WHITE PAPER

Screening for Atrial Fibrillation

A Report of the AF-SCREEN International Collaboration

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 that 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 in both the community and the clinic, but they 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.

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Key Words: atrial fibrillation ■ screening ■ stroke

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AF-SCREEN: ESTABLISHMENT AND GOALS

AF-SCREEN international collaboration was founded in September 2015 and includes >100 physicians (cardiologists, electrophysiologists, primary care physicians, stroke neurologists, and geriatricians), 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 undertreated AF to reduce stroke and death and to provide advocacy for implementation of country-specific AF screening programs (www.afscreen.org).

Although many patients 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 death[1] and potentially 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 that 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 reexamine 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 appendix in the online-only Data Supplement.

Incidence of Screen-Detected AF and Cardiac Implanted Electronic Device (CIED)-Detected Atrial High-Rate Episodes

Many terms have been used to describe screen-detected AF, including unrecognized, undiagnosed, silent, subclinical AF, and cardiac implanted electronic device (CIED)-detected atrial high-rate episodes. In this article, we will refer to AF detected on single-timepoint screening or patient-activated ECG recorders as screen-detected AF, whereas 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 caused by 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 of 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 ≥65 years of age detects undiagnosed AF in 1.4%,[3] and the AF detected is largely persistent. In a large population-based study of individuals 75 to 76 years of age, a more intense 2-week screening program using twice-daily intermittent handheld ECG recordings identified AF in 3.0% (0.5% on the initial ECG[4]). The identical protocol restricted to those with ≥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% to 60% depending on the population and the detection algorithm used.[6–15] In 2580 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 the occurrence of atrial high-rate episodes, other studies (ASSERT-II [Subclinical AF in older asymptomatic patients] NCT01694394, REVEAL-AF [Incidence of AF in high risk patients] NCT01727297, GRAF [Graz study on the Risk of Atrial Fibrillation] 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 common among individuals ≥65 years of age 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 episodes lasting ≥5 minutes was 34% per year.[17] The studies reporting incidence of CIED-detected atrial high-rate episodes[8,10–15,18,19] have been summarized in Table 1.

Risk of Stroke and Death in Untreated Screen-Detected AF

No data specifically address the risk of stroke and death in untreated screen-detected AF in the general population. The closest approximation includes cohort studies of individuals with AF detected incidentally in the absence of symptoms. One study[20] showed that individuals who were asymptomatic at presentation were 3 times as likely to have had an ischemic stroke before AF diagnosis, and in follow-up they had similar risk of stroke and death as those with symptomatic AF. In a later study from this group, 161 out of 476 individuals with new AF were asymptomatic at presentation, and these people

Table 1. Incidence of Cardiac Implanted Electronic Device–Detected Atrial High-Rate Episodes 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.[8]	PPMs for sinus node disease	All	70±12	52%	NA	NA	718±383 days	>1 min	157/231 (68%)
2003	Ancillary MOST[10]	PPMs for sinus node disease	All	Median 73 (68,81) for no AHRE Median 75 (68,79) for AHRE detected	45%	NA	NA	Median 27 mo	>5 min	156/312 (50%)
2010	TRENDS[15]	PPMs and ICDs All indications	History of prior stroke No history of AF No oral anticoagulant 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	NA	4.1±0.8 for no AHRE 4.2±0.8 for AHRE detected	Mean 1.4 y	>5 min	45/163 (28%)
2012	TRENDS[14]	PPMs and ICDs All indications	No history of prior stroke No history of AF No oral anticoagulant use ≥1 stroke risk factor	70.2±11.8	66%	NA	≥2 in 70%	1.1±0.7 y	>5 min	416/1368 (30%)
2012	ASSERT[11]	PPMs and ICDs All indications	History of hypertension No history of AF No oral anticoagulant use	76±7 for no AHRE 77±7 for AHRE detected	59% for no AHRE 56% for AHRE detected	NA	2.3±1.0 for no AHRE 2.2±1.1 for AHRE detected	2.5 y	>6 min	895/2580 (34.7%)
2012	Home monitor CRT[18]	CRTDs and CRTPs Congestive heart failure	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.[12]	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	NA	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[19]	ICDs and CRTDs All indications	No permanent AF No contraindications for oral anticoagulant	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[13]	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 mo (median)	> 3 atrial premature complexes	145/300 (48%) of PPM patients 155/300 (52%) of ICD patients of the representative samples studied

AF indicates atrial fibrillation; AHRE, atrial high-rate episode; ASSERT, Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial; CRT, cardiac resynchronization therapy; CRTD, cardiac resynchronization therapy defibrillator; CRTP, cardiac resynchronization therapy pacemaker; ICD, implanted cardioverter defibrillator; IMPACT, the IMPACT of BIOTRONIK Home Monitoring Guided Anticoagulation on Stroke Risk in Patients With ICD and CRT-D Devices; MOST, Mode Selection Trial; NA, not applicable; PPM, permanent pacemaker; RATE, Registry of Atrial Tachycardia and atrial fibrillation Episodes; and TRENDS, A Prospective Study of the Clinical Significance of Atrial Arrhythmias Detected by Implanted Device Diagnostics.

had an increased risk for cardiovascular (hazard ratio [HR], 3.12; 95% confidence interval [CI], 1.50–6.45) and all-cause mortality (HR, 2.96; 95% CI, 1.89–4.64) compared to those with typical symptoms after adjustment for CHA_2DS_2-VASc score and age (Figure 1).[21]

In 5555 patients with asymptomatic clinical AF detected incidentally in general practice, the adjusted stroke rate in the 1460 untreated patients was 4% and all-cause mortality 7% over 1.5 years of follow-up compared with 1% and 2.5%, respectively, in matched controls without AF.[22,23] In the EORP AF registry (Eurobservational Research Programme), mortality at 1 year was >2-fold higher in asymptomatic versus symptomatic AF (9.4% versus 4.2%, $P<0.0001$).[24] In the Belgrade AF study, survival free of AF progression or ischemic stroke was worse in those with an asymptomatic presentation.[25]

The major studies regarding thromboembolic risk of CIED-detected atrial high-rate episodes in patients with implanted pacemakers, defibrillators, and cardiac resynchronization devices all 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 CHA_2DS_2-VASc score.[6,7,9–11,13,18] A minimum 5-minute duration of atrial high-rate episodes was found to have clinical relevance in the MOST study (Mode Selection Trial).[10] Alternative arbitrary or data-derived atrial high-rate episodes burden cut points have been explored over the subsequent 10 years, ranging from 5 minutes to 24 hours.[11] Uncertainty remains about the minimum burden that increases thromboembolic risk. A recent reevaluation of the ASSERT study indicated that stroke risk was increased only in patients with atrial high-rate episodes duration ≥24 hours.[26] These studies are summarized in Table 2.

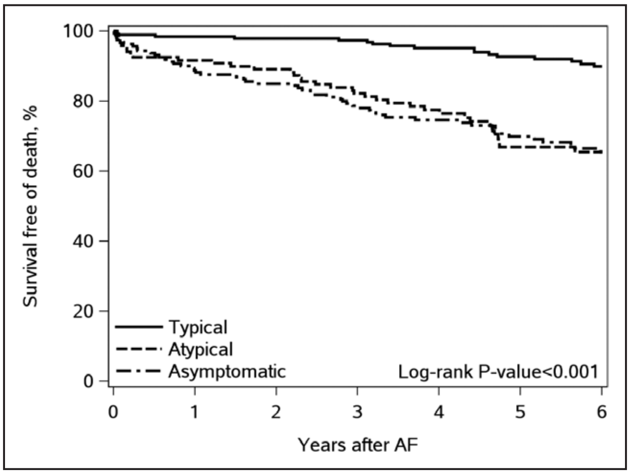

Figure 1. Survival stratified by type of AF presentation. Kaplan-Meier curve for all-cause mortality according to presentation with either typical AF symptoms (palpitations with or without other symptoms), atypical symptoms (fatigue, chest pain, shortness of breath, lightheadedness, syncope, decreased exercise tolerance, but without palpitations), or asymptomatic (AF detected incidentally during a routine visit for an unrelated problem). AF indicates atrial fibrillation. Reprinted from Siontis et al[21] with permission of the Heart Rhythm Society. Copyright © 2016, Heart Rhythm Society.

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 an effective therapy improves outcomes. For AF, OACs have a major impact on reducing stroke, systemic embolism, and all-cause mortality.[28] The nonvitamin-K antagonist OACs further improve outcomes with less intracranial bleeding.[29] 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 studies have not been analyzed separately.[28] No randomized controlled trials exist, 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 (CHA_2DS_2-VASc score) according to guidelines[1,30] and by the duration of the AF episode in the case of CIED-detected atrial high-rate episodes.

In the cohort study of 5555 asymptomatic patients with AF detected incidentally in general practice, OAC therapy (n=2492) compared with no antithrombotic therapy (n=1460) 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.[22,23] Ongoing studies, including ARTESiA (Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation; NCT01938248) and NOAH (Non-vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes; NCT02618577), will help refine the benefit of nonvitamin-K antagonist OACs 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

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Table 2. Summary of Studies Regarding Cardiac Implanted Electronic Device–Detected Atrial High-Rate Episodes and Thromboembolic Risk

Trial (Year)	Number of Patients	Duration of Follow-Up	Atrial Rate Cutoff (bpm)	AF Burden Threshold	Hazard Ratio for TE Event	TE Event Rate (Below vs. Above AF Burden Threshold)
Ancillary MOST[10] (2003)	312	27 mo (median)	>220	5 min	6.7 (*P*=0.020)	3.2% overall (1.3% vs. 5%)
Italian AT500 Registry[7] (2005)	725	22 mo (median)	>174	24 h	3.1 (*P*=0.044) (95% CI, 1.1–10.5)	1.2% annual rate
Botto et al[6] (2009)	568	1 y (mean)	>174	$CHADS_2$+AF burden	n/a	2.5% overall (0.8% vs. 5%)
TRENDS[9] (2009)	2486	1.4 y (mean)	>175	5.5 h	2.2 (95% CI, 0.96–5.05, *P*=0.06)	1.2% overall (1.1% vs. 2.4%)
Home Monitor CRT[18] (2012)	560	370 days (median)	>180	3.8 h	9.4 (95% CI, 1.8–47, *P*=0.006)	2.0% overall
ASSERT[11] (2012)	2580	2.5 y (mean)	>190	6 min	2.5 (*P*=0.007) (95% CI, 1.28–4.85)	(0.69% vs. 1.69%)
SOS[27] (2014)	10016	2 y (median)	>175	1 h	2.11 (*P*=0.008) (95% CI, 1.22–3.64)	0.39% per year overall
RATE Registry[13] (2016)	5379 (3141 with pacemakers and 2238 with ICDs)	22.9 mo (median)	NA	Nonsustained atrial high-rate episodes with a duration from 3 atrial premature complexes to 15–20 s	0.87 (95% CI, 0.58–1.31, *P*=0.51)	For nonsustained atrial high-rate episodes: 0.55% (0.34%–0.76%) per year for pacemakers and 0.81% (0.50%–1.12%) per year for ICDs

AF indicates atrial fibrillation; AHRE, atrial high-rate episode; ASSERT, Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial; bpm, beats per minute; CI, confidence interval; CRT, cardiac resynchronization therapy; ICD, implanted cardioverter defibrillator; MOST, Mode Selection Trial; NA, not applicable; RATE, Registry of Atrial Tachycardia and Atrial Fibrillation Episodes; SOS, stroke prevention strategies; TE, thromboembolic; and TRENDS, A Prospective Study of the Clinical Significance of Atrial Arrhythmias Detected by Implanted Device Diagnostics.

high-rate episodes/CHA_2DS_2-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 known[31,32] or newly detected AF at the time of stroke.[33] Stroke was the first manifestation of AF in >25% of AF-related strokes.[31] The association with AF is even higher if prolonged poststroke external or implanted monitoring is performed.[34,35] In the Swedish Riks-Stroke register of >94 000 ischemic strokes, ≈9% were associated with previously unknown AF and 20% with known but undertreated AF,[31,32] whereas in a global registry 10% were caused by previously unknown AF.[36]

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.[9,37–39] In several studies, there does not appear to be a proximate temporal relationship between device-detected atrial high-rate episodes and strokes although patients with atrial high-rate episodes are at increased risk for stroke.[19,37,38] Only a small minority of patients with CIED-detected atrial high-rate episodes who have a stroke experience arrhythmia in the month before a stroke.[9,37] One third had no atrial high-rate episodes during ≈1 year of rhythm monitoring before their stroke and only manifested atrial high-rate episodes after their stroke.[19,37] Furthermore, multiple markers of abnormal atrial substrate have been associated with stroke independently of AF.[40] In a small proportion of patients, however, a close proximate relationship exists between a daily atrial high-rate episode burden ≥5.5 hours and stroke, with risk highest in the 5 days before stroke, falling to a nonsignificant increase in risk by 30 days before stroke (Figure 2), pointing to AF being a risk factor in these patients.[41] The temporal relationship between CIED-detected atrial high-rate episodes and stroke is summarized in Table 3. A limitation of these studies is the small numbers of strokes and usually lack of adjudication as cardioembolic.

Even short AF episodes can create a prothrombotic state that persists for some time after the episode. Furthermore, atrial cardiomyopathy related to aging or systemic risk factors[43] can lead to AF or atrial thromboembolism. Once AF develops, it impairs atrial function and secondarily leads to atrial remodeling, which in addition

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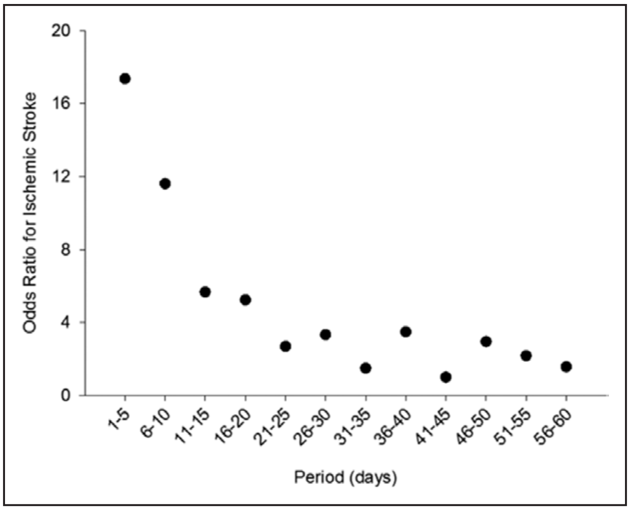

Figure 2. Time trend of risk of stroke for AF in 60 days before stroke.
Odds ratio for nonoverlapping 5-day epochs of AF burden in implanted devices ≥5.5 hours in 1 day during the 5-day epoch, from 1 to 5 days before stroke (left-hand point), through 56 to 60 days before stroke (right-hand point). Each stroke case epoch is matched to six 5-day control epochs between 91 and 120 days before stroke. There is a progressive fall in odds ratio of stroke from 17.4 for AF occurring 1 to 5 days before stroke to nonsignificant increases for AF >21 days before stroke. AF indicates atrial fibrillation. Reprinted from Turakhia et al[41] with permission of the American Heart Association, Inc. Copyright © 2015, American Heart Association, Inc.

to flow abnormalities further increases thromboembolic risk.[43] 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 neurocardiac imaging and continuous monitoring may provide further insights into the pathophysiology in future.

Nevertheless, AF remains an important risk marker as well as risk factor for stroke, with well-documented efficacy of OAC for stroke prevention. Anticoagulated patients with AF have residual stroke rates similar to matched individuals without AF, which underlines the efficacy of OACs in prevention of AF-related stroke.[23] OACs remain underused in AF patients at risk of stroke: 30% to 50% of eligible patients with AF are not being given OAC, many are mistreated with aspirin monotherapy, and the remainder are not receiving any antithrombotic therapy.[31,34,44]

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 or Individuals to Screen?

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 1 of the best predictors of AF.[45] The prevalence of AF <50 years of age is negligible in most populations and may not justify screening in this group.[45] 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.[46]

If the screening procedure is inexpensive and easy to use (eg, pulse palpation or single-timepoint handheld devices),[47,48] screening can be nonselective and just age-based. A threshold ≥65 years of age (a CHA_2DS_2-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.[30] Opportunistic screening in all patients contacting the health system ≥65 years of age has been adopted in the ESC AF guidelines[30] but might

Table 3. Temporal Relationship Between Cardiac Implanted Electronic Device–Detected Atrial High-Rate Episodes and Stroke

Year	Trial	Number of Patients With TE Event	Definition of AF Episode	Any AF Detected Before TE Event	AF Detected Only After TE Event	No AF in 30 Days Before TE Event	Any AF in 30 Days Before TE Event
2012	Boriani et al[42]	33/3438	5 min	21/33 (64%)	NA	12/33 (67%)	11/33 (33%)
2011	TRENDS[9]	40/2486	5 min	20/40 (50%)	6/40 (15%)	29/40 (73%)	11/40 (27%)
2014	ASSERT[11,37]	51/2580	6 min	18/51 (35%)	8/51 (16%)	47/51 (92%)	4/51 (8%)
2014	IMPACT[19]	69/2718	36/48 atrial beats ≥200 beats per minute	20/69 (29%)	9/69 (13%)	65/69 (94%)	4/69 (6%)
2015	Turakhia et al[41]	187/9850	≥5.5 h or ≥6 min on any day 120 days previously	36/187 (19%) ≥5.5 h 50/187 (26%) ≥6 min	NA	NA	NA

AF indicates atrial fibrillation; ASSERT, Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial; IMPACT, the IMPACT of BIOTRONIK Home Monitoring Guided Anticoagulation on Stroke Risk in Patients With ICD and CRT-D Devices; NA, not applicable; TE, thromboembolic; and TRENDS, A Prospective Study of the Clinical Significance of Atrial Arrhythmias Detected by Implanted Device Diagnostics.

be more efficient if an older age threshold is chosen or an additional stroke risk factor is required.[49] Superiority over a simple age-based criterion, however, needs to be proven.

Among individuals 75 years of age in Sweden, a single ECG detected 0.5% to 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 factors.[5] Even more AF is detected with continuous recording by 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 (eg, older age plus additional risk factors or embolic stroke of undetermined source [ESUS]). Adding biomarkers (eg, natriuretic peptides, high-sensitivity troponin) to existing clinical predictors may improve the prediction of AF incidence.[50,51] However, there is marginal improvement in model discrimination and reclassification.

Key Point 2

Single-timepoint screening of people ≥65 years of age in the clinic or community appears justified based on yield of screening and likely cost-effectiveness. For those >75 years of age or in younger age groups at high risk of AF or stroke, 2 weeks of twice-daily intermittent AF screening may be warranted.

Ischemic Stroke and ESUS

Randomized controlled trials and observational studies have established the effectiveness of ECG monitoring after stroke for improving AF detection (number needed to screen=8–14), [33,52] with longer monitoring durations increasing AF detection probability. ECG monitoring after stroke is likely cost-effective.[53,54] However, randomized controlled trials have not been powered to assess the effect of prolonged ECG monitoring on stroke or mortality.

After an acute ischemic stroke/transient ischemic attack 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,[30] but more research is required to identify non-ESUS subgroups benefitting most from more prolonged monitoring. Ongoing randomized controlled trials are exploring an alternative strategy of blanket nonvitamin-K antagonist OAC therapy after limited negative Holter monitoring in ESUS (RE-SPECT [Randomized, Double-Blind, Evaluation in Secondary Stroke Prevention Comparing the Efficacy and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate Versus Acetylsalicylic Acid] ESUS NCT02239120 and NAVIGATE ESUS [Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients with Recent 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

Pulse palpation to assess pulse irregularity is a readily accessible method for screening in primary care, shown to be effective as a screening strategy in the SAFE study (Screening for Atrial Fibrillation in the Elderly).[65] It can also be used in the community, in both high- and low-middle-income countries, but has some limitations.[55] In the clinic, it is usually performed by physicians or nurses, whereas in the community, nonphysician 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 that improve feasibility and cost-effectiveness of widespread screening (Table 4). These devices are recognized as valid for AF detection by the European Primary Care Cardiovascular Society[66] 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% to 100%) and specificity (90% to 97%) and are superior to pulse palpation.[57,61,62] 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.[67] 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.[64,68,69] 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,[1,70] either 12-lead (current gold standard) or single-lead documenting P-waves.

A range of handheld devices produce diagnostic quality lead 1 single-lead ECGs, most with automated algorithms more accurate than pulse palpation (sensitivity 94% to 99% and specificity 92% to 97%).[57,58,60,71] These devices have been widely used for single-timepoint AF screening.[48,58] Repeated handheld ECG recordings over 14 to 28 days have diagnostic accuracy equivalent to standard event recorders, superior to 12-lead ECG and 24-hour Holter for paroxysmal AF,[5,60,72] and have been used successfully in large-scale AF screening studies.[4,5] Although 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, although the prognos-

Table 4. Sensitivity and Specificity of Different Methods of Screening for Atrial Fibrillation

Device	Method of Interpretation	Sensitivity (%)	Specificity (%)	Reference
Pulse palpation		94 (84–97)	72 (69–75)	Cooke et al[55]
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[56]
Merlin ECG event recorder	Cardiologist interpretation	93.9	90.1	Kearley et al[57]
Mydiagnostick	Algorithm only (based on RR irregularity)	94 (87–98)	93 (85–97)	Tieleman et al[58]
				Vaes et al[59]
Omron HCG-801	Algorithm only (based on RR irregularity)	98.7 (93.2–100)	76.2(73.3–78.9)	Kearley et al[57]
Omron HCG-801	Cardiologist interpretation	94.4	94.6	Kearley et al[57]
Zenicor EKG	Cardiologist interpretation	96	92	Doliwa et al[60]
Modified blood pressure monitors				
Microlife BPA 200 Plus	Algorithm only (based on pulse irregularity)	92	97	Marazzi et al[61]
Microlife BPA 200	Algorithm only (based on pulse irregularity)	97 (81.4–100)	90 (83.8–94.2)	Wiesel et al[62]
Omron M6	Algorithm only (based on pulse irregularity)	100	94	Marazzi et al[61]
Omron M6 comfort	Algorithm only (based on pulse irregularity)	30 (15.4–49.1)	97 (92.5–99.2)	Wiesel et al[62]
Microlife WatchBP	Algorithm only (based on pulse irregularity)	94.9 (87.5–98.6)	89.7 (87.5–91.6)	Kearley et al[57]
Plethysmographs				
Finger probe	Algorithm only (based on pulse irregularity)	100	91.9	Lewis et al[63]
iPhone photo-plethysmograph	Algorithm only (based on pulse irregularity)	97.0	93.5	McManus et al[64]*

The comparator for all studies was a 12-lead ECG; RR irregularity indicates irregularity of intervals between successive R waves on the ECG.
*Three-lead telemetry used.

tic significance of brief episodes is uncertain. Continuous monitoring can be accomplished by noninvasive devices (eg, prolonged Holter monitoring, a wearable nonadhesive dry-electrode belt,[73] or a wearable-patch: feasible for 2 to 4 weeks[74] and superior to 24-hour Holter).

The main disadvantages of prolonged external monitoring are skin irritation from electrodes and 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).[70] Device performance, therefore, must be tested in the setting where it will be used for screening to optimize performance.

Key Point 4

Mass 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 be the preferred screening tool. 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

Interest in community screening has increased recently in a number of countries.[3–5,75–78] Prospective studies have used pulse palpation, single- or multilead 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[76]). The STROKESTOP study[4] invited half of the 75- to 76-year-olds in 2 Swedish regions to attend screening, and 53% accepted, similar to the rate in the SAFE study.[65] This approach was stepped, with an initial single-lead ECG, followed by twice-daily intermittent patient-activated ECG recordings over a 2-week period in those individuals without AF.

Pharmacies offer an attractive setting for community screening.[48,79] People ≥65 years of age with chronic con-

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ditions in many countries visit their community pharmacy every 1 to 3 months. AF screening with pulse check and smartphone-based ECG in Australian pharmacies was found to be feasible, cost-effective,[48] and well accepted.[80] The major issue is ensuring referral and then treatment of detected individuals,[79] so an established referral pathway is crucial.

Primary care is an ideal setting: In addition to regular primary care physician visits, nursing support for screening is available, and there is a direct link with the practitioner to prescribe OAC. Two challenges remain: (1) developing a sustainable strategy for detecting undiagnosed AF, and (2) providing adequate treatment for patients with known or newly discovered AF because undertreatment is common.[81]

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 of age, and more cost-effective.[65] Although some guidelines recommend screening using pulse palpation,[30] pulse taking is not common practice.[82] The new ESC guidelines have added ECG rhythm strip to the recommendation on pulse palpation for opportunistic screening.[30] For scalability and sustainability, screening could be linked to existing workflow (eg, cardiovascular risk management programs or influenza vaccination).[47,58,83–85] Computerized medical records linked to electronic decision support tools[86] could provide prompts for regular screening, calculate stroke risk, and advise guideline-recommended therapy to assist workflow and treatment decisions (eg, AF SMART ACTRN12616000850471).

In some countries, large generalist or specialized outpatient clinics provide an alternative setting to primary care for screening[87] but may 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- and healthcare 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 offering a direct link with treatment and a potentially sustainable workflow (see online-only Data Supplement for country-specific considerations).

Health-Economic Assessments

Economic assessment of AF screening depends on a range of factors, including: (1) rate of undiagnosed AF in the target population, (2) difference in AF detection between the screening intervention and routine practice without screening (3) stroke and mortality risk of the target population, (4) expected reduction in stroke and mortality and increase in bleeding risk from OAC, (5) cost of the screening methodology, and (6) country-specific "willingness-to-pay" thresholds to avoid 1 stroke. In the first paper on health economic modeling for AF screening,[88] 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[65,89] 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 study[4] confirmed that ECG screening was likely to be cost-effective using a lifelong decision-analytic Markov model.[90] Two other smaller studies evaluating smartphone ECG screening in community pharmacies[48] (relying on estimated stroke and death rates and improvements with OAC treatment in incidentally detected asymptomatic AF)[22] and pulse checking in an influenza vaccination clinic[91] also described cost-effectiveness. A simulation of direct medical costs in the United States concluded that costs were greater in those patients with undiagnosed AF than for similar people without AF, justifying strategies to identify and treat undiagnosed AF.[92]

Most recently, a study of lifetime costs and effects of a single handheld ECG screening of patients >65 years of age during the annual influenza vaccination in The Netherlands[83] found that screening would decrease overall costs by €764 (USD$939) and increase quality-adjusted life years by 0.27 per patient. That is, AF screening for patients >65 years of age during the influenza vaccination was likely to be cost-saving.

Reviews of systematic and opportunistic screening for AF detection[93,94] indicate that both were more cost-effective than routine practice for those ≥65 years of age, although this outcome 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 quality-adjusted life year varying between €792 619 (USD$936 902) for screening annually from 55 years of age to €8037 (USD$9500) for a single screening at 75 years of age,[95] but no data are available 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 Undertreated Known AF

Undertreatment exposes patients to a significant risk of fatal or disabling strokes. Population surveys[96,97] and registries indicate that treatment remains suboptimal with large country differences.[31] Population screening using a variety of techniques[3,4,76] would identify undertreated patients and may provide an opportunity to refer

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to appropriate physicians or clinics to initiate OACs or reinitiate OACs in those who have discontinued.[4,30,31]

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 patients were not on OAC.[5] Through the screening program, 52% of undertreated individuals had OAC initiated. A similar number of patients had known AF (9.3%) in the STROKESTOP study,[4] but only 22% were not on OAC. After cardiologist follow-up, more than half without contraindications commenced OAC therapy. This finding 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 undertreated known AF.

Patient Preferences and Advocacy

A large patient survey reported that a majority of patients with persistent AF were in favor of AF screening with handheld ECGs (T. Lobban and M. T. Hills, personal 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.[98,99] Patient-led organizations can more effectively identify the challenges patients face and engage policymakers to bring about change,[98] 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 successful in raising awareness and bringing about policy change.

Numerous governing bodies such as the National Institute for Health and Care Excellence (UK) and scientific organizations now seek the input of patients and patient organizations in developing clinical guidelines and scientific publications.[1,30]

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 ≥65 years of age or in high-risk subgroups, followed by an ECG if irregular, to allow for timely AF detection.[30,89] Pulse taking in practice is recommended by the National Institute for Health and Care Excellence (UK) guidelines but only for symptoms. However, the new 2016 ESC guideline[30] also includes an ECG rhythm strip as an alternative to pulse palpation, at least 72 hours of ECG monitoring after a transient ischemic attack or stroke with additional longer term monitoring considered, and consideration of systematic screening in patients ≥75 years of age 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 American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines[1] 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 (eg, poststroke, >75 years of age), 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 end points (including stroke, systemic embolism, and death), of strategies for screening, to strengthen the evidence base to inform guidelines and national systematic screening strategies.

CONCLUSIONS

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 that 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; as a further step, 2 weeks of twice daily intermittent recordings may be justified in people ≥75 years of age or in other groups at high risk of AF or AF-related stroke. 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. Although the World Health Organization criteria for screening appear to be met[100] and the evidence is strong for commencing screening ef-

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Figure 3. Diagrammatic representation of key points on screening.
Enrichment is the 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 are patients with known AF who are not receiving oral anticoagulant according to guidelines. (see page 1859 section, Screening for Undertreated Known AF). Although 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. BP indicates blood pressure; ESUS, embolic stroke of uncertain source; and PPG, photoplethysmography.

forts in many countries, 1 or more large and adequately powered randomized outcomes trials of a strategy of screening would strengthen the evidence for the adoption of larger scale systematic screening programs for AF to reduce ischemic stroke/systemic embolism and death (Figure 3).

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APPENDIX

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