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

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# Abstract

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 anticoagulation. 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. 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 discuss the draft document, and consider the key points arising from it using a Delphi process. These key points emphasize that screen-detected AF found at a single-timepoint or by intermittent ECG recordings over 2 weeks is not a benign condition, and with additional stroke factors, carries sufficient risk of stroke to justify consideration of anticoagulation. With regard to the methods of mass screening, handheld ECG devices have the advantage of providing a verifiable ECG trace which guidelines require for AF diagnosis and would therefore be preferred as screening tools. Certain patient groups such as those with recent embolic stroke of uncertain source (ESUS) require more intensive monitoring for AF. Settings for screening include various venues both in the community and the clinic, but must be linked to a pathway for appropriate diagnosis and management for screening to be effective. It is recognized that health resources vary widely between countries and health systems, so the setting for AF screening should be both country- and health–system specific. Based on current knowledge, this white paper provides a strong case for AF screening now, while recognizing that large randomized outcomes studies would be helpful to strengthen the evidence base.

# AF-SCREEN: establishment and goals

AF-SCREEN international collaboration was founded in September 2015 and includes over 130 physicians (cardiologists, electrophysiologists, primary care physicians, stroke neurologists and geriatricians), nurses, allied health professionals, epidemiologists, health economists and patient group representatives from 32 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](http://www.af-screen-intcollab.org/), accessed Feb 28th 2017).

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 effective therapy including oral anticoagulants (OACs) to reduce stroke and death1, and potentially to initiation of 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. This prompted the development of a white paper on screening for AF, developed from a consensus meeting of AF-SCREEN members held in Rome in August 2016. Full details of the genesis of the white paper and the Delphi process used are provided in the online-only supplementary material (Pages 1-2 online appendix).

# Incidence of screen-detected AF and CIED (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. 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 detected by CIEDs with atrial monitoring capability, are referred to as ‘CIED-detected atrial high rate episodes’. CIED-detected atrial high rate episodes could be due to oversensing, or other atrial tachyarrhythmias, and need close inspection of the stored electrograms before labeling them AF. CIEDs are not implanted to screen for AF, and CIED-detected atrial high rate episodes are not included in our definition of screen-detected AF, and should not be grouped with screen-detected AF. A full discussion on CIED-detected atrial high rate episodes has been included in this white paper principally to enhance our understanding of the significance of screen-detected AF and its relationship with stroke.

The incidence of screen-detected AF strongly depends on the population screened and duration/intensity of screening.2 Single timepoint screening of a general population aged ≥65 years detects undiagnosed AF in 1.4%,3 and the AF detected is largely persistent. 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 AF in 3.0% (0.5% on the initial ECG4). The identical protocol restricted to those with at least 1 additional stroke risk factor identified 7.4% with AF.5

The incidence of atrial high rate episodes in patients with CIEDs ranges from 30-60% depending on the population and the detection algorithm used (Table 1).6-18  In 2,580 patients with a history of hypertension and no prior AF history, CIED-detected atrial high rate episodes ≥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.11 Silent AF is more frequent than symptomatic AF in patients with a pacemaker or during external continuous rhythm monitoring.16 Because patients with CIEDs have a medical condition that may affect occurrence of atrial high rate episodes, other studies (ASSERT-II NCT01694394, REVEAL-AF NCT01727297, GRAF NCT01461434, Danish Loop study NCT02036450) 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. The initial report of the ASSERT-II study showed that brief episodes of subclinical AF are very common among individuals 65 years and older, who have stroke risk factors and evidence of left atrial enlargement. Among 256 patients with an average left atrial volume of 76.5 mL, receiving an implantable cardiac loop recorder, the rate of subclinical AF detection for AF episodes lasting at least 5 minutes was 34 % per year (presented at AHA Nov 2016).

# 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 individuals who were asymptomatic at presentation 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 these 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 asymptomatic clinical AF detected incidentally in general practice, 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 atrial high rate episodes in patients with implanted pacemakers, defibrillators, and cardiac re-synchronization devices are summarized in Table 2.6, 7, 9-11, 13, 17All show increased stroke rate with CIED-detected atrial high rate episodes, but the absolute risk of stroke was much lower than might be expected for patients with clinical AF and similar CHA2DS2-VASc score. A minimum of five minutes atrial high rate episodes was found to have clinical relevance in the MOST Study.10 Alternative arbitrary or data-derived atrial high rate episodes burden cut-points have been explored over the subsequent ten years, ranging from five minutes to 24 hours.11 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 atrial high rate episodes duration ≥24 hours.25

**Key point 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.27 The non-vitamin-K antagonist OACs (NOACs) further improve outcomes with less intracranial bleeding.28 It has been questioned 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.27 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, 1, 29 and by the duration of the AF episode in the case of CIED-detected atrial high rate episodes.

In the cohort study of 5,555 asymptomatic patients with AF detected incidentally in general practice, 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 Ongoing studies including ARTESiA (NCT01938248) and NOAH (NCT02618577) will help refine the benefit of NOAC in CIED-detected atrial high rate episodes and provide more information on the burden or duration of atrial high rate episodes that will benefit.

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. The absolute level of stroke risk for CIED-detected atrial high rate episodes may be lower than screen-detected AF and may modify the risk-benefit of OAC therapy. The burden threshold of CIED-detected atrial high rate episodes/CHA2DS2-VASc score associated with a positive risk-benefit ratio is under investigation.

# Role of AF in ischemic stroke

In stroke registries, at least a third of patients with ischemic stroke have either previously known30, 31 or newly-detected AF at the time of stroke.32 Stroke was the first manifestation of AF in over 25% of AF-related strokes.30 The association with AF is even higher if prolonged post-stroke external or implanted monitoring is performed.33, 34 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,30, 31 while in a global registry, 10% were due to previously unknown AF.35

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.9, 36-38 In several studies there does not seem to be a proximate temporal relationship between device-detected atrial high rate episodes and strokes, even though patients with atrial high rate episodes are at increased risk for stroke(Table 3).18, 36, 37 Only a small minority of patients with CIED-detected atrial high rate episodes who have a stroke experience the arrhythmia in the month prior to a stroke;9, 36 one-third had no atrial high rate episodes during approximately 1 year of rhythm monitoring before their stroke and only manifested atrial high rate episodes after their stroke.18, 36 Furthermore, multiple markers of abnormal atrial substrate have been associated with stroke independently of AF.39 In a small proportion of patients, however, there is a close proximate relationship between a daily atrial high rate episode burden ≥5.5h 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.40 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 factors42 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.42 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. 30, 33, 43

It is likely that both unknown and undertreated AF contribute to a substantial proportion of all strokes, which could be prevented by screening strategies. Regarding the role of AF in stroke, it is likely that AF is both a risk factor and a strong 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 disproportionally in older adults, rendering age one of the best predictors of AF.44 The prevalence of AF below age 50 is negligible in most populations and may not justify screening in this group.44 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.45

If the screening procedure is inexpensive and easy to use, e.g. pulse palpation or single timepoint handheld devices,46, 47 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,3 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.29 Opportunistic screening in all patients contacting the health system aged ≥65 has been adopted in the ESC AF guidelines, 29 but might be more efficient if an older age threshold is chosen or an additional stroke risk factor is required48. 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.4, 5 Adding 2 weeks of twice-daily patient-activated handheld ECG detected an additional 2.5% with undiagnosed AF,4 and 7.4% after enrichment with ≥1 additional stroke risk factor.5 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 (e.g. natriuretic peptides, high-sensitivity troponin) to existing clinical predictors may improve prediction of AF incidence.49, 50 However, there is marginal improvement in model discrimination and reclassification.

**Key Point 2**:

Single timepoint screening of people aged ≥65 in the clinic or community appears justified, based on yield of screening and likely cost-effectiveness. For those over age 75, or in younger age groups at high risk of AF or stroke, two weeks of twice-daily intermittent AF screening may be warranted.

# Ischemic Stroke and Embolic Stroke of Undetermined Source (ESUS)

RCTs and observational studies have established the effectiveness of post-stroke ECG monitoring for improving AF detection32, 51 (number needed to screen=8-14), with longer monitoring durations increasing AF detection probability. Post-stroke ECG monitoring is likely cost-effective.52, 53 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. ESC guidelines recommend ≥ 72 hours ECG monitoring in all stroke survivors,29 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).

**Key Point 3:**

Long-term continuous rhythm monitoring using either external or implanted devices or extended intermittent patient-activated recordings may diagnose clinically important AF in individuals with recent ESUS.

# Overview of screening methods: (Table 4)54-63

Pulse palpation to assess pulse irregularity is a readily accessible method for screening in primary care, shown effective as a screening strategy in the SAFE study.64 It can also be used in the community, in both high and low-middle income countries, but has some limitations.54 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. Cardiac auscultation can also detect AF, but is even less frequently performed in primary care.

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, 65 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.56, 60, 61 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.66 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.63, 67, 68 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,1, 69 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%).56, 57, 59, 70 These devices have been widely used for single timepoint AF screening.47, 57 Repeated handheld ECG recordings over 14-28 days have diagnostic accuracy equivalent to standard event recorders, superior to 12-lead ECG and 24-hour Holter for paroxysmal AF, 5, 59, 71 and have been used successfully in large scale AF screening studies.4, 5 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, e.g. prolonged Holter monitoring, a wearable non-adhesive dry-electrode belt,72 or by a wearable-patch: feasible for 2-4 weeks73 and superior to 24-hour Holter.

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.

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).69 Device performance, therefore, must be tested in the setting where it will be used for screening to optimize performance.

**Key Point 4:** 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. Because ECG confirmation is mandated by guidelines for the diagnosis of AF, handheld ECG devices have the advantage of providing a verifiable ECG trace, and would therefore would be preferred as screening tools. Prolonged continuous ECG monitoring with external or subcutaneous recorders 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.3-5, 74-77 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 (e.g. Heart Rhythm Week in Belgium.75) The STROKESTOP study,4 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.64 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.47, 78 People ≥65 years with chronic conditions in many countries visit their community pharmacy every 1-3 months. AF screening with pulse check and smartphone-based ECG in Australian pharmacies was found to be feasible, cost-effective47 and well accepted.79 The major issue is ensuring referral and then treatment of detected individuals,78 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.80

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.64 While some guidelines recommend screening using pulse palpation, 29 pulse taking is not common practice.81 The new ESC guidelines have added ECG rhythm strip to the recommendation on pulse palpation for opportunistic screening.29 For scalability and sustainability, screening could be linked to existing workflow e.g. cardiovascular risk management programs or influenza vaccination.46, 57, 82-84 Computerized medical records linked to electronic decision support tools85 (e.g. AF SMART, ACTRN12616000850471),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,86 but have similar issues with sustainable delivery of the screening intervention and subsequent treatment.

**Key Point 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 for screening to be effective. Settings that have been used effectively include some that are community-based and others based in primary care, specialist practices, or general or specialist clinics. Primary care and outpatient clinics have the advantage of a direct link with treatment and a potentially sustainable workflow (see online Supplementary material for country-specific considerations).

# 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
* country-specific “willingness-to-pay” thresholds to avoid one stroke

In the first paper on health economic modelling for AF screening,87 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 64, 88 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 study4 confirmed that ECG screening was likely to be cost-effective using a lifelong decision-analytic Markov model.89 Two other smaller studies evaluating smartphone ECG screening in community pharmacies47 (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 clinic90 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. 91

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 Netherlands82 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 AF92, 93 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 75,94 but there are no data on the detection rate for annual or other frequencies of repeated screening. More data are required to compare cost-effectiveness of different screening interventions and the effect of different age cutoffs.

# Screening for under-treated known AF

Under-treatment exposes patients to a significant risk of fatal or disabling strokes. Population surveys95, 96 and registries indicate treatment remains suboptimal with large country differences.30 Population screening using a variety of techniques3, 4, 75 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. 4, 29, 30

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.5 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 study4 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, in both newly diagnosed and under-treated known AF.

# 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.97, 98 Patient-led organizations can more effectively identify the challenges patients face, and engage policy makers to bring about change,97 leading to improved outcomes for patients and healthcare providers ([www.stopafib.org](http://www.stopafib.org), [www.heartrhythmalliance.org](http://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 such as the National Institute for Health and Care Excellence (NICE, UK) and scientific organizations now seek the input of patients and patient organizations in developing clinical guidelines and scientific publications. 1, 29

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 will be helpful to educate people about checking their pulse and the benefits of OAC for preventing AF-related stroke. It will be beneficial for professional health organizations to 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.

# Current guidelines

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.88 29 Pulse taking in practice is recommended by the National Institute for Health and Care Excellence (NICE, UK) guidelines, but only for symptoms. However, the new 2016 ESC guideline 29 also includes: an ECG rhythm strip as an alternative to pulse palpation; at least 72 hours ECG monitoring after TIAor 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 atrial high rate episodes and if detected, prompt further ECG monitoring to document AF before initiating therapy.

The ACC/AHA/HRS Guidelines1 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 6:** There is a need to perform large randomized controlled studies using hard endpoints (including stroke/systemic embolism and death), of strategies for screening, to strengthen the evidence base to inform guidelines and national systematic screening strategies.

# Conclusions (Fig 3)

In older individuals with screen-detected AF, the absolute risk of ischemic stroke and death appears sufficient to justify consideration of treatment with OACs. Irregularity of the pulse is a simple way to screen for AF, but 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 have an advantage over pulse-based devices and would be preferred as screening tools. Single timepoint screening for AF appears justified based on yield and cost-effectiveness, and as a further step, two weeks of twice daily intermittent recordings may be justified in people aged 75 or older, or in other groups at high risk of AF or AF-related stroke. Patient differences will modulate the type and intensity of screening (e.g. 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. While the WHO criteria for screening appear to be met99 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)

1. Process adopted by AF-SCREEN to achieve consensus
2. AF incidence and future projections
3. Consequences of undiagnosed AF other than stroke
4. Secondary AF
5. Table A: Arguments against screening for AF and responses.
6. Country by country plan of potential AF screening implementation specific to the health system.
7. AF Screening reference list

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**Tables**

Table 1: Incidence of CIED-detected atrial high rate episodes (AHREs) in the population with cardiac implanted devices

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Year** | **Trial** | **Device Indication** | **Clinical Profile of Patients** | **Mean age**  | **% male** | **LVEF%** | **Mean CHADS2** | **Follow-up**  | **AF burden threshold**  | **Incidence of AF** |
| 2002 | Gillis et al.8 | PPMs for sinus node disease | All  | 70 ± 12 | 52% | N.A. | N.A. | 718 ± 383 days | >1 min  | 157/231 (68%) |
| 2003 | Ancillary MOST 10 | PPMs for sinus node disease | All  | Median 73 (68,81) for no AHREMedian 75 (68,79) for AHRE detected | 45% | N.A. | N.A. | Median 27 months |  >5 min  | 156/312 (50%) |
| 2010 | TRENDS15 | PPMs and ICDsAll indications | History of prior strokeNo history of AFNo OAC use≥1 stroke risk factor | 72.8±9.9 for no AHRE74.0±9.1 for AHRE detected | 63% for no AHRE71% for AHRE detected | N.A. | 4.1±0.8 for no AHRE4.2±0.8 for AHRE detected | Mean 1.4 years | >5 min | 45/163 (28%) |
| 2012 | TRENDS14 | PPMs and ICDsAll indications | No history of prior strokeNo history of AFNo 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 | ASSERT11 | PPMs and ICDsAll indications | History of hypertensionNo history of AFNo OAC use | 76±7 for no AHRE77±7 for AHRE detected  | 59% for no AHRE56% for AHRE detected | N.A. | 2.3±1.0 for no AHRE2.2±1.1 for AHRE detected | 2.5 years | >6 min | 895/2580 (34.7%) |
| 2012 | Home Monitor CRT17 | CRTDs and CRTPsCHF | Heart failureNo 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.12 | PPMsAll indications | All  | 71.7 ±14.4 for no AHRE74.3±13.7 for AHRE detected  | 59% for no AHRE58% for AHRE detected | N.A. | 2.02± 1.30 for no AHRE2.23±1.47 for AHRE detected |  Single centerRetrospective | >5 min  | 246/445 (55.3%) |
| 2015 | IMPACT18 | ICDs and CRTDsAll indications | No permanent AFNo contra-indications for OAC | 64.2+11.5 for Control64.7+10.8 for Intervention  | 73% for Control74% for Intervention  | 29.4+11.3 for Control29.9+10.8 for Intervention  |  2 (median) | 701 days | >4-12 sec | 945/2718 (34.8%) |
| 2016 | RATE Registry 13  | PPMs and ICDs | AllNo permanent AF,  | 73.6±11.8 for PPMs, 64.5±12.6 for ICDs | 54% in PPM72% in ICDs | 57.8±10.5 for PPM29.2±11.3 for ICDs |  1.8±1.0 for PPM2.0±0.8 for ICDs | 22.9 months (median)  | > 3 atrial premature complexes | 145/300(48%) of PPM pts155/300 (52%) of ICD ptsOf the representative samples studied |

**Legend:** PPM = permanent pacemaker; ICD = Implanted cardioverter defibrillator; AHREs = atrial high rate episodes

**Table 2: Summary of studies regarding CIED-detected** atrial high rate episodes **(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 MOST10 | 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 Registry7 | 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.6  | 568 | 1 year (mean) | CHADS2+AF burden |  >174 bpm | CHADS2+AF burden |  n/a | 2.5% overall(0.8% vs. 5%) |
| 2009 | TRENDS9 | 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 CRT17 | 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 | ASSERT11 | 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 | SOS26 | 10016 | 2 years(median) |  1 hour |  >175 bpm |  1 hour | 2.11 (p=0.008)CI: 1.22–3.64 | 0.39% per yearoverall |
| 2016 | RATE Registry 13  | 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** atrial high rate episodes **(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 al41  | 33/3438 | 5 minutes |  21/33 (64%)  | NA  |  12/33 (67%) | 11/33 (33%) |
| 2011 | TRENDS9 | 40/2486 | 5 minutes  |  20/40 (50%) |  6/40 (15%) |  29/40 (73%) | 11/40 (27%) |
| 2014 | ASSERT11, 36 | 51/2580 | 6 minutes  |  18/51 (35%) |  8/51 (16%) |  47/51 (92%) | 4/51 (8%) |
| 2014 | IMPACT18 | 69/2718  | 36/48 atrial beats ≥200bpm  |  20/69 (29%) |  9/69 (13%) |  65/69 (94%) | 4/69 (6%) |
| 2015 | Turakhia et al40 | 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., 200654 |
| *Handheld single-lead ECGs* |  |  |  |
| AliveCor (Kardia) heart monitor | Algorithm only (based on presence of P wave and RR irregularity)  | 98 (89-100) | 97 (93-99) | Lau et al., 201355 |
| Merlin ECG event recorder | Cardiologist interpretation | 93.9 |  90.1 | Kearley et al., 201456 |
| Mydiagnostick | Algorithm only (based on RR irregularity) | 94 (87–98) |  93 (85–97) | Tieleman et al., 201457Vaes et al., 201458 |
| Omron HCG-801 | Algorithm only (based on RR irregularity) | 98.7 (93.2-100) | 76.2(73.3-78.9) | Kearley et al., 201456 |
| Omron HCG-801 | Cardiologist interpretation | 94.4 | 94.6 | Kearley et al., 201456 |
| Zenicor EKG | Cardiologist interpretation | 96 | 92 | Doliwa et al., 200959 |
| *Modified Blood pressure monitors* |  |  |  |
| Microlife BPA 200 Plus | Algorithm only (based on pulse irregularity) | 92 | 97 | Marazzi et al., 201260 |
| Microlife BPA 200 | Algorithm only (based on pulse irregularity) |  97 (81.4-100) |  90 (83.8-94.2) | Wiesel et al., 201461 |
| Omron M6 | Algorithm only (based on pulse irregularity) | 100 | 94 | Marazzi et al., 201260 |
| Omron M6 comfort | Algorithm only (based on pulse irregularity) | 30(15.4-49.1) | 97(92.5-99.2) | Wiesel et al., 201461 |
| Microlife WatchBP | Algorithm only (based on pulse irregularity) | 94.9 (87.5-98.6) | 89.7 (87.5-91.6) | Kearley et al., 201456 |
| *Plethysmographs* |  |  |  |
| Finger probe | Algorithm only (based on pulse irregularity) | 100 | 91.9 | Lewis et al., 201162 |
| iPhone photo-plethysmograph | Algorithm only (based on pulse irregularity) | 97.0 | 93.5 | ¶McManus et al., 201663 |

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

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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 201540)



**Legend:** Odds ratio for non-overlapping 5-day epochs of AF burden in implanted devices ≥5.5h 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 key points on screening



**Legend:** BP = blood pressure; PPG = photoplethysmography; enrichment = use of additional risk factors or biomarkers to either increase the proportion with unknown AF in the screened population, or increase the risk of stroke in those with AF detected by screening in that population; patients who are undertreated = patients with known AF who are not receiving oral anticoagulant according to guidelines, (see Page XXX section on “Should screening include undertreated known AF”). While this is not strictly speaking screening, such patients will be detected by population screening for AF, so this has been placed in a different shape with a dotted line connector; ESUS = embolic stroke of uncertain source.

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