources and must be linked to a pathway for appropriate diagnosis and management. This can be community-based or in primary care or specialist practices or clinics. *105 votes, 99% agreed*
6. Mass screening or opportunistic screening for AF can be accomplished by pulse palpation; oscillometric (blood pressure) or photoplethysmographic (smartphone camera) devices; and handheld ECG devices providing a rhythm strip. ECG confirmation is always required for diagnosis of AF. Handheld ECG devices have the advantage of providing a verifiable ECG trace and are preferred. *105 votes, 93% agreed*
7. Large randomized controlled studies using hard endpoints (including stroke/systemic embolism and death), of strategies for screening should be performed to strengthen evidence to inform national systematic screening strategies. *105 votes, 97% agreed*

NB None of these recommendations relate to CIED-detected AHREs

Incidence of screen-detected AF and CIED-detected AHREs (Cardiac Implantable Electronic Device-detected Atrial High Rate Episodes)

Many terms have been used to describe screen-detected AF, including unrecognized, undiagnosed, silent, subclinical AF (SCAF), and implanted cardiac device (CIED)-detected atrial high rate episodes (AHREs). In this document we will refer to AF detected on single timepoint screening or

patient-activated ECG recorders as 'screen-detected AF', while brief transient AF (≥ 5 -6 mins) detected by CIEDs with atrial monitoring capability, are referred to as 'CIED-detected AHREs'. CIED-detected AHREs could be due to oversensing, or other atrial tachyarrhythmias, and need close inspection of the stored electrograms before labeling them AF. CIED-detected AHREs are not included in our definition of screen-detected AF, or in any AF-SCREEN recommendations.

The incidence of screen-detected AF strongly depends on the population screened and duration/intensity of screening.¹ Single timepoint screening of a general population aged ≥ 65 years detects undiagnosed AF in 1.4%². In a large population-based study of individuals aged 75-76 years, a more intense 2-week screening program using twice-daily intermittent handheld ECG recordings identified screen-detected AF in 3.0% (0.5% on the initial ECG³). The identical protocol restricted to those with at least 1 additional stroke risk factor identified 7.4% with AF.⁴

The incidence of AHREs in patients with CIEDs ranges from 30-60% depending on the population and the detection algorithm used (Table 1).⁵⁻¹⁴ In 2,580 patients with a history of hypertension and no prior AF history, CIED-detected AHREs ≥ 6 minutes were found in 35% of patients with implanted devices over a mean follow-up of 2.5 years and doubled the risk of stroke.¹⁰ Silent AF is up to 10 times more frequent than symptomatic AF in patients with a pacemaker^{15,16} or during external continuous rhythm monitoring,¹⁷ and is more prevalent after pulmonary vein isolation than before ablation.¹⁸ Because patients with CIEDs have a medical condition that may affect occurrence of AHREs, other studies (ASSERT-II NCT01694394, REVEAL-AF NCT01727297, GRAF NCT01461434) using subcutaneous long-term continuous monitoring in people at risk of AF may provide a more reliable estimate of AF in non-CIED populations and elucidate its clinical significance.

Key points:

- 1: Single timepoint recording in people aged ≥ 65 will detect largely persistent screen-detected AF.
- 2: CIED-detected AHREs should not be grouped with screen-detected AF

Risk of stroke and death in untreated screen-detected AF

There are no data which specifically address the risk of stroke and death in untreated screen-detected AF in the general population. The closest approximation are cohort studies of individuals with AF detected incidentally in the absence of symptoms. One study¹⁹ showed that asymptomatic individuals (25% of 4618 with new AF) were three times as likely to have had an ischemic stroke prior to AF diagnosis, and in follow-up had similar risk of stroke and death as those with symptomatic AF. In a later study from this group, 161/476 individuals with new AF

were asymptomatic at presentation, and had an increased risk for cardiovascular (HR 3.12, 1.50-6.45) and all-cause mortality (HR 2.96, 1.89-4.64) compared to those with typical symptoms, after adjustment for CHA₂DS₂-VASc score and age (Figure 1).²⁰

In 5555 patients with incidentally-detected asymptomatic AF, adjusted stroke rate in the 1460 untreated patients was 4% and all-cause mortality 7% over 1.5 years of follow-up, compared to 1% and 2.5% respectively in matched controls without AF.^{21,22} In the EORP AF registry, mortality at 1 year was more than 2-fold higher in asymptomatic versus symptomatic AF (9.4% vs 4.2%, P < .0001).²³ In the Belgrade AF study, survival free of AF progression or ischemic stroke was worse in those with an asymptomatic presentation.²⁴

The major studies regarding thromboembolic risk of CIED-detected AHREs in patients with implanted pacemakers, defibrillators, and cardiac resynchronization devices are summarized in Table 2.^{6,9,10,25-27 14} All show increased stroke rate with CIED-detected AHREs, but the absolute risk of stroke was much lower than might be expected for patients with clinical AF with similar CHA₂DS₂-VASc score. A minimum of five minutes AHREs was found to have clinical relevance in 2003.⁹ Alternative arbitrary or data-derived AHRE burden cut-points have been explored over the subsequent ten years, ranging from five minutes to 24 hours.¹⁰ but uncertainty remains about the minimum burden that increases thromboembolic risk. A recent re-evaluation of ASSERT indicated that stroke risk was increased only in patients with AHRE duration ≥24 hours.²⁸ In Holter studies, 720 supraventricular beats/day or atrial runs >20 beats increased the risk of thromboembolic events.²⁹ While absolute event rate was lower than in symptomatic AF, other studies confirm increased risk.³⁰

Recommendation 1: Screen-detected AF as found on single timepoint screening, or intermittent 30 second recordings over 2 weeks, is not a benign condition, and with additional stroke risk factors, carries sufficient risk of stroke to justify consideration of screening and therapy to prevent stroke.

Response to treatment of screen-detected AF

Screening for a particular disease implies that there is an effective therapy that improves outcomes. For AF, OACs have a major impact on reducing stroke, systemic embolism and all-cause mortality.³¹ The non-vitamin-K antagonist OACs (NOACs) further improve outcomes with less intracranial bleeding.³² It is uncertain whether screen-detected AF should prompt OAC treatment, and whether the response to treatment is the same as for symptomatic AF. An undetermined proportion of asymptomatic patients with incidentally-detected AF were included in the pivotal anticoagulant studies, but these have not been analyzed separately.³¹ There are no randomized controlled trials (RCTs), and it may be unethical to randomize patients with screen-detected AF to no therapy or an ineffective drug such as aspirin. The treatment decision for a given individual

with screen-detected AF is determined by stroke risk factors (CHA₂DS₂-VASc score) according to guidelines,³³⁻³⁵ and by the duration of the AF episode in the case of CIED-detected AHREs.

In the cohort study of 5,555 asymptomatic patients with incidentally-detected AF, OAC therapy (n=2,492) compared to no antithrombotic therapy (n=1,460) was associated with significantly reduced adjusted risk of stroke from 4% to 1%, and death from 7% to 4% in only 1.5 years, suggesting that screen-detected AF may respond similarly.^{21,22} The minimum CIED-detected AHRE duration that increases risk sufficiently to justify treatment is debated, as discussed previously (Table 2). Ongoing studies including ARTESiA (NCT01938248) and NOAH (NCT02618577) will help refine the benefit of NOAC in CIED-detected AHREs and provide more information on the burden or duration of AHREs that will benefit.

Key Points

- 1:** Screen-detected AF (single timepoint screening or patient-initiated recording) is likely to have the same response to OAC therapy as incidentally detected AF and symptomatic AF, with significant reduction in stroke and death.
- 2:** The absolute level of stroke risk for CIED-detected AHREs may be lower than screen-detected AF and may modify the risk-benefit of OAC therapy. The burden threshold of CIED-detected AHREs/CHA₂DS₂-VASc score associated with a positive risk-benefit ratio is under investigation.

Consequences of undiagnosed AF other than stroke

In addition to stroke, patients with undiagnosed AF are susceptible to cardiac remodeling, heart failure, silent cerebrovascular events and dementia.

AF is associated with atrial and ventricular structural damage,^{36,37} which serves as the substrate for AF progression and may lead to ventricular arrhythmias that might explain the excess incidence of sudden cardiac death observed in AF patients in RCTs and registries.³⁸

When conducted to the ventricle at rapid rates, AF causes ventricular dysfunction and heart failure, by way of a tachycardia-induced cardiomyopathy³⁹ that can be the first clinical manifestation of the arrhythmia.⁴⁰

Silent brain infarcts commonly occur in patients with AF,⁴¹ and are of particular concern with catheter ablation procedures.⁴² Likewise, patients with AF have a higher frequency of premature dementia and cognitive decline than matched patients in sinus rhythm.⁴³ The large community-based Rotterdam study has shown an increased risk of dementia, independent of clinical stroke, in subjects with both prevalent and incident AF.

Although direct causal relationship has not been proven between silent ischemic events and dementia, increased use of OAC in susceptible populations may ultimately impact dementia. Whether patients with undiagnosed AF have a higher risk of adverse outcomes such as heart failure or dementia compared to symptomatic AF is not known.

Key Points: Trials and registries monitoring asymptomatic people at risk for AF should be supported. These should incorporate comorbidities such as heart failure and dementia in addition to traditional endpoints (stroke, death, bleeding). Since these outcomes are ubiquitous in AF populations by virtue of co-morbidity and age, rigorous endpoint definition and experimental design, with longer follow-up (especially for dementia), will be required for reliable conclusions.

Role of AF in ischemic stroke

In stroke registries, at least a third of patients with ischemic stroke have either previously known⁴⁴⁻⁴⁷ or newly-detected AF at the time of stroke.⁴⁸ Stroke was the first manifestation of AF in over 25% of AF-related strokes.⁴⁷ The association with AF is even higher if prolonged post-stroke external or implanted monitoring is performed.^{49,50} In the Swedish Riks-Stroke register of over 94,000 ischemic strokes, approximately 9% were associated with previously unknown AF, and 20% with known but undertreated AF,^{44,47} while in a global registry, 10% were due to previously unknown AF.⁵¹ For information on the incidence of AF and projections see online supplement.

Recent evidence from CIEDs raises questions about the temporal and mechanistic relationship between AF and stroke, and whether AF is necessary for left atrial thromboembolism to occur.^{26,52-54} There does not seem to be a proximate temporal relationship between device-detected AHREs and strokes, even though patients with AHREs are at increased risk for stroke. Several studies highlighting this point are summarized in Table 3.^{52,53,55} Only a small minority of patients with CIED-detected AHREs who have a stroke experience the arrhythmia in the month prior to a stroke;^{8,52} one-third had no AHREs during approximately 1 year of rhythm monitoring before their stroke and only manifested AHREs for the first time afterward.^{52,55} Furthermore, multiple markers of abnormal atrial substrate have been associated with stroke independently of AF.^{29,56-58} In a small proportion of patients, however, there is a close proximate relationship between a daily AHRE burden ≥ 5.5 h and stroke, with risk highest in the 5 days prior to stroke, falling to a non-significant increase in risk by 30 days prior to stroke (Figure 2), pointing to AF being a risk factor in these patients.⁵⁹ A limitation of the CIED studies is small numbers of strokes, and usually, lack of adjudication as cardio-embolic.

Even short AF episodes can create a prothrombotic state that persists for some time after the episode. Furthermore, an atrial cardiomyopathy related to aging and systemic risk factors³⁰ can lead to AF and/or atrial thromboembolism. Once AF develops, it impairs atrial function and

secondarily leads to atrial remodeling, which in addition to flow abnormalities, further increases thromboembolic risk.³⁰ Atrial cardiomyopathy as a cause of thromboembolism before AF could explain why a brief period of AF is associated with stroke months later, why many patients manifest AF for the first time after a stroke, and why one-third of strokes are currently of unknown cause. Advanced neuro-cardiac imaging and continuous monitoring may provide further insights into the pathophysiology in future.

Nevertheless, AF remains a very important risk marker as well as risk factor for stroke, with well documented efficacy of OAC for stroke prevention. Anticoagulated AF patients have residual stroke rates similar to matched individuals without AF, which underlines the efficacy of OACs in prevention of AF-related stroke.²² OACs remain underused in AF patients at risk of stroke: 30-50% of eligible AF patients not being given OAC, many mistreated with aspirin monotherapy, and the remainder not receiving any antithrombotic therapy.^{47,50,60,61}

Key Points:

1. Both unknown and undertreated AF contribute to a substantial proportion of all strokes, which could be prevented by screening strategies.
2. AF is both a risk factor and risk marker for stroke.

Which patients to screen?

In order for a screening program to be efficient, the screening technique must have a high positive predictive value using a low-risk tool at low cost. Screening yield depends on disease prevalence and diagnostic test performance. AF increases disproportionately in older adults, rendering age one of the best predictors of AF.⁶² The prevalence of AF below age 50 is negligible in most populations and may not justify screening in this group.⁶² The prevalence of AF differs by ethnicity; for example indigenous Australians have a higher burden of AF and higher risk at much younger ages than Europeans.^{63,64}

If the screening procedure is inexpensive and easy to use, e.g. pulse palpation or single timepoint handheld devices,^{65,66} screening can be non-selective and just age-based. A threshold ≥ 65 years (a CHA₂DS₂-VASc score of at least 1 in a male and 2 in a female) will detect undiagnosed AF in 1.4% in clinic or population settings,⁶⁷ in which case European Society of Cardiology (ESC) guidelines recommend *that OAC be considered* (Class IIa); *OACs are recommended (Class I)* for a score of 2 in a male or 3 in a female.³⁵ Opportunistic screening in all patients contacting the health system aged ≥ 65 has been adopted in the ESC AF guidelines,^{33,35} but might be more efficient if an additional stroke risk factor is required⁶⁸ or an older age threshold chosen. Superiority over a simple age-based criterion, however, needs to be proven.

Among individuals aged 75 in Sweden, a single ECG detected 0.5-1% with undiagnosed AF.^{3,4} Adding 2 weeks of twice-daily patient-activated handheld ECG detected an additional 2.5% with undiagnosed AF,³ and 7.4% after enrichment with ≥ 1 additional stroke risk factor.⁴ Even more AF is detected with continuous recording via external or implanted devices (Table 1), but that technology is costly and may only be justified in populations at high risk and with sufficient yield from screening, e.g. older age plus additional risk factors, or embolic stroke of undetermined source (see below). Adding biomarkers (eg natriuretic peptides, high-sensitivity troponin) to existing clinical predictors may improve prediction of AF incidence.⁶⁹⁻⁷³ However, there is marginal improvement in model discrimination and reclassification.

Recommendation 2:

Single timepoint screening of people aged ≥ 65 in the clinic or community is recommended, based on yield of screening and cost-effectiveness.

Recommendation 3:

As a further step after single timepoint screening, two weeks of twice-daily intermittent handheld ECG recording should be considered for screening for AF in people aged ≥ 75 , or in younger age groups at high risk of AF or stroke.

Key points:

1. A lower age threshold may be considered for non-Caucasian populations or those at high risk of AF or stroke.
2. Knowledge of absolute stroke risk of those with CIED-detected AHREs, or AF on long-term continuous monitoring, will inform future strategies.
3. It is uncertain whether thromboembolic risk scores add to age for single timepoint screening, but are likely required if using more costly screening strategies.
4. Discriminatory ability of current blood biomarkers is insufficient to justify widespread use to select patients for screening, but further research is required to determine whether new biomarkers or their combination could achieve this goal.

Special cases:

a. Ischemic Stroke and Embolic Stroke of Undetermined Source (ESUS)

RCTs⁷⁴⁻⁷⁷ and observational studies^{48,78} have established the effectiveness of post-stroke ECG monitoring for improving AF detection (number needed to screen=8-14), with longer monitoring durations increasing AF detection probability. Post-stroke ECG monitoring is likely cost-effective.^{74,79} However, RCTs have not been powered to assess the effect of prolonged ECG monitoring on stroke or mortality.

After an acute ischemic stroke/transient ischemic attack (TIA), in patients not known to have AF and without contraindications to OACs, a tiered AF ECG monitoring approach is advised (key points). ESC guidelines recommend ≥ 72 hours ECG monitoring in all stroke survivors,³⁵ but more research is required to identify non-ESUS subgroups benefitting most from more prolonged monitoring. Ongoing RCTs are exploring an alternative strategy of blanket NOAC therapy after limited negative Holter monitoring in ESUS (RE-SPECT ESUS NCT02239120, and NAVIGATE ESUS NCT02313909).

Recommendation 4

Long-term continuous rhythm monitoring using either external or implanted devices or extended intermittent patient-activated recordings is recommended for individuals with recent ESUS.

Key points:

- 1) At least 72 hours ECG monitoring is recommended as part of initial etiological work-up for most stroke patients.
- 2) ECG monitoring for at least 2-4 weeks is recommended for selected patients aged ≥ 55 years not currently on OAC with recent imaging-confirmed non-lacunar ESUS⁸⁰ who have an estimated good life expectancy and quality of life.
- 3) Longer ECG monitoring may be considered when there is a very high clinical suspicion of unrecognized AF due to manifest atrial disease (e.g. excessive supraventricular ectopy, enlarged or poorly contracting left atrium, elevated natriuretic peptide levels), older age, or a high CHA₂DS₂-VAsc score.

b. AF in the context of concurrent major illness: Secondary AF

AF may be triggered by reversible, acute, secondary causes such as cardiac and non-cardiac surgery, hyperthyroidism, myocarditis/pericarditis, myocardial infarction, pulmonary embolism, pneumonia, sepsis, and alcohol intoxication.⁸¹ In 2,275,588 hospitalized patients, secondary AF occurred in 22,780 (1%). The majority were post-surgery (30% cardiothoracic, 20% non-cardiothoracic), infections (23%), or post-myocardial infarction (18%).⁸² AF recurrence, stroke risk and mortality are similar for primary and secondary AF.⁸³

New-onset postoperative AF (POAF) complicates 16-32% of cardiac surgery,⁸⁴⁻⁹¹ and is associated with longer hospitalization and more postoperative complications.⁹² POAF often recurs post discharge,^{84,86,93} with an absolute recurrence rate of ~20% during 3.5 years of follow-up.⁹³ Following cardiac surgery, POAF carries a higher risk of stroke, hazard ratio 1.3 in 2 years after adjusting for confounders,⁹⁴ and higher mortality.^{87-89,95,102} POAF occurs after 1-3% of non-cardiac procedures,^{85,94} and doubles stroke risk within 2 years.⁹⁴

Screening for recurrent AF in POAF following cardiac surgery using patient-activated handheld ECGs, revealed recurrent AF in 25% within 3 weeks, mostly asymptomatic.⁹⁶ The prognostic significance of recurrence is unknown, as is the incidence after return to sinus rhythm with other secondary AF.

Key Points: Transient AF occurs frequently during intercurrent illnesses. Prognosis is comparable to common AF, therefore, targeted screening appears warranted, although specific data on silent secondary AF are not available. Further research is needed to develop an evidence base to guide management of secondary AF, and whether screening for recurrence is warranted.^{97,98}

Overview of screening methods (Table 4)

Pulse palpation to assess pulse irregularity is the low-tech readily accessible method for screening in primary care, shown effective as a screening strategy in the SAFE study.⁹⁹ It can also be used in the community, in both high and low-middle income countries, but has some limitations.¹⁰⁰ In the clinic it is usually performed by physicians or nurses, while in the community non-physician health professionals and lay people can be trained to detect pulse irregularity. In routine primary care, the pulse is infrequently assessed.

Innovation in technology has produced new screening devices which improve feasibility and cost-effectiveness of widespread screening. These devices are recognized as valid for AF detection by the European Primary Care Cardiovascular Society,¹⁰¹ and could be used to complement traditional screening by pulse palpation.

Oscillometric blood pressure monitors with an AF detection function based on pulse irregularity offer high sensitivity (92-100%) and specificity (90-97%), and are superior to pulse palpation.¹⁰²⁻¹⁰⁴ The devices can be used by health workers or patients, provide single timepoint or multiple patient-activated recordings and have been evaluated by health technology assessments.¹⁰¹ Finger photoplethysmography, using a smartphone camera and flash, has sensitivity 93% and specificity 98% for AF detection using proprietary algorithms with variable techniques to deal with ectopic beats.¹⁰⁵⁻¹⁰⁷ Similar algorithms are being built into smart-watches and fitness bands. The technology is attractive given the wide distribution of smartphones, but requires a noise-free trace for optimal performance. Ultimately with all pulse-based detection systems, an ECG is required to confirm AF,^{34,39} either 12-lead (current gold standard) or single-lead documenting P-waves.

A range of handheld devices produce diagnostic quality single-lead (L1) ECGs, most with automated algorithms more accurate than pulse palpation (sensitivity 94-99%, and specificity 92-97%^{35,108-110}). These devices have been widely used for single timepoint AF screening.^{37,66,111} Repeated handheld ECG recordings over 14-28 days have diagnostic accuracy equivalent to standard event recorders,²⁴ superior to 12-lead ECG and 24-hour Holter for paroxysmal AF,^{51,112-114} and have been used successfully in large scale AF screening studies.^{3,4} While single lead ECGs may not always show P-waves, the advantages outweigh this limitation. The accepted arbitrary episode duration for defining AF is 30 seconds.

Continuous monitoring coupled with a diagnostic algorithm will detect paroxysmal AF more effectively than repeated patient-activated devices, though the prognostic significance of very brief episodes is uncertain. This can be accomplished by non-invasive devices, eg:

- prolonged Holter monitoring
- a wearable non-adhesive dry-electrode belt,¹¹⁵ or
- by a wearable-patch: feasible for 2-4 weeks,²⁸ and superior to 24-hour Holter.¹¹⁶

The main disadvantages of prolonged external monitoring are skin irritation from electrodes/patches leading to reduced patient compliance, and the large amounts of data generated.

Implantable/insertable subcutaneous devices can capture ECG data for months to years, but have lower sensitivity and specificity than implanted pacemaker devices with atrial endocardial leads.

All devices with automated AF diagnostic algorithms require low-noise high-quality signals for optimal performance. This may be difficult when devices are given to patients or used in the community. High sensitivity is desirable, but there is a trade-off with lower specificity which can create much extra work and cost in verifying diagnoses with an ECG (if not recorded by the device).³⁹ Device performance, therefore, must be tested in the setting where it will be used for screening to optimize performance.

Recommendation 5: Mass screening or opportunistic screening for AF can be accomplished by pulse palpation; oscillometric (blood pressure) or photoplethysmographic (smartphone camera) devices; and handheld ECG devices providing a rhythm strip. ECG confirmation is always required for diagnosis of AF. Handheld ECG devices have the advantage of providing a verifiable ECG trace and are preferred.

Key Point: Prolonged continuous ECG monitoring with external or subcutaneous devices will diagnose more paroxysmal AF, but requires further evaluation. Cost-effectiveness will be limited by expense, and detection of AF with lower absolute stroke risk.

Settings for screening

There has been increasing interest recently in community screening in a number of countries.^{3,4,67,117-122} Prospective studies have used pulse palpation, single or multi-lead ECG; and single timepoint or intermittent recordings, using systematic or opportunistic approaches across entire populations or age-specific strata of total populations, or defined populations in cohort studies. Screening has also been performed opportunistically in volunteers during annual events (eg Heart Rhythm Week in Belgium.¹¹⁹) The STROKESTOP study,³ invited half of the 75-76 year olds in two Swedish regions to attend screening, and 53% accepted, similar to the rate in the SAFE study.⁹⁹ This was a stepped approach, with an initial single-lead ECG, followed by twice-daily intermittent patient-activated ECG recordings over a 2-week period in those without AF.

Pharmacies offer an attractive setting for community screening. People ≥ 65 years with chronic conditions generally visit their community pharmacy at least monthly. AF screening with pulse check and smartphone-based ECG in Australian pharmacies was found to be feasible, cost-effective⁶⁶ and well accepted.¹²³ The major issue is ensuring referral and then treatment of detected individuals, so an established referral pathway is crucial.

Primary care is an ideal setting: in addition to regular primary care physician visits, there is nursing support for screening, and there is a direct link with the practitioner to prescribe OAC. There are two challenges: first is a sustainable strategy for detecting undiagnosed AF and second, providing adequate treatment for patients with known or newly discovered AF, as under-treatment is common.¹²⁴

The SAFE study showed that opportunistic screening with pulse palpation in primary care was as effective as systematic 12-lead ECG screening in detecting undiagnosed AF in patients ≥ 65 years, and more cost-effective.⁹⁹ While some guidelines recommend screening using pulse palpation,¹²⁵ pulse taking is not common practice.¹²⁶ The new ESC guidelines have added ECG rhythm strip to the recommendation on pulse palpation for opportunistic screening.³⁵ For scalability and sustainability, screening could be linked to existing workflow eg cardiovascular risk management programs or influenza vaccination.^{37,113,127} Computerized medical records linked to electronic decision support tools¹²⁸ (e.g. AF SMART, ACTRN12616000850471 and Arts et al¹²⁹), could provide prompts for regular screening, calculate stroke risk, and advise guideline-recommended therapy to assist workflow and treatment decisions.

In some countries, large generalist or specialized outpatient clinics provide an alternative setting to primary care for screening,¹³⁰ but have similar issues with sustainable delivery of the screening intervention and subsequent treatment.

Recommendation 6: The setting for AF screening needs to be individualized according to country-specific and health care system-specific requirements and resources and must be linked to a pathway for appropriate diagnosis and management. This can be community-based or in primary care or specialist practices or clinics. See Supplementary material for country-specific considerations.

Key point: Screening in primary care or outpatient clinics offers the advantage of a direct link with treatment, with a potentially sustainable workflow.

Health-economic assessments

Economic assessment of AF screening depends on a range of factors, including:

- rate of undiagnosed AF in the target population,
- the difference in AF detection between the screening intervention and routine practice without screening,
- stroke and mortality risk of the target population,
- the expected reduction in stroke and mortality and increase in bleeding risk from OAC,
- the cost of the screening methodology, and
- country-specific “willingness-to-pay” thresholds to avoid one stroke.

In the first paper on health economic modelling for AF screening,¹³¹ both annual ECG screening and pulse palpation with confirmatory ECG were cost-effective in a Japanese population. Later, the SAFE study evaluated opportunistic versus systematic screening using pulse palpation followed by ECG^{99,132} and showed, using probabilistic sensitivity analyses, a 60% likelihood that opportunistic screening was cost-effective in both men and women. The Swedish STROKESTOP population screening study³ confirmed that ECG screening was likely to be cost-effective using

a lifelong decision-analytic Markov model.¹³³ Two other smaller studies evaluating smartphone ECG screening in community pharmacies⁶⁶ (relying on estimated stroke and death rates and improvements with OAC treatment in incidentally-detected asymptomatic AF),²¹ and pulse checking in an influenza vaccination clinic¹³⁴ also described cost-effectiveness. A simulation of direct medical costs in USA concluded that costs were greater in those with undiagnosed AF than for similar people without AF, justifying strategies to identify and treat undiagnosed AF.³⁶

Most recently, a study of lifetime costs and effects of a single handheld ECG screening of patients >65 during the annual influenza vaccination in the Netherlands¹⁰⁹ found that screening would decrease overall costs by €764 (USD\$939) and increase QALYs by 0.27 per patient. That is AF screening for patients >65 during the influenza vaccination was likely to be cost-saving.

Reviews of systematic and opportunistic screening for AF detection AF^{135,136} indicate that both were more cost-effective than routine practice for those ≥65, though this depends on method chosen, frequency of screening and age. For example, a formal Health Technology Assessment in Ireland considered a number of models and found costs per QALY varying between €792,619 (USD\$ 936,902) for screening annually from age 55 to €8,037 (USD\$9,500 for a single screening at age 75,¹³⁷ but there are no data on the detection rate for annual or other frequencies of repeated screening.

Key point: More work is required to compare cost-effectiveness of different screening interventions and the effect of different age cutoffs.

Should screening include under-treated known AF?

Under-treatment exposes patients to a significant risk of fatal or disabling strokes. Population surveys^{138,139} and registries indicate treatment remains suboptimal with large country differences.⁴⁷ Population screening using a variety of techniques^{3,67,119} would identify under-treated patients and may provide an opportunity to refer to appropriate physicians or clinics to initiate OACs or to re-initiate OACs in those who have discontinued.^{3,35,140}

A prospective, Swedish population-based study found 9.5% of individuals (81/848) were known to have AF on a 12 lead ECG: 43% of these were not on OAC.⁴ Through the screening program, 52% of under-treated individuals had OAC initiated. A similar number of patients had known AF (9.3%) in the STROKESTOP study³ but only 22% were not on OAC. After cardiologist follow-up, more than half without contraindications commenced OAC therapy. This highlights the importance of future implementation research in which AF screening programs incorporate well-defined referral pathways and strategies for initiating OAC therapy.

Patient preferences and advocacy

A large patient survey reported a majority of patients with persistent AF were in favor of AF screening with handheld ECGs (T. Lobban and M.T. Hills, written communication, September 2016). Patients also believed healthcare professionals needed to be better educated about AF symptoms.

The patient voice is as important as the clinician voice in driving change. Political advocacy from patients, caregivers and patient-led organizations has demonstrated the need for improved awareness, education and disease information.^{141,142} Patient-led organizations can more effectively identify the challenges patients face, and engage policy makers to bring about change,¹⁴¹ leading to improved outcomes for patients and healthcare providers (www.stopafib.org, www.heartrhythmalliance.org). Campaigns such as the Arrhythmia Alliance's 'Know Your Pulse' campaign to screen for AF can be very successful in raising awareness and bringing about policy change.

Numerous governing bodies and scientific organizations now seek the input of patients and patient organizations in developing clinical guidelines and scientific publications.^{33,34,143}

Key points:

- Patients support screening to detect AF earlier. Increased education about AF for healthcare professionals is required, ensuring they respond to any reported patient symptoms. Public awareness campaigns are recommended to educate people about checking their pulse and the benefits of OAC for preventing AF-related stroke.
- Professional health organizations should work in partnership with professional patient-led organizations to drive AF education and detection programs, advocate for screening, and evidence-based treatment for those with diagnosed AF.

What current guidelines recommend

The ESC recommends opportunistic pulse-taking in all patients aged ≥ 65 years or in high risk subgroups, followed by an ECG if irregular, to allow timely AF detection.³³ The evidence base for this recommendation is the SAFE study.¹³² Pulse taking in practice is recommended for symptoms in the National Institute for Health and Care Excellence (NICE) guidelines.¹⁴³ However, the new 2016 ESC guideline includes: an ECG rhythm strip

as an alternative to pulse palpation; at least 72 hours ECG monitoring after TIA or stroke with additional longer term monitoring considered; and consideration of systematic screening in patients aged ≥ 75 or those at high stroke risk. An additional recommendation is to interrogate CIEDs for AHREs and if detected, prompt further ECG monitoring to document AF before initiating therapy.³⁵

The ACC/AHA/HRS Guidelines³⁴ make no recommendation on the topic of screening but do state that early detection and treatment of asymptomatic AF before the first complications occur is a recognized priority for the prevention of stroke.

Guidelines address specific subgroups where screening may be worthwhile, including high risk patients (e.g. post-stroke, >age 75), in whom prolonged monitoring is more likely to detect AF.

Key Point: To further change guidelines and health policy may require large trials of a strategy of screening versus no screening, powered to detect differences in outcomes such as ischemic stroke/systemic embolism and death.

Conclusions

The consensus of expert opinion on screening for AF, is that screen-detected AF in older subjects is not low risk. The absolute risk of ischemic stroke and death appears sufficient to justify consideration of treatment with OACs. While irregularity of the pulse is a simple way to screen for AF, pulse palpation is seldom done in routine practice, and inexpensive screening devices are available. Because an ECG is required to confirm AF diagnosis, devices which provide a medical quality ECG trace are preferred. Patient differences will modulate the type and intensity of screening (eg ESUS requires higher intensity). The setting for screening is highly dependent on the health system in each country and needs to be individualized, but must crucially be linked to a pathway for appropriate diagnosis and management. The consensus was that while the WHO criteria for screening appear to be met¹⁴⁴ and the evidence is strong for commencing screening efforts in many countries, one or more large and adequately powered randomized outcomes trials of a strategy of screening would strengthen the evidence for adoption of larger scale systematic screening programs for AF to reduce ischemic stroke/systemic embolism and death.

Supplementary material (online only)

- (a) AF incidence and future projections
- (b) Table A: Arguments against screening for AF.
- (c) Country by country plan of potential AF screening implementation specific to the health system.

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Tables

Table 1: Incidence of CIED-detected AHREs in the population with cardiac implanted devices

Year	Trial	Device Indication	Clinical Profile of Patients	Mean age	% male	LVEF%	Mean CHADS ₂	Follow-up	AF burden threshold	Incidence of AF
2002	Gillis et al. ⁷	PPMs for sinus node disease	All	70 ± 12	52%	N.A.	N.A.	718 ± 383 days	>1 min	157/231 (68%)
2003	MOST ⁹	PPMs for sinus node disease	All	Median 73 (68,81) for no AHRE Median 75 (68,79) for AHRE detected	45%	N.A.	N.A.	Median 27 months	>5 min	156/312 (50%)
2010	TRENDS ¹³	PPMs and ICDs All indications	History of prior stroke No history of AF No OAC use ≥1 stroke risk factor	72.8±9.9 for no AHRE 74.0±9.1 for AHRE detected	63% for no AHRE 71% for AHRE detected	N.A.	4.1±0.8 for no AHRE 4.2±0.8 for AHRE detected	Mean 1.4 years	>5 min	45/163 (28%)
2012	TRENDS ¹²	PPMs and ICDs All indications	No history of prior stroke No history of AF No OAC use ≥1 stroke risk factor	70.2± 11.8	66%	N.A.	≥2 in 70%	1.1 ± 0.7 years	>5 min	416/1368 (30%)

2012	ASSERT ¹⁰	PPMs and ICDs All indications	History of hypertension No history of AF No OAC use	76±7 for no AHRE 77±7 for AHRE detected	59% for no AHRE 56% for AHRE detected	N.A.	2.3±1.0 for no AHRE 2.2±1.1 for AHRE detected	2.5 years	>6 min	895/2580 (34.7%)
2012	Home Monitor CRT ²⁷	CRTDs and CRTPs CHF	Heart failure No history of AF	66 ±10	77%	25 (20–30)	≥2 in 64%	370 days (253-290)	≥14 min	126/560 (23%)
2013	Healey et al. ¹¹	PPMs All indications	All	71.7 ±14.4 for no AHRE 74.3±13.7 for AHRE detected	59% for no AHRE 58% for AHRE detected	N.A.	2.02± 1.30 for no AHRE 2.23±1.47 for AHRE detected	Single center Retrospective	>5 min	246/445 (55.3%)
2015	IMPACT ⁵⁵	ICDs and CRTDs All indications	No permanent AF No contra-indications for OAC	64.2±11.5 for Control 64.7±10.8 for Intervention	73% for Control 74% for Intervention	29.4±11.3 for Control 29.9±10.8 for Intervention	2 (median)	701 days	>4-12 sec	945/2718 (34.8%)
2016	RATE Registry	PPMs and ICDs	All No permanent AF,	73.6±11.8 for PPMs, 64.5±12.6 for ICDs	54% in PPM 72% in ICDs	57.8±10.5 for PPM 29.2±11.3 for ICDs	1.8±1.0 for PPM 2.0±0.8 for ICDs	22.9 months (median)	> 3 atrial premature complexes	145/300(48%) of PPM pts 155/300 (52%) of iCD pts Of the representative samples studied

Legend: PPM = permanent pacemaker; ICD = Implanted cardioverter defibrillator

Table 2: Summary of studies regarding CIED-detected AHREs and thromboembolic risk

Year	Trial	Number of patients	Duration of Follow-up	AF Burden Threshold	Atrial Rate Cutoff	AF Burden Threshold	Hazard Ratio for TE Event	TE Event Rate (below vs. above AF burden threshold)
2003	Ancillary MOST ⁹	312	27 months (median)	5 minutes	>220 bpm	5 minutes	6.7 (p=0.020)	3.2% overall (1.3% vs. 5%)
2005	Italian AT500 Registry ⁶	725	22 months (median)	24 hours	>174 bpm	24 hours	3.1 (p=0.044) CI 1.1 to 10.5	1.2% annual rate
2009	Botto et al. ²⁵	568	1 year (mean)	CHADS ₂ +AF burden	>174 bpm	CHADS ₂ +AF burden	n/a	2.5% overall (0.8% vs. 5%)
2009	TRENDS ²⁶	2486	1.4 years (mean)	5.5 hours	>175 bpm	5.5 hours	2.2 (p=0.060) (0.96 to 5.05, p= 0.06)	1.2% overall (1.1% vs. 2.4%)
2012	Home Monitor CRT ²⁷	560	370 days (median)	3.8 hours	>180 bpm	3.8 hours	9.4 (p=0.006) (1.8–47, 0, p=0.006)	2.0% overall
2012	ASSERT ¹⁰	2580	2.5 years (mean)	6 minutes	>190 bpm	6 minutes	2.5 (p=0.007) CI, 1.28 to 4.85	(0.69% vs. 1.69%)
2014	SOS ¹⁴⁵	10016	2 years (median)	1 hour	>175 bpm	1 hour	2.11 (p=0.008) CI: 1.22–3.64	0.39% per year overall
2016	RATE Registry ¹⁴	5379 (3141 with pacemakers and 2238 with ICDs)	22.9 months (median)	Non-sustained episodes of AHRE with a duration from 3 atrial premature complexes to 15-20 seconds	N.A.	Non-sustained episodes of AHRE with a duration from 3 atrial premature complexes to 15-20 seconds	HR 0.87 (95% CI 0.58–1.31, p=0.51)	For non-sustained episodes of AHRE : 0.55 (0.34–0.76) % per year for pacemakers and 0.81 (0.50–1.12) % per year for ICDs

Legend TE = Thrombo-embolic

Table 3: Temporal relationship between CIED-detected AHREs and stroke

Year	Trial	Number of patients with TE Event	Definition of AF episode	Any AF Detected Prior to TE Event	AF Detected only after TE Event	No AF in 30 Days Prior to TE Event	Any AF in 30 Days Prior to TE Event
2012	Boriani et al ¹⁴⁶	33/3438	5 minutes	21/33 (64%)	NA	12/33 (67%)	11/33 (33%)
2011	TRENDS ²⁶	40/2486	5 minutes	20/40 (50%)	6/40 (15%)	29/40 (73%)	11/40 (27%)
2014	ASSERT ^{10,52} ENREF 51	51/2580	6 minutes	18/51 (35%)	8/51 (16%)	47/51 (92%)	4/51 (8%)
2014	IMPACT ⁵⁵	69/2718	36/48 atrial beats ≥200bpm	20/69 (29%)	9/69 (13%)	65/69 (94%)	4/69 (6%)
2015	Turakhia et al ⁵⁹	187/9850	≥ 5.5 hours or ≥ 6min on any day 120 days prior	36/187 (19%) ≥ 5.5 hours 50/187 (26%) ≥ 6 min	N/A	N/A	

Table 4: Sensitivity and specificity of different methods of screening for AF

Device	Method of interpretation	Sensitivity (%)	Specificity (%)	Reference
Pulse palpation		94 (84-97)	72 (69-75)	Cooke et al., 2006 ¹⁰⁰
<i>Handheld single-lead ECGs</i>				
AliveCor (Kardia) heart monitor	Algorithm only (based on presence of P wave and RR irregularity)	98 (89-100)	97 (93-99)	Lau et al., 2013 ¹⁴⁷
Merlin ECG event recorder	Cardiologist interpretation	93.9	90.1	Kearley et al., 2014 ¹⁰²
Mydiagnostick	Algorithm only (based on RR irregularity)	94 (87-98)	93 (85-97)	Tieleman et al., 2014 ¹¹¹ Vaes et al., 2014 ¹⁴⁸
Omron HCG-801	Algorithm only (based on RR irregularity)	98.7 (93.2-100)	76.2(73.3-78.9)	Kearley et al., 2014 ¹⁰²
Omron HCG-801	Cardiologist interpretation	94.4	94.6	Kearley et al., 2014 ¹⁰²
Zenikor EKG	Cardiologist interpretation	96	92	Doliwa et al., 2009 ¹⁰⁸
<i>Modified Blood pressure monitors</i>				
Microlife BPA	Algorithm only (based on	92	97	Marazzi et al., 2012 ¹⁰³

200 Plus	pulse irregularity)			
Microlife BPA 200	Algorithm only (based on pulse irregularity)	97 (81.4-100)	90 (83.8-94.2)	Wiesel et al., 2014 ¹⁰⁴
Omron M6	Algorithm only (based on pulse irregularity)	100	94	Marazzi et al., 2012 ¹⁰³
Omron M6 comfort	Algorithm only (based on pulse irregularity)	30 (15.4-49.1)	97 (92.5-99.2)	Wiesel et al., 2014 ¹⁰⁴
Microlife WatchBP	Algorithm only (based on pulse irregularity)	94.9 (87.5-98.6)	89.7 (87.5-91.6)	Kearley et al., 2014 ¹⁰²
<i>Plethysmographs</i>				
Finger probe	Algorithm only (based on pulse irregularity)	100	91.9	Lewis et al., 2011 ¹⁴⁹
iPhone photo-plethysmograph	Algorithm only (based on pulse irregularity)	97.0	93.5	¶McManus et al., 2016 ¹⁵⁰

LEGEND: The comparator for all studies was 12-lead ECG (¶also used 3-lead telemetry).

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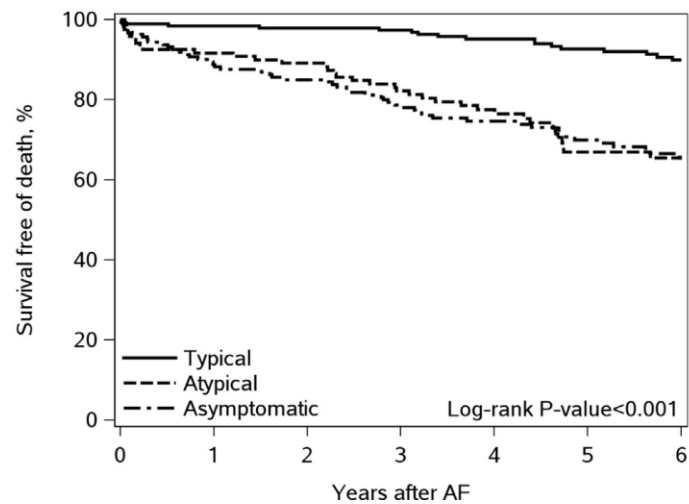
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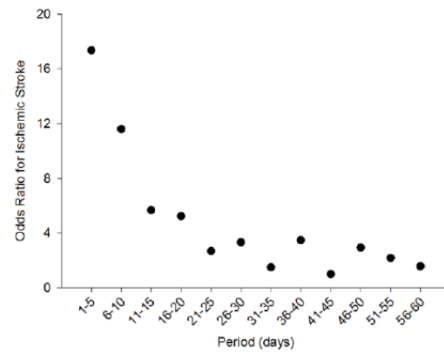
Figures

Figure 1: Survival stratified by type of AF presentation (with permission from Siontis et al, Heart Rhythm 2016²⁰)



Legend: Kaplan-Meier curve for all-cause mortality according to presentation with either typical AF symptoms (palpitations with or without other symptoms), atypical symptoms (fatigue, chest pain, shortness of breath, lightheadedness, syncope, decreased exercise tolerance, but without palpitations) or asymptomatic (AF detected incidentally during a routine visit for an unrelated problem).

Figure 2: Time trend of risk of stroke for AF in 60 days prior to stroke (with permission From Turakhia et al, Circ Arrhythm Electrophysiol 2015⁵⁹)



Legend: Odds ratio for non-overlapping 5-day epochs of AF burden in implanted devices ≥ 5.5 h in one day during the 5-day epoch, from 1-5 days before stroke (left-hand point) through 56-60 days before stroke (right-hand point). Each stroke case epoch is matched to six 5-day control epochs between 91- 120 days prior to stroke. There is a progressive fall in odds ratio of stroke from 17.4 for AF occurring 1-5 days before stroke, to non-significant increases for AF more than 21 days prior to stroke.

Figure 3: Diagrammatic representation of recommendations on screening

(NB “Consensus recommendation” to be replaced with “AF-SCREEN recommendation” in the figure legend)

