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EHRA CONSENSUS DOCUMENT

Screening for atrial fibrillation: a European Heart Rhythm Association (EHRA) consensus document endorsed by the Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLAECE)

Georges H. Mairesse[1]* (Chair, Belgium), Patrick Moran[2] (Ireland), Isabelle C. Van Gelder[3] (The Netherlands), Christian Elsner[4] (Germany), Marten Rosenqvist[5] (Sweden), Jonathan Mant[6] (UK), Amitava Banerjee[7] (UK), Bulent Gorenek[8] (Turkey), Johannes Brachmann[9] (Germany), Niraj Varma[10] (USA, HRS Representative), Gustavo Glotz de Lima[11] (Brazil, SOLAECE Representative), Jonathan Kalman[12] (Australia, APHRS representative), Neree Claes[13] (Belgium), Trudie Lobban[14] (UK), Deirdre Lane[15] (UK), Gregory Y.H. Lip (UK)[16], and Giuseppe Boriani[17] (Co-Chair, Italy)

Document Reviewers: Laurent Fauchier[18] (Reviewer Coordinator, France), Werner Jung[19] (Germany), Irina Savelieva[20] (UK), Benedict Freedman[21] (Australia), Shih Ann Chen[22] (Taiwan), Rodrigo Isa[23] (Chile), Mintu Turakhia[24] (USA), John Lewis Sapp[25](Canada)

[1]Department of Cardiology, Cliniques du Sud-Luxembourg, 137 rue des déportés, B6700 Arlon, Belgium; [2]Health Information and Quality Authority, George's Lane, Dublin 7, D07 E98Y, Ireland; [3]University of Groningen, University Medical Center Groningen, Hanzeplein 1, Groningen, 9713 GZ, The Netherlands; [4]University Clinic Of Schleswig Holstein, Maria Goeppert Strasse 7a-b, Luebeck, 23538, Germany; [5]Karolinska institute, Solnavðgen 1, 171 77 Solna, Sweden; [6]Primary Care Unit, University of Cambridge, Strangeways Research Laboratory, Wort's Causeway, Cambridge, CB1 8RN, United Kingdom; [7]University College London, Farr Institute of Health Informatics Research, 222 Euston Road, London, West Midlands NW1 2DA, United Kingdom; [8]Eskisehir Osmangazi University, ESOGÜ Meşelik Yerleşkesi, 26480 ESKİŞEHİR, Turkey; [9]Klinikum Coburg, Chefarzt der II. Medizinischen Klinik, Ketschendorfer Str. 33, Coburg, DE-96450, Germany; [10]Heart and Vascular Institute, Cleveland Clinic, 9500 Euclid Ave, Cleveland, Ohio 44195, USA; [11]Instituto de Cardiologia do RS / FUC, Eletrofisiologia Dept., Av. Princesa Isabel 370, Porto Alegre, 90620-001, Brazil; [12]The Royal Melbourne Hospital, Melbourne Heart Center, Royal Parade Suite 1, Parkville, Victoria, 3050, Australia; [13]University of Hasselt, Patient Safety in General Practice and Hospitals, Diepenbeek, Belgium, Antwerp Management School, Clinical Leadership, Antwerp, Belgium; [14]Arrhythmia Alliance & AF Association, Unit 6B, Essex House, Cromwell Business Park, Chipping Norton, Oxfordshire OX7 5SR, UK; [15]Institute of Cardiovascular Sciences, University of Birmingham, Edgbaston, Birmingham B15 2TT, United Kingdom; and Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Fredrik Bajers Vej 5, 9100 Aalborg, Denmark; [16]Institute of Cardiovascular Sciences, University of Birmingham, Edgbaston, Birmingham B15 2TT, United Kingdom; and Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Fredrik Bajers Vej 5, 9100 Aalborg, Denmark; [17]Cardiology Division, Department of Diagnostics, Clinical and Public Health Medicine, University of Modena and Reggio Emilia, Policlinico di Modena, Largo del Pozzo, 71, 41125 Modena, Italy; [18]Centre Hospitalier Universitaire Trousseau, Tours, France; [19]Academic Hospital Villingen-Schwenningen, Villingen-Schwenningen, Germany; [20]St George's University of London, London, UK; [21]Sydney Medical School, University of Sydney, Australia; [22]Taipei Veterans General Hospital, Taipei, Taiwan ROC; [23]Copahue 4267, Lo Barnechea, Santiago, Chile; [24]Stanford University, Stanford, USA; and [25]QEII Health Sciences Center, Halifax Infirmary Site, Canada

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* Corresponding author. Georges H. Mairesse, Department of Cardiology, Cliniques du Sud-Luxembourg, 137 rue des déportés, B6700 Arlon, Belgium, Tel: +32 63 231234; fax: +32 63 231193. *E-mail address:* drghmairesse@skynet.be

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, occurring in 1–2% of the general population. Its prevalence varies between continents and ethnicity, but the estimated number of patients with AF worldwide might be between 30 and 100 million.[1] This prevalence is expected to increase significantly in the next 30–50 years due to an ageing population, and increasing risk factors to develop AF, including arterial hypertension and diabetes.[2–5] In all populations studied, both prevalence and incidence are higher in men than in women and increase with age.[6]

The AF diagnosis requires at least 30 s of absolutely irregular RR intervals and no discernable, distinct P waves on electrocardiogram (ECG).[5] AF is associated with an increased mortality, increased incidence of heart failure with an increased hospitalization rate, and a higher risk of thrombo-embolic events, including strokes.[7] It can also be associated with a reduced exercise capacity and an altered quality of life.

Its natural evolution usually progresses from short self-terminating rare episodes with little or no symptoms to longer, more frequent, more prolonged and usually clinically detectable ones, even if individual variations can also be observed.[8] An earlier detection of AF could thus allow an earlier adequate management to avoid later complications.[9,10]

Screening for AF is not yet recommended by all scientific AF guidelines, even in specific 'at risk' populations. The present document aimed to summarize the available data, discuss the different strategies and highlight the importance of implicating all stakeholders from the various health systems.

Evidence review

Members of the Task Force were invited by the European Heart Rhythm Association (EHRA) board to perform a detailed literature review of screening for AF, weigh the strength of evidence for or against particular treatments or procedures, and include estimates of expected health outcomes where data exist. Patient-specific modifiers, comorbidities, and issues of patient preference that might influence the choice of particular tests or therapies were considered, as were frequency of follow-up and cost effectiveness. In controversial areas, or with regard to issues without evidence other than usual clinical practice, a consensus (with at least 85% agreement) was achieved by agreement of the expert panel. This document was prepared by the Task Force with representation from EHRA, Heart Rhythm Society (HRS), APHRS, and Societad Latinoamericana de Estimulation Cardiaca y Electrofisiologia (SOLAECE). The document was peer-reviewed by official external reviewers representing EHRA, HRS, APHRS, and SOLAECE.

Consensus statements are evidence-based, and derived primarily from published data. In contrast with current systems of ranking level of evidence, EHRA has opted for a simpler, perhaps, more user-friendly system of ranking that should allow physicians to easily assess current status of evidence and consequent guidance (*Table 1*). Thus, a 'green heart' indicates a recommended statement or recommended/indicated treatment or procedure and is based on at least one randomized trial, or is supported by strong observational evidence that it is beneficial and effective. A 'yellow heart' indicates that general agreement and/or scientific evidence favouring a statement or the usefulness/efficacy of a treatment or procedure may be supported by randomized trials based on small number of patients or not widely applicable. Treatment strategies for which there has been scientific evidence that they are potentially harmful and should not be used are indicated by a 'red heart'. European Heart Rhythm Association grading of consensus statements does not have separate definitions of Level of Evidence. The categorization used for consensus statements (used in consensus documents) should not be considered as being directly similar to that used for official society guideline recommendations which apply a classification (I–III) and level of evidence (A, B, and C) to recommendations in official guidelines.

Table 1 Definitions

Definitions where related to a treatment or procedure	Consensus statement	Symbol
Scientific evidence that a treatment or procedure is beneficial and effective. Requires at least one randomized trial, or is supported by strong observational evidence and authors' consensus (as indicated by an asterisk).	Recommended/ indicated	
General agreement and/or scientific evidence favour the usefulness/efficacy of a treatment or procedure. May be supported by randomized trials based on small number of patients or not widely applicable.	May be used or recommended	
Scientific evidence or general agreement not to use or recommend a treatment or procedure.	Should NOT be used or recommended	

Relationships with industry and other conflicts

It is an EHRA/ European Society of Cardiology (ESC) policy to sponsor position papers and guidelines without commercial support, and all members volunteered their time. Thus, all members of the writing group as well as reviewers have disclosed any potential conflict of interest in detail, at the end of this document.

Rationale for screening

The atrial fibrillation-related stroke risk

Atrial fibrillation is a well-known risk factor for stroke,[11] through a cardio-embolic mechanism, but recent studies have highlighted that ischaemic stroke risk in the presence of multiple stroke risk factors is similarly high, whether or not documented AF is present.[12,13] The latter data do not question the benefit that can be derived by investing in screening strategies targeted to detect AF in specific populations at risk. In a cohort of patients with multiple stroke risk factors and no

known AF at baseline, one-third developed new onset AF by 1 year.[14] There is a significant overlap between risk scores to predict AF in the general population and scores to predict the risk of stroke in patients with documented AF. Indeed, the risk of stroke is not homogeneous in these patients and is dependent on the presence or absence of various stroke risk factors, the most common of which have been used to formulate stroke risk stratification schemes, such as the CHA_2DS_2-VASc score.[15] These observations indicate that it is possible to identify target populations of patients that may present a previously undetected AF with a significant AF-related risk of stroke.

Oral anticoagulation with the vitamin K antagonists (VKA, e.g. warfarin) significantly reduces stroke/systemic thromboembolism and all-cause mortality, compared with control or placebo.[16] The non-VKA oral anticoagulants (NOACs) offer additional advantages in overall efficacy (with a significant reduction in stroke and mortality), safety (especially the reduction in intracranial bleeding) and relative convenience compared to the VKAs.[17]

The CHA_2DS_2-VASc score is used in many guidelines, and is best at initially identifying low risk patients (i.e. CHA_2DS_2-VASc 0 in males, 1 in females) who do not need any antithrombotic therapy, following which the next step is to offer stroke prevention to those with ≥1 additional stroke risk factors.[5,18] Given that many patients have associated comorbidities and would seek medical attention, opportunistic screening may be one way of improving detection of AF. Available screening technologies are improving, and the key issue becomes whether AF screening can be conducted in a more systematic, comprehensive, and cost effective manner.[19] However, given the possible paroxysmal nature of AF, any screening, apart from continuous monitoring, will only give single or occasional snapshots, resulting in possible false negative results.

On the other hand, the relationship between AF and stroke is more complex than previously considered and many recent findings from continuous monitoring of AF in patients implanted with a cardiac implantable electronic device (CIED), showing the lack of strict temporal relationship between AF and stroke, suggest that AF, especially of short duration, can act as a simple marker, and not a causal factor of vascular risk.[20] Moreover, the brief episodes of silent AF detected by CIED were recently shown to have a lower than expected stroke incidence rate, and do not seem to have the same significance as more prolonged episodes.[21]

Asymptomatic or clinically silent atrial fibrillation

Asymptomatic or clinically silent AF is common and patients may not report any symptom commonly attributable to an arrhythmia (i.e. palpitations, shortness of breath, lightheadedness, chest pain, presyncope, or syncope) or may experience both symptomatic and asymptomatic episodes of AF, of variable duration, with a ratio up to more than 10 asymptomatic per 1 symptomatic episode in some patient groups.[22]

The precise prevalence of patients with asymptomatic or clinically silent AF is by definition unknown, but it has been estimated that among patients with diagnosed AF, one-third does not report symptoms.[22–24] In general, early detection of AF, even at the stage of an asymptomatic arrhythmia, incidentally discovered at a routine physical examination, during blood pressure measurement, at a preoperative ECG or cardiology visit, or as a result of a systematic or opportunistic screening may have a series of potential expected advantages, some of which are unproven, and therefore have to be reported as hypothetical (*Table 2*). Prevention of thromboembolism and stroke, achievable by institution of oral anticoagulation in patients at risk, is at present the most plausible advantage of detecting asymptomatic or clinically silent AF and is the basis for proposing preventive strategies based on screening of AF.[20,22–25]

Table 2 Expected or hypothetical potential advantages of detecting AF in an asymptomatic stage

- Prevention of thromboembolic events and stroke by institution of oral anticoagulation in patients at risk
- Prevention of subsequent onset of symptoms
- Prevention and/or reversal of electrical/mechanical atrial remodeling
- Prevention and/or reversal of tachycardiomyopathy at atrial and ventricular level
- Prevention and/or reversal of AF-related hemodynamic derangements
- Prevention of AF-related morbidity and reduction of AF-related hospitalizations
- Reduction of AF-related mortality

AF, atrial fibrillation.

Few studies evaluated the prognostic implications of asymptomatic or clinically silent AF. In a substudy of AFFIRM, (Atrial Fibrillation Follow-up Investigation of Rhythm Management) the presence or absence of symptoms associated with AF were not associated with differences in the risk of stroke or death, taking into account differences in baseline clinical parameters.[26] The negative prognostic implications of asymptomatic AF emerged in the EurObservational Research Programme-Atrial Fibrillation (EORP-AF) Pilot General Registry, where asymptomatic AF was commonly associated with elderly age, high burden of comorbidities, and high thromboembolic risks, with higher 1-year mortality compared with symptomatic AF.[27] In the Belgrade AF study, asymptomatic AF carried a worse prognosis compared with symptomatic AF.[28] In a study performed in the Olmsted county, more than half of patients with AF presented with atypical or no symptoms and this mode of presentation was associated with worse outcome in terms of stroke or transient ischaemic attack (TIA) as well as mortality even after further adjustments for comorbidities and warfarin use.[29] One explanation for these observations could be the delay in anticoagulation prescription in these patients at potentially high stroke risk, due to the absence of early diagnose.

A systematic review of the literature evaluated if single time-point screening for AF could identify a sufficient number of patients with previously undiagnosed AF to be effective for stroke prevention.[30] Taking into account 30 studies it emerged that prevalence of AF across all studies was 2.3%, increasing to 4.4% in those ≥65 years. Overall the incidence of previously unknown AF was 1.4% in patients ≥65 years and 67% were at high risk of stroke indicating that many patients could benefit from anticoagulation to prevent stroke.

Identifying AF patients at higher risk of stroke (because of the asymptomatic nature of AF) might thus even be more effective than what might be expected.

Epidemiological considerations

Effectiveness of screening depends on the target population, the test's diagnostic accuracy, and cost-effectiveness.[31,32] Prevalence and incidence vary by baseline characteristics. It is thus of crucial importance to target the most at risk population to increase the screening efficiency. Two different strategies could theoretically be proposed: screening in subjects with a high risk of detecting unknown AF, or screening in subjects with a higher risk of stroke in case of AF detection. Because the majority of risk factors are similar for both strategies, there is considerable overlap between these two theoretical approaches.

Age and gender

Atrial fibrillation prevalence and incidence increase with age (*Figure 1*) and ageing populations.[6,33–35] In screening studies, prevalence varies between <1% and >15% according to the age category, and incidence ranges between 0.21 and 0.41 per 1.000 person/years. Although opportunistic screening has been recommended at ≥65 years by ESC guidelines since 2012,[36] systematic screening may be effective at older age,[37] despite lower participation rates.[38] There is little evidence to recommend screening whole populations or subjects without additional risk factors at <65 years.

Asymptomatic AF is associated with male sex, irrespective of age.[39] Recent data indicate that the incidence of AF has increased during the last decade, in relationship with population ageing, and increased occurrence of AF evidenced during hospitalizations of elderly patients admitted for reasons other than AF.[40]

Ethnicity

All ethnicities, whether immigrant[32,41–43] or indigenous,[44,45] in any parts of the world, have lower prevalence of AF than Caucasians. There is regional variation in burden of AF and available data, with poorer countries under-represented. In both sexes, prevalence, and incidence are higher in high-income countries, and this does not seem to be only explained by more intensive screening and reporting.[46] Differences by country or by continent already start with differences in screening rates. Specific data from lower-income countries and specific ethnic groups are still required. Asian patients have been reported to have a lower prevalence of AF,[42] however, they may carry a specifically increased stroke risk.[47–50]

When knowledge and literacy about AF is lower in the community, fewer patients may already have been diagnosed, which could artificially increase the potential for detecting unknown AF, thus affecting the yield of AF screening strategies. This phenomenon should be kept in mind while comparing screening studies between different populations.

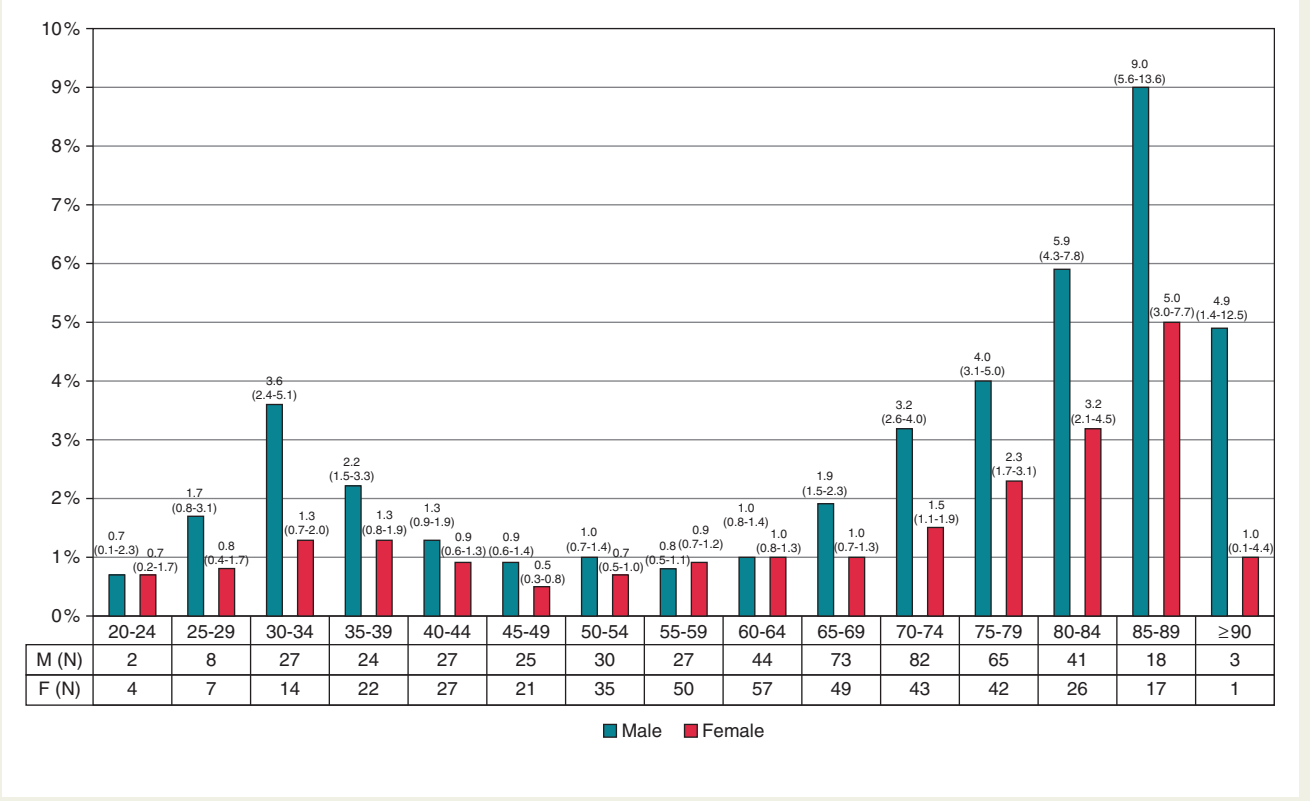

Figure 1 Prevalence of AF in the overall population according to gender and age in 65.747 subjects screened in Belgium during the week of the heart rhythm from 2010 to 2014.[35] M, Males; F, Females. Values are displayed with 95% confidence interval.

Body size

Atrial fibrillation is associated with obesity[51] and height.[52] The relationship with body size spans the life-course, from birth weight,[53,54] to large body size at age 20, and weight gain from age 20 to midlife.[55] However, the critical weight or height for increasing the risk of a positive screening, as well as the way these parameters would influence age cut-off values, are un-researched.

Other risk factors

Most AF occurs with identifiable causes, comorbidities, or structural cardiac disease. Different AF risk factors can be identified and their prevention requires a tailored approach to the individual patient.[5,9,56] Critically ill patients,[57] particularly with sepsis,[58] or patients with chronic obstructive pulmonary disease, smokers, and/or sleep apnoea syndrome[59–61] also have a high AF prevalence, but data to guide screening are currently unavailable. Atrial fibrillation incidence increases with increasing CHA_2DS_2-VASc score, suggesting its use for targeting the population to screen. A threshold of CHA_2DS_2-VASc ≥ 2 is also pragmatic, since anticoagulation may not be advised at lower scores.[62] Also, Independently on CHA_2DS_2-VASc score, patients with cryptogenic stroke or TIA of undetermined cause are populations to target for AF detection, in view of the important therapeutic implications.[5]

Although several genetic loci and biomarkers, such as the N-terminal Pro-brain natriuretic peptide or troponin I, are implicated in the pathophysiology of AF,[63–67,69] there is currently no evidence for their use in screening.

Review of studies

A number of prospective controlled and non-controlled studies have examined the effect of screening on the detection rate of previously undiagnosed AF, using a range of different screening programmes and target populations. These studies are summarized in *Table 3*. Further details of each study are provided in evidence tables in the Appendix.

Three randomized controlled trials (RCTs) have compared screening to routine care or another screening programme. The UK Screening for Atrial Fibrillation in the Elderly (SAFE) trial[70] compared opportunistic pulse palpation (followed by ECG confirmation if an irregular pulse was found) and systematic screening by 12-lead ECG in people over 65 years to routine care and found that both were associated with a small but statistically significant absolute increase in the proportion of people diagnosed with AF [risk difference (RD) 0.6%, 95% confidence interval (CI) 0.1–1.1 for both]. An earlier UK RCT[71] comparing opportunistic pulse palpation to systematic screening by ECG (lead II rhythm strip) also reported modest increases in the overall AF detection rate in both groups (0.5% and 0.8%, respectively) with no significant difference in the proportion of new AF cases diagnosed using the two screening strategies (RD 0.3%, 95% CI -0.2% to 0.9%). The remaining RCT[69] compared a 2 year detection programme for people with one or more risk factors for AF with routine care in Spain. The programme involved an index assessment during which an ECG was carried out and participants were trained to check their own pulse and calculate their heart rate. Atrial fibrillation detection outcomes are reported for those that were recruited from the study population into both groups at the end of the 2 years (as opposed to all those who were invited), and show that this pilot programme was associated with a non-statistically significant absolute increase of 1.1% in the proportion of people diagnosed with AF in the screened group (95%CI -0.6 to 2.8).

Twenty-three prospective, cross sectional studies reporting the proportion of new AF cases yielded by different screening programmes have been reported (see *Table 3* and Appendix). Taken together, the weighted average for the detection rate of new AF cases across all studies is 0.9% (95% CI: 0.7–1.1), meaning a number needed to screen of 111 subjects to detect one patient with AF. All of these are limited by the absence of a control group with which to compare the number of cases diagnosed over the study period. Many also use different denominators to calculate the effect of screening (all invited, all screened, with or without known AF cases in the screened population), which limits the comparability of the results. Four of these studies relied on self-reporting to ascertain AF history, rather than conducting a search of individual patient records.[82,88,90,92] In two others, it was unclear whether or not patient records were searched.[76,86]

In general the highest yields were observed in the studies with the highest expected baseline prevalence of AF, as indicated by the age range and/or number of AF risk factors of participants, and those that involved prolonged testing rather than testing at a single point in time. Examples include two separate Swedish studies examining screening of 75 and 76 years olds using intermittent single-lead ECG screening twice daily for 2 weeks, which reported yields of 3% and 4.7%, and one study of screening people aged ≥55 years with two or more AF risk factors using 14 day continuous monitoring, which reported a yield of 5.3%.[37,78,80], Another study that involved subjects over 75 taking their own pulse twice a day for one month resulted in a detection rate of 2% for newly diagnosed AF within the screened population, while screening patients on a geriatric ward, using handheld ECG reviewed by a physician, resulted in a new AF detection rate of 2.1%.[72,79] Conflicting results were reported by three studies that examined the effect of screening people attending influenza vaccination clinics, with two UK studies that screened subjects over 65 using pulse palpation reporting yields of 0.3–0.6%, while a Dutch study that screened subjects over 60 using single lead ECG achieved a yield of 1.1%.[73,86,83] Diverse results were also reported for screening programmes aimed at the general public that were advertized through mass media, which have reported yields ranging from 0.2 to 1.1%.[27,55]

The most common target population for screening was those aged ≥65 years in a primary care setting, with screening being carried out opportunistically at GP appointments or pharmacy visits, or through invitation to attend for an ECG. Reported yields from these studies ranged from 0.4 to 1.5%.[9,74,84,89–91] In a systematic review of literature, Lowres *et al.*[29] found that the overall incidence of previously unknown AF was 1.0% (CI, 0.89–1.04%), increasing to 1.4% (CI, 1.2–1.6%) in patients aged ≥65 years and that among subject with previously unknown AF, 67% were at high risk of stroke. In view of these data many patients aged ≥65 years identified through AF screening would be eligible for, and benefit from anticoagulation to prevent stroke, thus justifying the value of AF screening strategies in at risk older age groups.[93]

A number of trials are currently in progress which may strengthen the evidence base for screening. Of particular interest is the STROKESTOP (Systematic ECG screening for Atrial Fibrillation

Table 3 Screening studies

Study (Design)	Type of screening programme	New AF cases detected (%)
Benito 2015[68] (RCT)[a]	Two year programme of early detection of AF for people with one or more AF risk factors comprising ECG, physical examination and medical history every 6 months compared with routine care in an urban primary care center in Spain.	Control: 6/465 (1.3%) Screening: 11/463 (2.4%) [OR 1.86, 95%CI 0.68 to 5.08]
Hobbs 2005[70] (RCT)[a]	Opportunistic pulse palpation of over 65's during routine GP consultations, with ECG confirmation of an irregular pulse and Systematic screening of over 65's by invitation to 12-lead ECG versus routine care in 50 primary care practices in the UK.	Control: 47/4513 (1.0%) Opportunistic: 75/4575 (1.6%) [OR 1.57, 95% CI 1.08 to 2.26] Systematic:74/4562 (1.6%) [OR 1.58, 95% CI 1.10–2.29]
Morgan 2002[71] (RCT)[b]	Systematic screening of over 65's by invitation to lead II rhythm strip ECG versus routine care in four primary care practices in the UK.	Opportunistic:7/1502 (0.5%) Systematic: 12/1499 (0.8%) [OR 1.72, 95%CI 0.68 to 4.39]
Desteghe 2016[72] (Cross sectional)[a]	AF screening using two handheld ECG devices (MyDiagnostick and AliveCor) plus physician review among hospitalized patients in geriatric and cardiac wards in a large tertiary hospital in Belgium.	Cardiology px: 4/700 (0.6%)[c] Geriatric px: 14/680 (2.1%)[c]
Kaasenbrood 2016[73] (Cross sectional)[b]	AF screening using a single-lead handheld ECG (MyDiagnostick) of patients attending an influenza vaccination programme in 10 general practices in the Netherlands.	37/3269 (1.1%)
Proietti 2016[35] (Cross sectional)[a]	Untargeted voluntary screening programme held 1 week a year from 2010 to 2014 in 89 national hospitals in Belgium inviting over 18's for a one lead ECG through a mass media campaign.	603/52 741 (1.1%)
Smyth 2016[74] (Cross sectional)[a]	Opportunistic pulse palpation of over 65's during routine GP consultations, with ECG confirmation of an irregular pulse, in 37 general practices in rural areas in the west of Ireland.	55/6527 (0.8%)
Bury 2015[75] (Cross sectional)[a]	Systematic screening of over 70's using 3-lead ECG in 25 general practices in Ireland.	12/1003 (1.2%)
LePage 2015[76] (Cross sectional)[b]	Cardiac screening involving blood pressure monitoring, single lead ECG and a questionnaire, advertised to members of the general public though local press and radio on the island of Jersey.	2/989 (0.2%)
Svennberg 2015[37] (Cross sectional)[b]	People aged 75 or 76 years were invited to attend an ECG at the screening clinic followed by intermittent 1-lead ECG recordings twice daily or whenever they noticed palpitations over a 2 week period in 2 regions in Sweden.	218/7,173 (3.0%)
Kearley 2014[77] (Cross sectional)[b]	Patients ≥75 years, with or without AF, were screened using an AF-detecting blood pressure monitor, two single lead ECG devices and a 12-lead ECG in six general practices in the UK.	12/999 (1.2%)
Lowres 2014[9] (Cross sectional)[b]	Opportunistic screening of patients aged ≥65 attending 10 community pharmacies in Australia using pulse palpation and handheld lead I ECG.	10/1000 (1.0%)
Turakhia 2014[78] (Cross sectional)[a]	Over 55's without a history of AF with 2 or more AF risk factors attending one VA health centre in the US were screened using a wearable 1-lead ECG sensor that records up to 14 days of continuous monitoring.	4/75 (5.3%)
Virtanen 2014[79] (Cross sectional)[a]	Over 75's from one municipality in Finland were invited to an index assessment that included an ECG and were trained to palpate their own pulse and requested to do so twice a day for one month.	4/205 (2.0%)
Engdahl 2013[80] (Cross sectional)[b]	People aged 75 or 76 years from one region in Sweden were invited to undergo a 12-lead ECG. Those in sinus rhythm with at least one AF risk factor in addition to their age ($CHADS_2$ ≥2) requested to perform intermittent 1-lead ECG recordings twice daily or whenever they noticed palpitations over a two week period.	40/848 (4.7%)

Continued

Table 3 *Continued*

Study (Design)	Type of screening programme	New AF cases detected (%)
Clua-Espuny 2013[81] (Cross sectional)[b]	People aged ≥60 years from one region in Spain were requested to attend for an (unspecified) ECG in their local primary care center.	23/1043 (2.2%)
Frewen 2013[82] (Cross sectional)[b]	3 lead ECG as part of a population study of ageing in a nationally representative population of over 50's in Ireland.	45/4890 (0.9%)
Rhys 2013[83] (Cross sectional)[b]	AF screening by pulse palpation, followed by ECG if pulse is irregular, of all over 65's attending influenza vaccination clinics in one primary care area in the UK.	2/573 (0.3%)
Sanmartin 2013[84] (Cross sectional)[a]	Over 65's without a history of AF from 3 primary care centres and 1 tertiary hospital in Spain were sent a letter inviting them to attend screening involving pulse palpation, blood pressure monitoring and heart rate measurement.	17/1486 (1.1%)
Wiesel 2013[85] (Cross sectional)[b]	Patients (with or without AF) with at least one risk factor for AF from an unspecified number of general practices in the US were monitored daily for 30 days using an AF-detecting blood pressure monitor and an ECG event monitor.	2/139 (1.4%)
Gordon 2012[86] (Cross sectional)[a]	Screening of people aged ≥65 years without a history of AF attending influenza vaccination clinics in two areas in the UK over the course of two years, using pulse palpation and 12-lead ECG of those found to have an irregular pulse.	232/36 290 (0.64%) in year 1142/31 908 (0.44%) in year 2
Schnabel 2012[87] (Cross sectional)[b]	12 lead ECG screening as part of a population based study of cardiovascular disease prevalence in one region in Germany.	25/5000 (0.5%)
Meschia 2010[88] (Cross sectional)[b]	7 or 12 lead ECG performed as part of a study examining geographical and racial differences in stroke incidence among over 45's in the US.	174/29 861 (0.6%)
Wheeldon 1998[89] (Cross sectional)[b]	Over 65's from a single urban UK practice were invited to attend screening using 12-lead ECG.	5/1207 (0.4%)
Furberg 1994[90] (Cross sectional)[b]	12 lead ECG performed as part of a study examining risk factors for coronary artery disease and stroke in over 65's in 4 areas in the US.	77/5151 (1.5%)
Hill 1987[91] (Cross sectional)[b]	Over 65's without AF symptoms from 1 primary care area in the UK were sent a letter inviting them to undergo a screening assessment that included a 12 lead ECG.	10/819 (1.2%)
Weighted average for the detection rate of new AF cases in screened group across all studies		**0.9% (95% CI 0.7–1.1)**

[a]Denominator for detection rate of new AF cases excludes those with a prior history of AF.
[b]Denominator for detection rate of new AF cases includes those with a prior history of AF.
[c]Study authors reported outcomes for a hypothetical cohort of 1000 people.
CI, confidence interval; ECG, electrocardiogram; Px, patients; VA, Veterans Affairs.

Among 75-year-old Subjects) study, an RCT that began in 2012 and has already reported data on AF detection in the screening group, which will also compare stroke outcomes, mortality and AF-associated dementia in screened and unscreened groups at 5 years follow-up.[37,94] This is due to be the first study to measure the benefits of treating patients detected through screening, who may have a different stroke risk profile to AF patients detected because of symptoms. Two other RCTs with a primary outcome of AF detection are also in progress,[95–97] including one examining the use of wearable sensors in a screening cohort with different start ages for men (55 years) and women (65 years), which includes stroke as a secondary outcome (mHealth Screening to Prevent Strokes trial), as well as a cluster randomized trial comparing pulse palpation, blood pressure monitoring, and handheld ECG screening with routine care in the Netherlands (D2AF trial). Finally, a controlled non-randomized study is ongoing in Hong Kong to assess utilization rates of evidence-based stroke prevention therapy and clinical outcomes in patients diagnosed with AF during an outpatient screening program and compare routine care vs. an individualized stroke prevention strategy.[98]

Risk scores

Risk scores may be used to predict the future risk of an individual developing AF, and target AF screening initiatives. This has potential value in informing screening strategies, in identifying possible targets for AF prevention initiatives, and in clarifying the potential value of genetic and novel biomarkers in predicting risk of AF. A risk score derived from the Framingham Heart Study assigned points for simple

clinical features, with most points assigned for increasing age and for diagnosis of heart failure at a young age.[99,100] The other factors found to increase risk were gender, the presence of a significant heart murmur, obesity, high blood pressure, treatment for hypertension, and a long PR interval. A score derived from the Atherosclerosis Risk in Communities (ARIC) study, based in a younger and biracial cohort, also found race (higher risk in white than African American), smoking status, height, history of diabetes and coronary heart disease, and left ventricular hypertrophy and left atrial enlargement (using ECG criteria) to be predictive of future AF risk.[101]

Potential limitations of the risk scores derived from the Framingham Heart Study and the ARIC study include that they were derived from single cohorts, and did require an ECG to complete score. Therefore, the Cohort for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium developed and validated a further risk score using data from five European and US cohorts[102] In the CHARGE study, a model incorporating age, race, height, weight, systolic and diastolic blood pressure, current smoking, use of antihypertensive drugs, diabetes, and history of myocardial infarction and heart failure was found to have reasonable discrimination (C statistic 0.77, 95% CI 0.75–0.78) in prediction of AF over 5 years. A further risk score,[103] validated using an administrative database, similarly found that a score based on seven risk factors for AF (age, coronary artery disease; diabetes; sex; heart failure; hypertension; valvular disease) showed reasonable prediction of subsequent AF (C statistic 0.81, 95% CI 0.80–0.82).

There is considerable overlap in terms of factors between scores that predict risk of AF, and scores that predict risk of stroke in AF, such as CHA_2DS_2-VASc,[104] with age, heart failure, diabetes, and hypertension featuring in both types of score. Therefore, a strategy for identifying the target population through these scores has the potential advantage that the people they identify, if they do subsequently develop AF, are likely to benefit from anticoagulation.

Screening tools

Effectiveness of screening is obviously strongly influenced by its duration, whether it is a 10-s ECG strip or a continuous recording over a few weeks. Apart from the relatively high yields obtained from studies that used prolonged screening in older age groups or those with AF risk factors, no obvious correlation was observed between the type of screening test used and the overall yield of new AF cases achieved. A recent systematic review of diagnostic test accuracy of AF screening tests grouped these tests into four major categories; blood pressure monitors, pulse palpation, non-12-lead ECG, and smartphone applications.[105] Based on this pooled analysis the authors conclude that pulse palpation is inferior to blood pressure monitoring and non-12-lead ECG, because although the sensitivity of all four methods was broadly comparable, pulse palpation had a considerably lower specificity, and would therefore result in a greater number of false positive tests.[105]

Pulse taking

The simplest method of screening for AF in a clinical context is to take the pulse. The sensitivity and specificity depend upon what is being sought: looking for any pulse irregularity has the highest sensitivity, whereas looking for continuous pulse irregularity has the highest specificity.[71] In general, high sensitivity is preferred for a screening test. Studies of the more sensitive method of pulse palpation for any irregularity have reported sensitivity rates varying between 87% and 97%, with specificities between 70% and 81%.[106] A strategy of opportunistic screening of the pulse, followed by ECG if positive, has been found to be effective at detecting new cases of AF.[70]

Blood pressure automated measurement

A commonly performed screening test in primary care is to take the blood pressure. Historically, this would have incorporated pulse palpation, but with the advent of automated sphygmomanometers, this is now no longer the case. Automated blood pressure devices are now available that also detect AF (or at least diagnose an 'irregular heart rate') on the basis of oscillometric analysis. These are more accurate than pulse palpation, with sensitivity between 93% and 100%, and specificity between 86% and 92%.[107–109] One such device, the WatchBP Home A, was evaluated by the English National Institute for Health & Clinical Excellence (NICE), who concluded that using an automated BP device to detect AF would be cost saving compared to a strategy of pulse palpation.[110]

Any clinical suspicion of AF, or irregular heart rate evidenced using these devices, should however be confirmed by an ECG recording before assessing the patient for the need of anticoagulation protection.

ECG screening

Traditional non-invasive monitoring may not detect paroxysmal and asymptomatic AF episodes. Non-invasive devices are now available which can improve sensitivity for AF detection (*Figure 2*). In primary prevention screening in large patient groups, the method utilized has to be low-cost and easy to use with recordings easy to analyse, whereas, in secondary prevention screening after stroke, with a higher possibility of detecting AF, more costly resources can be motivated at a preserved cost-effectiveness.

Single-lead ECG handheld devices

A number of non-invasive devices for a simplified 1-lead ECG registration have been validated and used in various screening studies. These include single or intermittent ECG registration, using hand held ECG that can store or transmit several recordings to a database. So far, a few devices have been used in clinical studies serving as a model for screening in larger groups.[73,85,111,112] Repeated registrations are 2–3 times more effective in catching intermittent episodes compared to single ECG recordings or 24–48 h of long-term ECG.[113,114] The detection rate is most likely to be dependent of the length of the registration period and the comorbidity of the patients.

A single ECG recording detects unknown AF in approximately 1.5% of the screened population varying according to age and comorbidities.[9] In a large prospective cohort screening study of 7000 individuals 75–76 years old without known AF, 3.1% of the patients had a previously unknown paroxysmal silent AF detected by intermittent recordings performed twice a day over a 2 week period.[37] A significant problem with screening studies is the burden of work related to ECG analysis performed with visual control of the tracings. Additionally, it can sometimes be difficult to differentiate atrial flutter

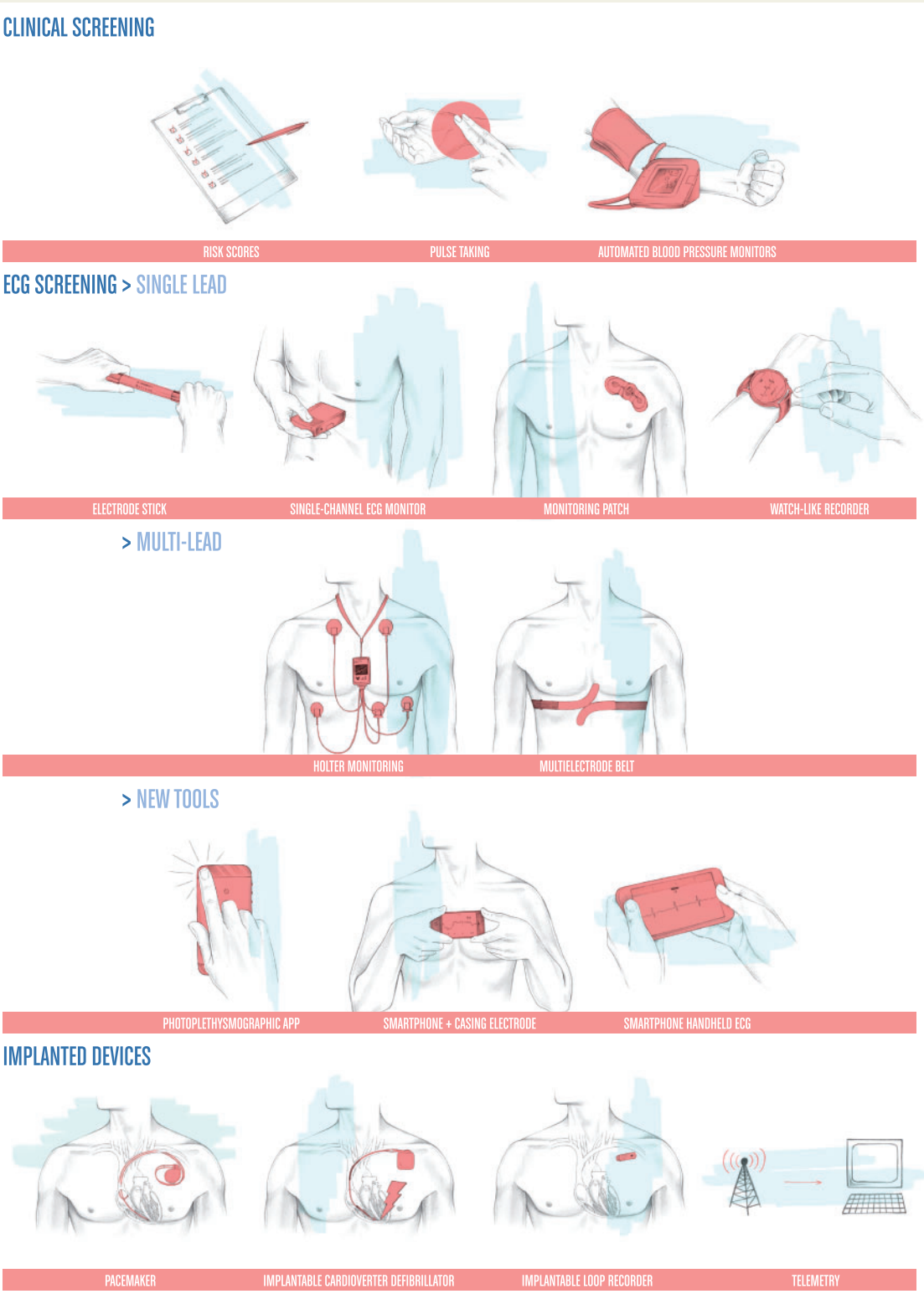

Figure 2 Screening tools.

from sinus tachycardia on the basis of a single lead recording corresponding to lead I. Therefore, automatic algorithms capable to efficiently discriminate normal sinus rhythm from any kind of supraventricular arrhythmias including AF are most welcome.[115]

Patches, belts, watches, and more

Single-use non-invasive waterproof continuous recording ambulatory cardiac rhythm monitoring patches, capable for continuous use up to 14 days have been tested in patients, and were found to be more sensitive to 24-h Holter monitor with regard to AF episodes detection.[116] Recorders attached to a dry-electrode multi-lead non-adhesive belt worn around the chest have also be proposed with prolonged monitoring, using long-term batteries, and 30 min memory capacity capable of recording up to 2.5 min per episodes.[117,118] Better compliance was observed from the patients compared to conventional adhesive skin-contact electrodes. However, while high sensitivity is required to diagnose AF, automated diagnostic algorithms should be able to discriminate from external noise signals, and noise will always tend to increase with an increasing recording duration, and a possible decrease of the electrode-skin contact. New technology have also been integrated in watches, either using a sensor, working through photo-plethysmography, which flashes light-emitting diode lights hundreds of times per second to detect blood flow through the wrist, or using electrodes integrated in the band. The combination of these technologies could provide relevant information for patient's management in a very near future. Ongoing studies will soon be available to determine sensitivity and specificity of these new tools.[119]

Smartphones

Smartphone based ambulatory monitoring introduces the ability for patient activated monitoring without the need for wearable devices, and for indefinite periods.[120]

For heart rhythm monitoring, some technologies partner sensors into a casing added to the smartphone which, when held between both hands, records an ECG tracing which can be interpreted by the patient or transmitted to a physician.[121] Another technology derives heart rhythm analysis from pulse waveforms recorded from finger apposition to the smartphone camera through an oscillometric analysis.[122] This is attractive because it operates without the need for any special additional hardware. Diagnostic accuracy of smartphone detection of AF was equivalent to 12-lead ECG in some studies. In one community screening study, an automated AF algorithm was retrospectively applied to collected iECGs among 1000 pharmacy customers aged ≥65 years (mean 76 ± 7 years; 44% male), and this resulted in detection of new AF in 1.5% of subjects, all with CHA_2DS_2-VASc score ≥2. In comparison with other methods (*Table 4*), the automated iECG algorithm showed 98.5% sensitivity for AF detection and 91.4% specificity.[20]

Table 4 Sensitivity and specificity of various AF screening tools

	Sensitivity	Specificity	Reference
Pulse taking	87–97%	70–81%	106
Automated BP measurements	93–100%	86–92%	107–109
Single lead ECG screening	94–98%	76–95%	73,85,111,112
Smartphone apps	98.5%	91.4%	19

AF, atrial fibrillation; BP, blood pressure; ECG, electrocardiogram.

Given the almost ubiquitous presence of smartphones, downloadable health care apps have the potential to be widely used and for unrestricted periods of time, with ability to transmit data over cellular networks or Wi-Fi, breaking the traditional use of ambulatory ECG monitoring. Already, more than two-thirds of adults own a smartphone, including an increasing proportion of those aged >65 years old. Skepticism, physical difficulties, and challenges in learning new technologies may be potential barriers to using the technology in a medical role, but acceptability is increasing. One study demonstrated that 50% of the entire 75- to 76-year-old population screened was willing and able to use a small portable device to screen for AF multiple times per day.[94] Longer term ECG monitoring of this form is likely to increase the detection of AF over time. Moreover, there are potential benefits of involving patients in their health care process, increasing their engagement and compliance with medical therapies and follow up management. This therefore develops a new facet to health care delivery. Patients reported the use of an app for AF detection as 'reassuring to their general sense of well-being,' and made them' 'conscious of their health'.[122] A feedback on transmitted events may consolidate this behavioural change. One study assessing the impact of a mobile phone text message support programs reported positive effect on cardiovascular risk factors.[123]

The role of smartphone AF screening is potentially disruptive to the traditional model of conventional diagnostic devices requiring physician interpretation, and blurs the definitions of patient vs. consumer. There is an accompanying set of challenges regarding the validation of recordings (e.g. noise correction, limitations of single lead ECG recordings), increased onus on the physician for interpretation of large volumes of transmissions (without established reimbursement), data storage and security. Regarding AF characterization, when used in a general population with low disease prevalence, the risk of false positive results may obviously increase. The snapshot recording will not provide information about the duration and burden of AF which may be necessary to assess the associated risk of stroke and guide anticoagulation, or the efficacy of treatment such as antiarrhythmic drug therapy or catheter ablation. This level of granularity is feasible only through use of continuous monitoring.

Finally, it has to be highlighted that the regulations for the validation of medical devices do not constantly apply to, nor are regulatory followed, for apps to be used with smartphones, so that a careful approach has to be advised both to customers and physicians.

Innovations

Newer technologies have also been proposed. Preliminary data have been published about facial video monitoring, recording the subtle beat-to-beat variations of skin colour reflecting the cardiac pulsatile signal from the videoplethysmographic signal acquired using a standard web camera.[124] This kind of technology could conceptualize contactless video-based monitoring solutions for detection of abnormal heart rates. However, further validation remains needed.

Screening strategies

Opportunistic versus systematic screening

In order to improve detection of silent AF, opportunistic screening for AF in all patients ≥65 years by taking the pulse is recommended by ESC guidelines since 2012,[36] and opportunistic screening by pulse taking or ECG strip received a class I level of evidence B recommendation in the most recent ECG guidelines.[5] Yet, it may be questioned whether the yield of this opportunistic way of screening is sufficient in higher risk patients and whether it should be extended to younger individuals. Further, systematic screening in higher risk groups may even be warranted. Detection of and screening of silent AF has been simplified thanks to the development of easy to use handheld and implantable devices. Guidelines evolution in the last 4 years is summarized in *Table 5*.

For a screening program to be efficient, high positive predictive values achieved at low cost using a low-risk tool is required (*Figures 4* and *5*). The screening yield depends on the prevalence of the disease and the diagnostic performance of the test. From epidemiological studies,[127] it is known that the number of AF cases increases disproportionally in older adults and with increasing comorbidities (reflected by the CHA_2DS_2-VASc score). Other parameters that influence the yield of AF screening include the duration of screening and number of electrocardiographic registrations and transmissions.[37,78,128,129]

Population screening strategies include opportunistic case finding and systematic screening (*Table 6*). In opportunistic case finding, the presence of AF is assessed whenever a patient visits e.g. a general practitioner (GP) by taking the pulse or using devices assessing the actual rhythm. Systematic screening can be performed in a targeted population, e.g. higher risk patients who all become invited for the screening. The first large scale screening trial was the Screening for Atrial Fibrillation in the Elderly (SAFE) trial.[130,131] In 50 primary care centres in England in 14 802 patients ≥65 years it was studied whether screening improved detection of silent AF. Patients were randomized to screening or routine care in detecting AF. After 12 months of follow-up, new AF was detected in 1.63% in the screening intervention group vs. 1.04% in the control group. This increased detection of AF at one point in time in patients at risk was confirmed by a systematic review that included 30 studies with more than 120 000 patients. Previous undiagnosed silent AF at a single time point screening identified new AF in 1% of patients and in 1.4% of those ≥65 years.[93] A subsidiary study of the SAFE trial randomized 9888 patients in 25 centres in the intervention screening arm to either systematic (invitation for ECG at one point in time) or

Table 5 Guidelines recommendations

2012	ESC[36]	Opportunistic screening for AF in patients >65 years of age using pulse taking followed by an ECG is recommended to allow timely detection of AF (Class I, LoE B).
2014	NICE[125]	In patients presenting with any of the following: breathlessness/dyspnoea, palpitations, syncope/dizziness, chest discomfort, stroke/TIA manual pulse palpation should be performed to assess for the presence of an irregular pulse that may indicate underlying AF (Class C). An ECG should be performed in all patients, whether symptomatic or not, in whom AF is suspected because an irregular pulse has been detected (Class B).
2014	AHA/ACC/HRS[4]	No formal recommendation for screening. In the full text: prolonged or frequent monitoring may be necessary to reveal episodes of asymptomatic AF.
2014	Canadian[126]	For patients being investigated for an acute embolic ischaemic stroke or TIA, we recommend at least 24 h of ECG monitoring to identify paroxysmal AF in potential candidates for OAC therapy (strong recommendation, moderate-quality evidence). For selected older patients with an acute, non-lacunar, embolic stroke of undetermined source for which AF is suspected but unproven, we suggest additional ambulatory monitoring (beyond 24 h) for AF detection, where available, if it is likely that OAC therapy would be prescribed if prolonged AF is detected (there are currently insufficient data to indicate what the minimum AF duration should be for OAC to be instituted, and expert opinion varies widely) (conditional recommendation, moderate-quality evidence).
2016	ESC[5]	Opportunistic screening for AF is recommended by pulse taking or ECG rhythm strip in patients >65 years of age (Class I, LoE B). In patients with TIA or ischaemic stroke, screening for AF is recommended by short-term ECG recording followed by continuous ECG monitoring for at least 72 h (Class I, LoE B). It is recommended to interrogate PMs and ICDs on a regular basis for AHRE. Patients with AHRE should undergo further ECG monitoring to document AF before initiating AF therapy (Class I, LoE B). In stroke patients, additional ECG monitoring by long term non-invasive ECG monitors or implanted loop recorders should be considered to document silent AF (Class IIa, LoE B). Systematic ECG screening may be considered to detect AF in patients aged >75 years, or those at high stroke risk (Class IIa, LoE B).

AF, atrial fibrillation; AHRE, atrial high rate events; ECG, electrocardiogram; ICD, implantable cardioverter defibrillator; LoE, level of evidence; TIA, transient ischaemic attack.

Table 6 Screening strategies

Systematic	Methodical screening of all subjects
Community	Methodical screening of all subjects living in one specific area
High risk populations	Methodical screening of all subjects presenting critical clinical characteristics
Opportunistic	Screening of some subjects taking advantage of opportunities and circumstances

opportunistic screening (patients were flagged to encourage pulse recording during routine consultation followed by an ECG if an irregular pulse was found). No difference was observed in the detection rate of new AF between the systematic and opportunistic screening strategies (1.62% vs. 1.64%). The STROKESTOP study assessed the yield of systematic screening in a targeted population in two regions in Sweden.[37] This study screened moderate to high risk individuals who were invited to undergo intermittent ECG recordings during 2 weeks using a handheld ECG. In total 14 387 individuals were invited of whom 7173 participated in the screening. New AF was detected in 218 individuals (3%). Only 0.5% was found with the first ECG emphasizing the advantage of repeated ECG recordings. Recently a population systematic screening programme for AF was published.[35] Data from 5 years of 1 week of screening in Belgium during the National Heart Rhythm week were analysed. All adults aged ≥18 years were invited on a voluntary basis to participate. Everyone underwent one 30 s one-lead ECG recording using a handheld device. The yield of new AF was 1.1%. Interestingly, also in younger subjects silent AF was detected, even at a higher rate than anticipated.

According to the evidence collected so far, opportunistic screening is now recommended in patients ≥65 years. It may even be started at a lower age in the presence of a higher CHA_2DS_2-VASc score (CHA_2DS_2-VASc ≥ 2 in individuals ≥ 55 years). The need for systematic screening is still uncertain. So far, no firm advantage of systematic above opportunistic screening has been demonstrated. Initiatives like the Belgian Heart Rhythm Week,[35] pharmacy screening and screening during influenza vaccination warrants further evaluation especially with regards to logistics and cost-effectiveness. In this respect new, innovative, less expensive, and easy to use devices may pave the way for systematic AF screening in targeted high risk populations.

One of the open issues related to systematic screening are related to evidence that only half of those approached for screening in the SAFE study, and the STOKESTOP study actually participated to the screening initiative.[37,70] Therefore, it appears that opportunistic case finding in primary care has currently the potential to screen a larger proportion of the population than systematic screening. In the future, the term systematic screening should probably be used in some more restrictive way, limiting it to initiatives with a large participation rate, or at least integrated with clear reporting of the ratio of participants in relationship to invited subjects. On the other hand, opportunistic screening rate was certainly higher in the SAFE study compared with the usual standard in primary care, so its translation to the community practice would require a wider acceptance and performance rate.

Secondary screening (after stroke or systemic embolism)

It is known that cardio-embolism accounts for 17–36% of all ischaemic strokes,[132–135] and that paroxysmal AF can often be undetected, especially in case of short duration episodes, frequently asymptomatic. This implies that it is challenging to rule out or, alternatively, to confirm the presence of AF at bedside, with the consequent risk of suboptimal secondary prevention.[136] It is thus likely that an undetermined proportion of strokes, labelled as cryptogenic, could be AF-related cardio-embolic strokes, in the setting of occult undiagnosed AF.[137–139]

Post-stroke in-hospital rhythm monitoring is limited by a finite window of observation, which is particularly problematic in the context of intermittent AF.[140] Traditionally, 24-h ambulatory ECG (Holter) monitoring has been used, though the utility is limited by low rates of arrhythmia detection, inadequate negative predictive value, and poor cost-effectiveness in unselected patients. Prolonged monitoring periods are advised.[141–143]

Given that arrhythmia detection is related to total AF burden and improves with increasing intensity of monitoring, prolonged monitoring utilizing external event loop recorders (ELR) has been employed. The open-label, multi-centre, randomized controlled EMBRACE (30-day cardiac Event Monitor Belt for Recording Atrial fibrillation after a Cerebral ischaemic Event) trial[129] enrolled 572 subjects without history of AF and cryptogenic stroke or TIA of undetermined cause within the previous 6 months. At 30 days, AF lasting 30s or longer was detected in 16.1% in the ELR group, as compared with 3.2% in the control group ($P < 0.001$). The strategy of minimally invasive rhythm monitoring through an implantable loop recorder (ILR) has been tested in CRYptogenic Stroke and underlying Atrial Fibrillation (CRYSTAL-AF) study,[128] where a total of 441 patients were prospectively enrolled and randomized 1:1 to standard arrhythmia monitoring vs. implantation of an ILR. The rate of AF detection at 6 months was 8.9%($n = 19$) in the ILR group compared to 1.4%($n = 3$) in the control group. Atrial fibrillation detection by continuous monitoring in the ILR arm increased progressively throughout the study and was eight-fold higher at 36 months (30%) compared with 1 month (3.7%) and 10-fold higher compared with the control arm (3%) at 36 months.[144]

Combined, EMBRACE and CRYSTAL-AF imply that detection of occult AF in cryptogenic stroke may warrant treatment with anticoagulation. Ongoing trials try to determine the minimal duration of AF needed to increase risk of ischaemic stroke and the total burden needed to warrant treatment with anticoagulation.[145,146] As an alternative, it has also been proposed that all embolic strokes of undetermined origin could benefit from secondary prevention using NOACs. Prospective studies are underway to test this hypothesis.[147,148]

Patients with a previous ischaemic stroke have a substantially increased risk of incident AF, particularly among individuals with higher $CHADS_2$ or CHA_2DS_2-VASc scores[149] and therefore these risk scores can be useful for identifying patients to propose for more prolonged rhythm monitoring.

The AF—stroke relationship is however complex, and there is evidence that AF may be either a risk factor or a simple marker of the risk of stroke.[20,146,149–151] This is supported by a series of studies performed on patients implanted with a CIED, with or without previous

documented AF, which found that ischaemic stroke may occur without the concurrent presence of atrial tachyarrhythmias or AF at the time of stroke or in the days before. These studies also showed that even if AF episodes of very short duration (minutes to hours) are associated with stroke/systemic embolism, thromboembolic events may occur at temporal distance from AF, and that sometimes AF is detected only after a stroke, with complete absence before, indicating that in some cases AF may not have a causative role with regard to stroke (mediated by a left atrial thrombus), but rather may simply represents a marker of vascular risk. This is further supported by the ASymptomatic atrial fibrillation and Stroke Evaluation in pacemaker (PM) patients and atrial fibrillation Reduction atrial pacing Trial (ASSERT) II study[152] where an ILR, implanted in older asymptomatic patients with atrial enlargement and associated risk factors, detected subclinical AF in 34.4% of patients at a 16-month follow up. The evidence that subclinical AF is so common in older patients with and without prior stroke could substantially weaken the causality link between subclinical AF and stroke.

Screening and managing subclinical atrial fibrillation detected in patients with cardiac implantable electronic devices

Current evidence on appropriate management of subclinical AF in patients with CIEDS is limited. Several observational and randomized studies demonstrated that atrial high rate events (AHRE) detected by CIEDs were associated with increased risk of subsequent stroke, systemic embolic events and mortality in patients with implanted cardioverter-defibrillators (ICDs), PMs and cardiac resynchronization therapy devices (CRTs).[20,145,146,153]

In the Mode Selection Trial,[153] AHRE of >5 min were associated with a 2.48 fold (95% CI 1.25–4.91) increase in risk of total mortality and a 2.79 fold (95%CI 1.51–5.15) increase in risk of thromboembolic events in patients with PMs. In another recent study of patients with implanted PMs, AHRE episodes ≥5 min within 6 months of PM implantation had 2.8 fold increase in risk of cardiovascular mortality and ninefold increase in risk of stroke mortality during 6.6 years of follow-up.[154] Risk of thromboembolic events was found doubled in the presence of total atrial tachycardia/atrial fibrillation (AT/AF) burden of >5.5 h during 30-day after implantation of device in the TRENDS (The Relationship between daily atrial tachyarrhythmia burden from implantable device Diagnostics and Stroke) study, that included population with ICD, PM, and CRT.[154] In the ASSERT trial,[145] subclinical tachyarrhythmias of >6 min duration detected by 3 months after implantation of ICD or PM in patients >65 years and hypertension but without baseline AF, were associated with 2.49 fold (95%CI 1.28–4.85, $P = 0.007$) increased risk of ischaemic stroke or systemic embolism during 2.5 years of follow-up. This increased risk sustained after adjustment for $CHADS_2$ score. In patients with implanted CRT-D, the risk of composite outcomes death or heart failure hospitalizations was twice higher in those with cumulative episodes of AT/AF of >10 min per day detected during 13 months of follow-up, in the presence of high NYHA class, low ejection fraction and the absence of beta-blocker therapy.[155] In another recent study of population with implanted CRT and without AF history before implantation, early detection (<6 months) of AHRE >6 min duration was associated with doubled risk of thromboembolic events [hazard ratio (HR) 2.35, 95% CI 1.09–4.83].[156]

The Stroke prevention Strategies based on atrial fibrillation information from implanted devices project analysed data of three studies, that included ICD, CRT, or PM population, with 60% having $CHADS_2$ score >2.[151] Authors demonstrated that AF burden of >5 min per day and >1 h per day were associated with risk of stroke or TIA development (HR: 1.76 and 2.11, respectively) during median 24 months of follow-up. In patients without oral anticoagulation at baseline and AF burden >1 h/day, the risk was twice higher than in those with AF burden <1 h. The HR remained significant after adjustment for $CHADS_2$ score.

These studies on AF and AHRE that are incidentally detected through CIEDs have highlighted the issue of 'subclinical AF' (Table 7), corresponding to episodes of atrial tachy-arrhythmias and AF with duration between 5 min and 24 h that can be measured in terms of 'daily AF burden', documented during continuous monitoring of patients without clinical history of typical symptoms of AF.[24]

On the other hand, very brief episodes of AT/AF, defined as episodes in which both the onset and offset of the arrhythmia were present within a single intra-cardiac electrogram recording, were not associated with any risk of clinical events compared with patients with longer documented AT/AF.[157]

Remote and home monitoring

Remote and home monitoring of CIEDs provides earlier detection of arrhythmias compared to periodic office device interrogation of devices.[158,159] Automated home monitoring of ICDs has been shown to reduce routine office device follow-up as well as to detect arrhythmias early (2 days vs. 36 days) providing a window for timely management.[160] Remote monitoring in patients with ICDs and PMs was cost-effective and new-onset AF was detected earlier in patients followed by remote monitoring (2 days vs. 78 days) compared with standard care.[161] Continuous home monitoring in heart failure CRT patients revealed that AHRE > 3.8 h was associated with 4 times increased risk in cardiovascular mortality and 9 times increase in risk of thromboembolic events during 370 days of follow-up.[162] However, the clinical benefit of an earlier management of these patients has not yet been demonstrated.

The recently published IMPACT (randomized trial to IMProve with AntiCoagulanTs in patients with atrial fibrillation) study,[163] included patients with ICDs or CRT without history of stroke or documented AF, randomized to control and intervention arms (remote monitoring of CIEDs and oral anticoagulation according to $CHADS_2$ if AT was detected) . Atrial tachycardia, (AF in 60% and atrial flutter 30% of cases) developed in 33.2% and 36.3% of patients with and without remote monitoring. There were no differences in primary outcomes (stroke, systemic embolism, major haemorrhage, and mortality) between control and intervention arms during follow-up, however, the treatment of arrhythmia was initiated significantly earlier in the remote monitoring group (3 vs. 54 days, $P < 0.001$).

Remote monitoring can also be applied to ILRs. The presence of AF was accurately detected using P wave filters in specific algorithms in the Reveal LINQ Usability study.[164]

Based on limited current evidence, remote monitoring of CIEDS may be considered for prompt clinical evaluation of the

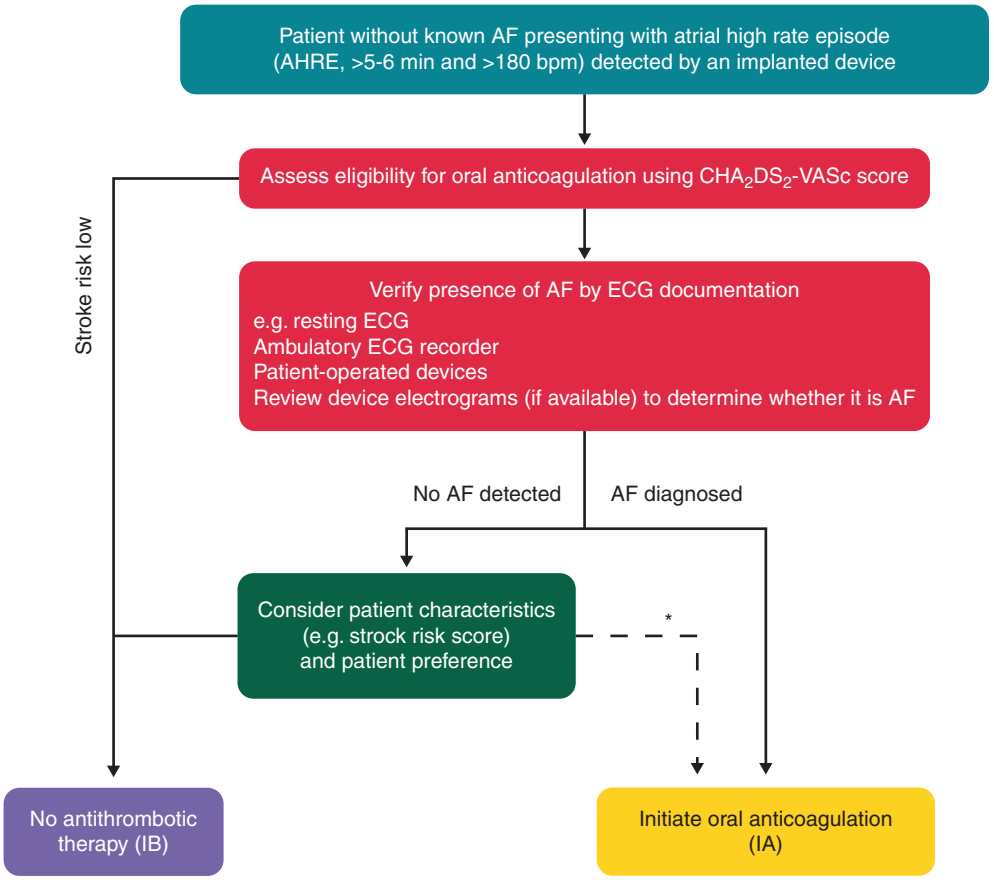

Figure 3 Management of AHRE detected by CIED, from the 2016 ESC guidelines.[5] AF, atrial fibrillation; AHRE, atrial high rate episodes; CIED, cardiac implanted electric devices; ECG, electrocardiogram; ESC, European Society of Cardiology; OAC, oral anticoagulants.

significance of AHRE and AF in patients at risk of stroke and thromboembolic events. There is a need for randomized studies to clarify the role of automatic home/remote monitoring of CIEDS in screening of AF and to define populations with CIEDs at risk for AF and its complications.

Management of patients with atrial high rate events

As it is not yet confirmed if AHRE carry exactly the same thromboembolic risk as overt AF, current ESC guidelines[5] recommend confirmation of AF through ECG or analysis of electrograms before taking into consideration prescription of oral anticoagulation in high risk patients (*Figure 3*). The threshold of AHRE or AF burden at which prescription of anticoagulants in advisable, for a positive risk/benefit ratio, is still object of debate. A *post hoc* analysis of ASSERT[21] suggests that in patients with CIEDs detected AHRE, the highest risk of stroke is for episodes >24 h, while episodes of shorter duration did not confer an increased risk of stroke. The precise effect of anticoagulation therapy on stroke and systemic embolism, when prescribed only on the basis of device-detected AHRE episodes of short duration, in combination with clinical risk stratification is currently prospectively evaluated by ongoing trials.[165–167] Additionally, being asymptomatic, these patients would routinely not require any specific rate or rhythm control therapeutic strategy.[5]

The role of the general practioners and other primary care health care professionals

In many cases the (GPs) is the first to face a patient with suspected AF, or simply at risk of developing AF. Screening for AF in asymptomatic patients in primary care is proposed as a way of reducing the burden of stroke by identifying those who would benefit from prophylactic anticoagulation prior to the onset of arrhythmia-related symptoms.[106] Both systematic and opportunistic screening increase the rate of detection of new AF cases, compared with routine practice in patients >65 years in a primary care setting.[38] However, opportunistic screening demands far less efforts from the GPs.[38,131] Strategies used to identify patients with an unknown history of AF include several screening models and various clinical

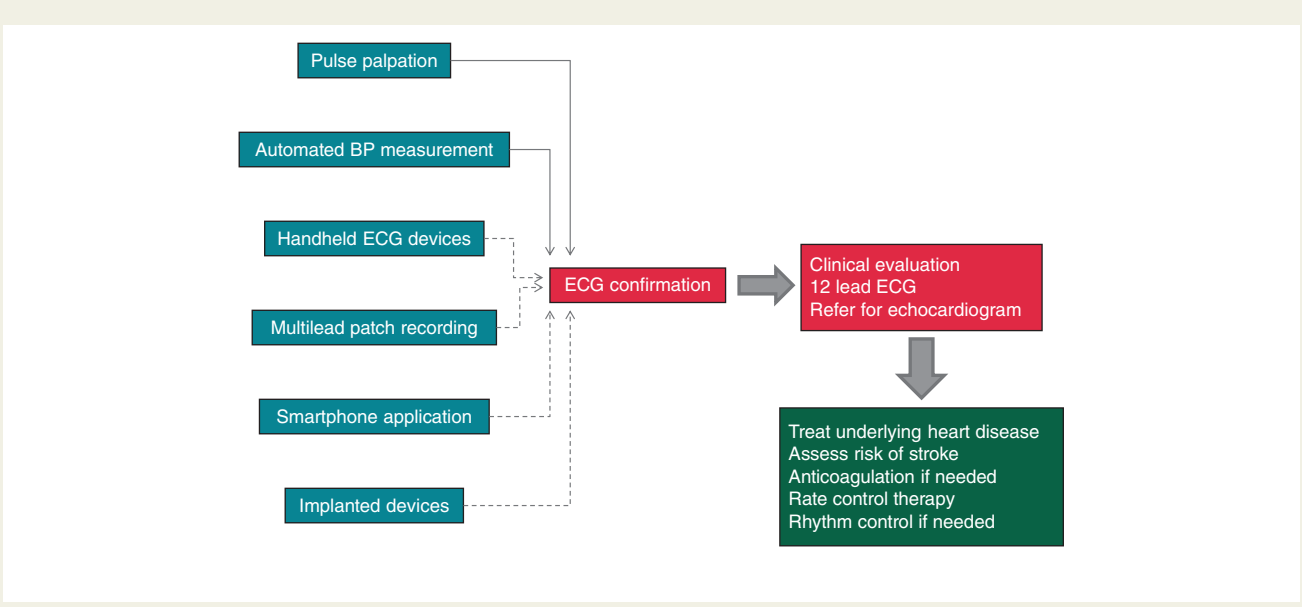

Figure 4 Screening and management strategy. BP, blood pressure; ECG, electrocardiogram.

techniques ranging from simple pulse checks to 12 lead ECG with expert interpretation.

When AF is suspected through any kind of clinical consideration, the GP remains the cornerstone of further assessing the patient, and when the diagnosis of AF is confirmed by ECG, calculating the risk of stroke and bleeding, referring the patient for an echocardiogram, and taking care of the follow-up and long-term treatment, including anticoagulation.[168,169] When the diagnosis of AF is confirmed (*Figure 4*), appropriate management will include an integrated and structured approach to evaluate and suggest lifestyle interventions, treatment of associated cardiovascular conditions and AF specific therapies.

Education also remains a crucial role for the primary care nurses and physicians, including understanding of the disease and related risks, and empowering of the patient in his disease management.

The role of patient organizations - awareness campaigns

Professional patient organizations (PPO's) also play a very important role in healthcare systems by raising awareness of medical conditions, providing support, delivering information, and education. Studies have shown awareness campaigns improve outcomes—earlier/quicker diagnosis, informed decision making by both healthcare professional and patient and greater access to appropriate care and treatments.[170]

Arrhythmia Alliance (AA) and AF Association[171,172] in the UK, StopAfib in the US,[173] and Heart4Heart in Australia[174] are global patient organizations, partnering with patients, governments, policy-makers, medical organizations and allied professionals, providing education, support, and advice to ensure that they receive speedy diagnosis, appropriate access to treatment leading to an improved quality of life. The Belgian week of the heart rhythm is an initiative from the Belgian Heart Rhythm Association to increase awareness about AF in the general population.[175]

As an example, AA brought about one of the most important policy changes to affect arrhythmia services in the UK in 2005, resulting in a new Chapter on Arrhythmias and Sudden Cardiac Death in the National Service Framework on Coronary Heart Disease (NSF CHD[176]) Prior to the awareness campaign, the word 'arrhythmia' was mentioned only one in the NSF CHD. Arrhythmia Alliance began an awareness campaign involving politicians, policy makers and the media to draw attention to the lack of guidelines on arrhythmias. A simple yet effective campaign that within nine months brought about policy change and even garnered support from the Prime Minister of UK and politicians from all political backgrounds. It brought together the cardiology and electrophysiology community in the UK who supported AA in their campaign—the first of its kind. This simple strategy has now been duplicated around the world by affiliated groups.

The 'Detect, Protect, Correct' campaign has grown on a global scale.[177,176] With earlier diagnosis (Detect) and the instigation of appropriate anticoagulation therapy (Protect), it is estimated that 50–70% of AF-related strokes could be avoided. It is also important that once diagnosed and receiving anticoagulation therapy to reduce the risk of AF-related stroke the patient should also be referred for treatment for AF (Correct).

Professional patient organizations have brought about national, European and global change due to their targeted, concise campaigns. Professional patient organizations can act independently and without any conflict of interest. They represent the patient and carer, those who are living with their condition on a daily basis and the reason why healthcare services are required. Governments, healthcare providers and allied professionals must listen to the patient—they are the end-user—the customer.

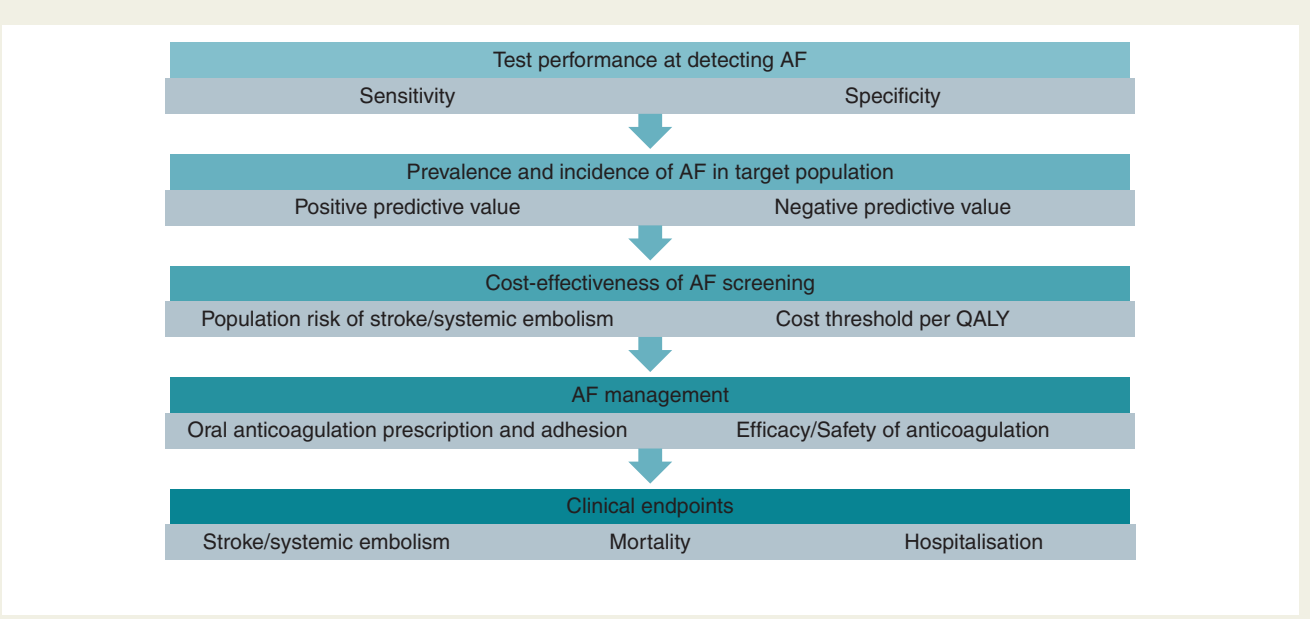

Figure 5 Epidemiological considerations in screening strategies for AF.

Therefore, public awareness campaigns led by PPO's may be more powerful, more acceptable and more successful than those initiated by other sectors.

Cost effectiveness

Economic evaluations are based on a systematic analysis and comparison of the costs and consequences (health effects) of alternative health care interventions.[179,180] The aim is usually to estimate whether a new treatment or a new strategy should be preferred in comparison to the currently used approaches. In these economic analyses, appropriate analytical methods allow to weight the benefits and costs of specific medical interventions/activities in order to provide a rational basis for policy making (*Figure 5*). A screening strategy cannot be viewed as a way of just increasing patient referral and would be of no interest if the subsequent management of patients would not be effective and cost-effective with significant hard endpoints in terms of mortality and hospitalizations.

Cost-effectiveness estimates express clinical consequences and outcome in terms of 'years of added life' and cost-utility in terms of 'quality-adjusted life years' gained, while cost-benefit analysis directly assigns a monetary value to therapeutic benefits.[181] With regard to the threshold of cost-effectiveness that is considered affordable by a payer or a health care system, various thresholds have been proposed and, usually, a threshold of 50 000 USD (US dollars)/ Quality adjusted life years (QALY), a figure derived from renal dialysis, has been proposed as a standard for approving decisions in the context of Medicare, while in UK, the National Institute of Clinical Excellence took decisions that indirectly suggest a cost-effectiveness threshold in the range of 20 000–30 000 Great Britain pound (GBP)/QALY.[182]

Table 7 Atrial fibrillation definitions

Overt AF	Episode of at least 30 s of ECG documented absolutely irregular RR intervals with no discernable, distinct P waves, in the presence of symptoms typically associated with AF (i.e. palpitations, shortness of breath, lightheadedness, chest pain, presyncope, or syncope)
Asymptomatic or clinically silent AF	Episode of at least 30 s of ECG documented absolutely irregular RR intervals with no discernable, distinct P waves, in the absence of symptoms typically associated with AF (i.e. palpitations, shortness of breath, lightheadedness, chest pain, presyncope, or syncope)
AHRE	Episodes of at least 5 min of AT/AF with an atrial rate >180 bpm, detected by the continuous monitoring of CIEDs
Subclinical AF	Episodes of AT/AF with duration between 5 min and 24 h, detected in patients without clinical history or clinical symptoms of AF

AF, atrial fibrillation; AHRE, atrial high rate episode; AT, atrial tachycardia; bpm, beats per minute; CIED, cardiac implanted electronic device; ECG, electrocardiogram; NYHA, New York Heart Association.

Opportunistic and systematic screening have similar efficacy in improving AF detection and increasing the amount of patients with appropriately diagnosed asymptomatic AF compared with routine clinical practice. However, a strategy for AF detection based on

Table 8 Cost-effectiveness

	Method used	Screening cost per Pt.	Cost per detected AF Pt	QALYs saved per 1000 Pts yr	Cost (ICER) per QALY gained	Cost Savings per 1000 Pt yrs
Moran *et al.* 2013	intermittent ECG screening	n.a.	421.25 €[a]	n.a.	n.a.	n.a.
Moran *et al.* 2013	systematic ECG screening	n.a.	1892.50 €[a]	n.a.	n.a.	n.a.
Levin *et al.* 2015	intermittent ECG recordings	108.00 €	n.a.	1.5	Dominant vs. no screening	2200.00 €
Levin *et al.* 2015	short term 24h Holter ECG	471.00 €	n.a.	1.5	n.a.	13 950.00 €
Aronsson *et al* 2015	Systematic screening with intermittent ECG recordings	50.00 €	n.a.	1.2	4313 €	32 536.86 €
Desteghe *et al.* 2017	handheld single-lead ECG in-hosp cardiology ward population	n.a.	193.00 €	n.a.	n.a.	n.a.
Desteghe *et al.* 2017	handheld single-lead ECG in-hosp geriatric ward population	n.a.	82.00 €	n.a.	n.a.	n.a.
Lowres *et al.* 2014	12-lead ECG in pharmacy population	10.50 € per ECG screen	132 €per diagnostic assessment +422 € per year if anticoagulation with warfarin or 7 91 € per year if anticoagulation with a non-vitamin K antagonists	n.a.	3142 €	n.a.
Moran *et al* 2016	opportunistic ECG screening	n.a.	GBP 337	n.a.	n.a.	n.a.
Moran *et al* 2016	systematic ECG screening	n.a.	GBP 1514	n.a.	n.a.	n.a.
Jacobs *et al.* 2016	opportunistic screening with handheld single-lead ECG	n.a.	11 790.33 €	8.02 (+0.27)	Dominant vs. no screening	764 000 € Lifetime

[a]Calculated from GBP with factor 0,8 GBP = 1 Euro.
ECG, electrocardiogram; auto, automated; in-hosp, in hospital; pop, population; Pt, patient; Pt yrs, patient years.

opportunistic screening is associated with lower costs compared with systematic screening and this is the basis for evaluating cost-effectiveness.

A systematic search of published literature was performed in order to obtain information on cost-effectiveness evaluations on different screening strategies for AF. The focus of the search (performed in February 2017) were the last 5 years, databases were MEDLINE/PUBMED/Cochrane Database of Systematic Reviews/Health Technology Assessment database. For the time before 2012 a Cochrane publication[31] was included referencing only on one RCT meeting the high criteria of the Cochrane meta-review. The results of this systematic search are shown in *Table 8*.

Overall five publications and two Cochrane reviews[9,38,72,112,183–185] matched our criteria to include the comparison of an AF screening method with another or with the 'no screening at all' case and the inclusion of cost data. The publications showed that intermittent opportunistic screening for AF detection (i.e. an ECG recording handheld at the free disposal of the patient itself to be used at predefined recording intervals) may cost—depending on device, calculation method and intensity—between 10 EUR[184] and 108 EUR[38] per patient and screening. In comparison, systematic Holter-ECG based screening may cost up to 471 EUR[38] per patient and screening, depending on device calculation method and intensity.

For the most relevant cost-utility parameter, all investigations focusing on QALYs showed quite affordable costs per QALY, all below 5000 EUR per QALY.[38,81,183] One publication[38] even found a dominant cost-benefit analysis: intermittent screening would save 44 000 EUR per 1000 simulated patients screened over 20 years.

Overall, it turns out that, even with a simple filter of 'persons aged over 65' the method is cost-effective in terms of QALYs saved below a value of 5000 EUR. From the economic standpoint, staged screening, using entry selection criteria and simple diagnostic tools, seems to be most feasible and cost-effective in terms of meaningful resource utilization.

Currently, the cost-effectiveness of screening is improved by the lack of reimbursement or financial incentives for screeners.

However, it also is an obvious limitation to adoption of these strategies in most settings.[186]

Finally, in the setting of patients with previous cryptogenic stroke, an economic model evaluated the cost-effectiveness of ILR on the basis of CRYSTAL-AF trial and other published literature from a UK National Health Service perspective.[187] The incremental cost per QALY of ILR vs. standard of care was 17 175 GBP, below established QALY willingness-to-pay thresholds.

Patient perceptions and engagements

General public awareness about AF related risks is poor.[188] There is need to educate people about AF, the potential consequences of having it, and the risks and benefits of treatment when needed. Atrial fibrillation may be first detected opportunistically, when the patient attends a physician for a different reason; therefore, many patients inadvertently discover they have AF, and are not given the chance to decline 'screening' or to consider the consequences (physical and psychological) of an AF diagnosis beforehand.[189] Symptoms of anxiety commonly accompany an AF diagnosis[190–192]: anxiety over having AF, the risk of stroke, the risk of bleeding associated with OAC etc. In addition, screening may result in false positives, subjecting patients to further tests and resultant anxiety. Further, false negatives may occur in asymptomatic paroxysmal AF patients; this could falsely reassure people who are at risk. If AF is suspected or detected following screening then a comprehensive assessment and follow-up package are required to ensure patients are promptly and appropriately investigated, treated, and reassured.

None of the studies which have screened for AF have assessed patient perceptions of screening, the psychological impact of screening and/or diagnosis of AF, or included pre-screening counselling. However, the Screening Education And Recognition in Community pHarmacies of atrial fibrillation screening programme,[9] conducted in Australian pharmacies, included qualitative interviews reviewing its implementation.[111] Although taken from the pharmacist's perspective (no patients were interviewed), one perceived barrier for AF screening was public engagement. Overall the initiative received positive customer feedback; people were happy for pharmacists to conduct the screening but were not aware that pharmacies could offer this facility. Pharmacists perceived that some people were apprehensive about screening because of fears over the results and of AF being detected; concerns they felt could be allayed by providing clear and simple explanations. In order to promote patient engagement with AF screening, programmes need to be acceptable: not too time-consuming (trade-off between time required and recording ECG long enough to detect AF); ideally non-invasive; and utilizing reliable diagnostic methods. Novel technologies are usually well received. However, multiple strategies are likely to be warranted in order to engage a greater proportion of the general public.

Future research and challenges

First, the critical duration of episodes of AF detected through screening in different populations of asymptomatic subjects have to be determined. It seem clear that short runs or AF on a long-term monitoring in a healthy septuagenarian does not carry the same thromboembolic risk as permanent asymptomatic AF detected after stroke or systemic embolism.

Patients with AHRE are known to be at risk of developing sustained overt AF. Risk scores might be helpful to identify those patients most at risk and susceptible to benefit from a closer follow-up to allow earlier intervention.

It is also still unclear whether it is better, in the perspective of the health care system, to focus screening strategies on relatively few patients at very high risk, or, rather, to target these strategies to a wider proportion of subjects potentially exposed at an intermediate risk of stroke, if AF is detected. Assessments through economic studies of the return of investment related to these different strategies are needed.

Further, no studies have as yet reported the effect of screening for AF on stroke incidence or severity, so there remains a lack of evidence about the clinical benefit of earlier detection and treatment of screen detected patients

When economical resources are lacking, one may consider to specifically focus AF screening on target populations at higher risk, such as patients above a certain age, patients with previous stroke, high CHA_2DS_2-VASc score patients, screening in diabetic clinics, peripheral artery disease clinics, or screening in nursing homes. The cost-effectiveness of each of these strategies should be compared to help national health systems in deciding their screening strategies. As randomized trials comparing these strategies will have little chance to happen, analytic modelling may be an alternative.

Also the psychological aspects of AF screening have not yet been investigated: what is the impact of detecting AF in asymptomatic patients with low CHA_2DS_2-VASc scores not indicated for anticoagulation protection? What is the risk associated with over-detection and over-anticoagulation of patients with short runs of atrial arrhythmias?

Finally, funding of AF detection campaigns is always a challenge and depends on the national income level, until national health authorities will realize the benefit of an early diagnosis of AF with an early start of anticoagulation in high risk patients.

Consensus statements

		References
Opportunistic screening for AF in the community by pulse taking or ECG strip recording is recommended by ESC guidelines in persons aged 65 years and older.	♥	5
Systematic ECG screening can be considered to detect AF in patients aged 75 years or older, or those at high stroke risk.	♥	5

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Continued

		References
ECG confirmation of AF is needed before considering the patient for anticoagulation therapy.		5,125
Detection of AF is of crucial importance in stroke survivors and efforts to screen for AF should include prolonged ECG monitoring, eventually using external, or implanted loop recorders.		4,5,126
Regular interrogation of PMs and ICDs memories, possibly using tele-surveillance, should be considered for an earliest detection of subclinical AF and of AHRE		5
AHRE of > 5–6 min burden in combination with stroke risk factors (e.g. CHA_2DS_2-VASc ≥2) is associated with an increased risk of stroke or systemic embolism, although the low incidence of stroke associated with AHRE duration below 24 h makes uncertain the risk-benefit ratio of anticoagulation in this setting (randomized studies are ongoing). Intracardiac electrograms, rather than mode switching counters or marker channel analysis of AHRE episodes are recommended to confirm subclinical AF. Patients with AHRE should be referred for further individualized evaluation.		145,153
In patients with AF or AHRE, but without additional stroke risk factors, anticoagulation is not recommended for stroke prevention.		5
Repeated recordings can be considered to document AF in selected asymptomatic patients.		96,123
When performed in high risk populations, screening for AF is advised because of its cost-effectiveness.		181,183,186
Screening for AF should not be limited to symptomatic patients		5,30
All stakeholders in healthcare systems, and especially those in closest contact with patients, should be involved to increase awareness and education, increase patient's consciousness about the risks of untreated AF, and increase auto-surveillance, resulting in an earlier management of these patients as soon as AF is confirmed.		168,169

Appendix

Study, design, risk of bias[a]	Intervention and comparator	Method of allocation	Setting number of participants	Participant characteristics	Length of follow-up and methods of analysis	Results (new cases detected (%))	Additional comments
Benito 2015,[69] Design: RCT, Risk of bias: High	Intervention: A 2 year programme of early detection of AF for people without AF but with one or more AF risk factors comprising ECG, physical examination, and medical history every 6 months; participants were also trained to take their own pulse and requested to do so once a month	A random sample of 4000 patients taken from the total study population (7498 patients with one or more risk factors for AF were) and randomly allocated to either the screening group (2000 patients) or the control group (2000 patients).	Spain, primary healthcare centre in an urban area Intervention: 463 recruited, control: 465 recruited	One or more AF risk factor (≥65, hypertension, ischaemic heart disease, valvular heart disease, diabetes, and heart failure) Intervention: 71% ≥65 years, 49% male Control: 66% ≥65 years, 49% male No significant difference between groups in the prevalence of other risk factors	Follow-up: 24 months Denominator did not include those who declined to participate in the intervention group (21%) or those within each randomized group that were not contacted (13% in intervention group, 72% in control group). Power calculations indicated that 2 year follow-up data from	11 new cases of AF were diagnosed in the intervention group (2.4%) compared with 6 new cases in the control group (1.3%). This corresponds with a non-significant odds ratio (OR) of 1.86 (95% CI 0.68–5.08) of being detected in the systematic screening group compared with	At 6 months there was a significant difference in AF detection between the two groups (OR 8.16, 95% CI 1.02–65.49), but this was not maintained at 12 months. Time to diagnosis was shorter in the interventions group (median 7 days [IQR 192] in the

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Appendix *Continued*

Study, design, risk of bias[a]	Intervention and comparator	Method of allocation	Setting number of participants	Participant characteristics	Length of follow-up and methods of analysis	Results (new cases detected (%))	Additional comments
	Comparator: Routine care				458 patients per group could detect a 2% difference in AF detection per year	the opportunistic screening group.	intervention group compared with 277 days [IQR 188] in the control group ($P < 0.05$).
Hobbs 2005,[70] Design: RCT, Risk of bias: Low	Intervention: (i) Opportunistic pulse palpation of over 65's during routine GP consultations, with ECG confirmation of an irregular pulse. (ii) Systematic screening of over 65's by invitation to 12-lead ECG Comparator: routine care	Stratified cluster randomization of GP practices (25 intervention, 25 control), with random selection of 5000 patients aged 65 years and older from routine care practices, and 10 000 patients aged 65 years and older from intervention practices, which were then randomized to either systematic (5000 patients) or opportunistic (5000 patients) screening	UK primary care Control: 4963, opportunistic screening: 4933, systematic screening: 4933. (When existing AF cases and patients with missing data are excluded the number of patients in each arm was: Control 4513, opportunistic: 4575, systematic: 4562)	Aged ≥65 years Control: mean age 76 years, 42% male Opportunistic screening: mean age 75 years, 43% male Systematic screening: mean age 75 years, 43% male	Follow up: 12 months Intention to treat, sample size was chosen to detect a 1% difference between the groups with 90% power at a 5% significance level. Denominator used for detection rate of new cases of AF was all patients without a previous diagnosis of AF.	47 new cases of AF were identified in the control group (1.04%), compared with 75 in the opportunistic screening group (1.64%) and 74 in the systematic screening group (1.62%). (Both systematic and opportunistic screening was more effective than routine practice (OR 1.57, 95% CI 1.08–2.26 and OR 1.58, 95% CI 1.10–2.29, respectively).)	Baseline AF prevalence in the control population was higher than in the intervention population (7.9% vs. 6.9%). Among those without a diagnosis of AF, the uptake rate of systematic screening was 53%, while the uptake rate of pulse palpation was 69%, and 73% of those found to have an irregular pulse agreed to have an ECG.
Morgan 2002,[71] Design: RCT, Risk of bias: High	Intervention: systematic screening of over 65's by invitation to lead II rhythm strip ECG Comparator: opportunistic pulse palpation of over 65's during routine GP consultations.	Random sample of 750 patients aged between 65 and 100 years from each of four general practices (3001 in total), which were then randomized to either opportunistic or systematic screening	UK primary care Opportunistic screening: 1502, systematic screening: 1499	Aged ≥65 years Opportunistic screening: mean age 76 years, 40% male Systematic screening: mean age 75 years, 43% male	Follow up: 6 months Intention to treat, sample size was chosen to detect a 2.5% difference between the groups with 80% power at a 5% significance level. Denominator used for detection rate of new cases of AF was all patients randomized, including those with a	Seven new AF cases were identified in the opportunistic screening group over the 6 month follow-up period (0.5%), compared with 12 new AF cases in the systematic screening group (0.8%). This corresponds with a non-significant odds ratio (OR) of 1.72	A confirmatory ECG was not required to confirm all AF cases diagnosed in the opportunistic screening arm. Uptake of systematic screening was 73%, compared with 29% for opportunistic pulse palpation. The percentage of those found with an irregular pulse

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Appendix *Continued*

Study, design, risk of bias[a]	Intervention and comparator	Method of allocation	Setting number of participants	Participant characteristics	Length of follow-up and methods of analysis	Results (new cases detected (%))	Additional comments
					previous diagnosis of AF.	(95% CI 0.68–4.39) of being detected in the systematic screening group compared with the opportunistic screening group.	who agreed to undergo an ECG was not reported.
Desteghe 2016,[72] Design: cross sectional study, Risk of bias: high	Intervention: AF screening using two handheld ECG devices (MyDiagnostick and AliveCor) among hospitalized patients in geriatric and cardiac wards	All patients on both wards were asked to consecutively hold the two devices to obtain ECG recordings, including those with known AF or an implanted device.	Cardiac and geriatric wards in a large tertiary hospital in Belgium. 344 cardiac px. 159 geriatric px.	Cardiac px: mean age 68, 57% male Geriatric px: mean age 83, 38% male	Follow up: N/A Using the results of the study the authors calculate the number of new AF cases diagnosed using both devices alone, and in combination with physician review, for a hypothetical sample of 1000 cases with or without AF. Denominator used to calculate yield is those without a prior history of AF.	Cardiology patients; Device algorithm alone: four new AF cases per 700 screened (0.05%) Device algorithm plus physician review: four new AF cases per 700 screened (0.06%) Geriatric patients: Device algorithm alone: nine new AF cases per 680 screened (1.3%) Device algorithm plus physician review: 14 new AF cases per 680 screened (2.1%)	The number of new cases detected using each of the devices was identical.
Kaasenbrood 2016,[73] Design: cross sectional study, Risk of bias: high	Intervention: AF screening using a single-lead handheld ECG (MyDiagnostick) of patients attending an influenza vaccination programme. Comparator: none	3269 of the 9450 people who attended an influenza vaccination clinic from 10 general practices were invited to participate, regardless of whether they had a prior diagnosis of AF	10 general practices in the Netherlands running influenza vaccination clinics 3269 invited to screening	Aged ≥60 years Mean age 69 years, 49% male	Follow up: N/A The denominator was all those who consented to screening. The number of people attending the vaccination clinic who refused to participate is not reported. Not all attendees were offered screening due to logistical difficulties in obtaining consent forms in such a large population.	37 new cases were diagnosed through screening (1.1%)	None

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Appendix *Continued*

Study, design, risk of bias[a]	Intervention and comparator	Method of allocation	Setting number of participants	Participant characteristics	Length of follow-up and methods of analysis	Results (new cases detected (%))	Additional comments
Proietti 2016,[35] Design: Cross sectional study, Risk of bias: high	Intervention: over 18's invited to attend for a one lead ECG through a media campaign that included flyers and advertisements in national radio stations, newspapers and magazines Comparator: none	A self-selected group of adults that responded to the national media campaign to attend screening	Five years of data from an voluntary screening programme held 1 week a year from 2010 to 2014 in 89 national hospitals in Belgium. 65 747 participants screened, of which 13 006 reported a history of AF	Median age 58 years, 41% male	Follow up: N/A The rate of detection of new cases is calculated based on the total number of screened participants with complete clinical data who did not report a prior history of AF ($n = 52\,741$)	603 new cases of AF were diagnosed (1.1%)	One year data from this programme was previously reported by Claes 2012.[32]
Smyth 2016,[74] Design: Cross sectional study, Risk of bias: high	Intervention: opportunistic pulse palpation of over 65's during routine GP consultations, with ECG confirmation of an irregular pulse Comparator: none	Consecutive patients aged 65 years and over attending 37 GP practices serving an overall population of 24 609 over 65's	General practices in rural areas in the west of Ireland 7262 patients screened	Aged ≥65 years Median age 74 years, 45% male	Follow up: 6 months The rate of detection of new cases was based on the total number screened (7262), however the number of people who declined an offer of pulse palpation, if any, is not reported.	55 new cases of AF were diagnosed (0.8%)	735 screened patients had a previous diagnosis of AF. The rate of new case detection as a percentage of the screened population without a history of AF was 0.8%
Bury 2015,[75] Design: cross sectional study, Risk of bias: high	Intervention: systematic screening of over 70's using 3-lead ECG Comparator: none	25 general practices were requested to randomly select 40 patients without a history of atrial fibrillation or flutter, who had attended the practice at least once in the last 3 years and who did not have a terminal illness or cognitive impairment that might impact on informed consent	Ireland, primary care 1003 patients invited for screening	Aged ≥70 years Mean age 77 years, 37% male	Follow up: N/A Intention to treat, where the rate of new AF cases detected was calculated based on those who were invited to screening	12 new cases of AF were diagnosed through 3-lead ECG screening (1.2%)	Of the 1003 patients invited, 639 (64%) consented to screening. Among these, 20 patients were found to have a history of AF from review of their charts and three cases were newly diagnosed prior to screening. Ultimately 566 of the 1003 patients invited to screening had a 3-lead ECG performed (56%)

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Appendix *Continued*

Study, design, risk of bias[a]	Intervention and comparator	Method of allocation	Setting number of participants	Participant characteristics	Length of follow-up and methods of analysis	Results (new cases detected (%))	Additional comments
LePage 2015,[76] Design: cross sectional study, Risk of bias: high	Intervention: cardiac screening involving blood pressure monitoring, single lead ECG and a questionnaire, advertised to members of the general public though local press and radio. Comparator: none	Invitations to screening were advertised to the general public via local newspaper and radio stations, in a region with a total population of 98 000. No age range was specified, but screening was targeted at those without known heart rhythm problems.	Island of Jersey, which has a total population of 98 000. 989 people attended for screening, with 954 having an ECG recorded	Unselected general population Mean age 54 years, 33% male	Follow up: N/A Rate of new case detection was calculated using the denominator of all those who attended for screening.	Two new cases of AF were diagnosed (0.2%) along with a further two cases of atrial flutter	Age range of those screened was 12-99 years. The extent to which the medical records of those diagnosed through screening were searched for a prior history of AF is unclear.
Svennberg 2015,[37] Design: cross sectional study, Risk of bias: high	Intervention: people aged 75 or 76 years were invited to attend an ECG examination at the screening clinic followed by intermittent 1-lead ECG recordings twice daily or whenever they noticed palpitations over a two week period Comparator: none	Total population of people aged 75 and 76 was 28 768. Half were randomly selected to be invited to screening (14 387). 1056 had died before the invitation process was completed. A total of 7173 people participated in screening (54% response rate).	Two regions (Stockholm County and Halland) in Sweden. 7173 participants (666 of which had a previous diagnosis of AF)	Aged 75–76 years, 46% male	Follow up: 2 weeks Rate of new case detection was calculated using the denominator of all patients screened, including those with a prior history of AF	218 new cases of AF were diagnosed (3.0%)	A further 2.1% of patients who already had a diagnosis of AF but were not using oral anticoagulants were also identified in the study.
Kearley 2014,[77] Design: cross sectional study, Risk of bias: high	Intervention: Patients ≥75 years, with or without AF, were screened using an AF-	2673 out of a total of 6529 patients aged ≥75 from 6 UK general practices were	Six general practices in the UK 999 patients for whom conclusive results	Aged ≥75 years Mean age 80 years, 49% male	Follow up: N/A Rate of new case detection was calculated using the denominator	12 new cases of AF were diagnosed (1.2%)	The authors of this study concluded that AF-detecting BP monitoring is

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Appendix *Continued*

Study, design, risk of bias[a]	Intervention and comparator	Method of allocation	Setting number of participants	Participant characteristics	Length of follow-up and methods of analysis	Results (new cases detected (%))	Additional comments
	detecting blood pressure monitor, two single lead ECG devices and a 12-lead ECG Comparator: none	invited to attend screening. Recruitment was stopped when 1000 patients were screened. One patient was excluded from the analysis due to an inconclusive 12-lead ECG, giving a total sample size of 999.	were available for the reference test (12-lead ECG)		of all patients screened, including those with a prior history of AF		superior to 1-lead ECG as it does not require any expertize for interpretation and its diagnostic performance is comparable. BP monitoring detected 11 of the 12 new cases of AF diagnosed in the study population (1.1%)
Lowres 2014,[9] Design: cross sectional study, Risk of bias: high	Intervention: opportunistic screening of patients aged ≥65 attending community pharmacies using pulse palpation and handheld lead I ECG. Comparator: none	All patients entering the pharmacies involved in the study were eligible for screening, unless they had an existing condition that prevented their participation, such as severe dementia or a terminal illness. Screening was advertised in the pharmacies and staff offered screening to potentially eligible customers.	10 community pharmacies in Sydney, Australia 1000 eligible participants screened	Aged ≥65 years Mean age 76 years. 44% male	Follow up: N/A Rate of new case detection was calculated using the denominator of all patients screened, including those with a prior history of AF	10 new cases of AF were diagnosed (1.0%)	A further five participants with a history of AF that had been successfully cardioverted, and who were not receiving oral anticoagulation, were also identified through screening (0.5%)

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Appendix *Continued*

Study, design, risk of bias[a]	Intervention and comparator	Method of allocation	Setting number of participants	Participant characteristics	Length of follow-up and methods of analysis	Results (new cases detected (%))	Additional comments
Turakhia 2014,[78] Design: cross sectional study, Risk of bias: high	Intervention: over 55's without a history of AF with two or more AF risk factors were screened using a wearable 1-lead ECG sensor that records up to 14 days of continuous monitoring Comparator: none	79 individuals were enrolled from outpatient cardiology, echocardiography and stress testing clinics, 75 of which completed monitoring. No data are available on whether consecutive patients were enrolled and how many declined to participate.	One health care provider in California, USA (Veterans Affairs Palo Alto Health Care System) 75 patients completed monitoring	Aged ≥55 years with two or more AF risk factors (coronary artery disease, heart failure, hypertension, diabetes, sleep apnoea) Mean age 69 years, 100% male	Follow up: 2 weeks Rate of new case detection calculated using the denominator of all those who successfully completed monitoring (none of which had a history of AF)	Two new cases of AF were diagnosed (5.3%)	Exclusion criteria included those with previously documented AF, supraventricular tachycardia, stroke, TIA, systemic embolism, palpitations or syncope in the previous 12 months
Virtanen 2014,[79] Design: cross sectional study, Risk of bias: high	Intervention: over 75's were invited to an index assessment that included an ECG and were trained to palpate their own pulse and requested to do so twice a day for one month Comparator: none	Total population of people over 75 was 1024. All contactable people (982) were sent a letter inviting their participation, of which 460 (48%) responded. Total number of people willing to participate in training after all exclusions (including prior AF diagnosis) was 300. Random sample of 206 was selected, one of which was excluded due to chronic AF.	One municipality in Finland 205 patients trained in pulse palpation	Aged ≥75 years Mean age 79 years, 43% male	Follow up: 1 month Rate of new case detection reported as the number of newly diagnosed cases divided by the total number trained (which excluded known AF cases)	Four new cases of AF were diagnosed (2.0%)	At 1 month follow up the capability for pulse palpation was rated as good for 69% of the study population, moderate for 18% (some difficulty finding pulse or calculating heart rate) and poor for 13% (unable to find pulse or calculate heart rate).

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Study, design, risk of bias[a]	Intervention and comparator	Method of allocation	Setting number of participants	Participant characteristics	Length of follow-up and methods of analysis	Results (new cases detected (%))	Additional comments
Engdahl 2013,[80] Design: cross sectional study, Risk of bias: High	Intervention: people aged 75 or 76 years were invited to undergo a 12-lead ECG. Those in sinus rhythm with at least one AF risk factor in addition to their age ($CHADS_2$ ≥2) were requested to perform intermittent 1-lead ECG recordings twice daily or whenever they noticed palpitations over a 2 week period Comparator: none	1330 people were invited, of which 848 attended for the index screening visit involving 12 lead ECG (uptake rate of 64%) 419 patients with a $CHADS_2$ score of ≥ 2 and proceeded to intermittent screening. 16 people either died or declined further participation after the index screening.	One region in Sweden (Halmstad)	Aged 75–76 years, 43% male At least one other risk factor (apart from age) was required for patients to be eligible for 2 week monitoring with 1-lead ECG	Follow up: 2 weeks Rate of new case detection is calculated here using the denominator of all patients screened, including those with a prior history of AF	10 new AF cases were diagnosed on the index ECG and 30 new cases were identified during the two week monitoring period, giving a total of 40 new cases (4.7%)	The rate of new case detection among those without a prior diagnosis of AF was 5.2%. Overall AF prevalence in the study population was 14%.
Clua-Espuny 2013,[81] Design: Cross sectional study, Risk of bias: high	Intervention: people aged ≥60 years were requested to attend for an ECG in their local primary care centre Comparator: none	A random sample of 1043 patients were selected from the overall study population	One region in Spain (Baix Ebre)	Aged ≥60 years Average age 79 years, gender distribution not reported	Follow up: N/A Rate of new case detection was calculated using the denominator of all patients screened, including those with a prior history of AF	23 new cases of AF were diagnosed (2.2%)	Type of ECG test performed is not reported. Study is described as retrospective, but the paper reports that selected patients were contacted to sign consent forms and agree to undergo ECG testing.
Frewen 2013,[82] Design: cross sectional study, Risk of bias: high	Intervention: 3-lead ECG as part of a population study of ageing in over 50's Comparator: none	8175 people were recruited from a nationally representative sample, corresponding to a response rate of 62%. No information is reported on	Ireland 5036 of the 8175 participants had a health assessment carried out, of which 4890 underwent 3-lead ECG	Aged ≥50 years Average age not reported, 54% male	Follow up: N/A Rate of new case detection is calculated here using the denominator of all patients screened, including those who were	45 new cases of AF diagnosed (0.9%)	Study outcome was self-reported awareness of AF and no search of individuals' medical files was conducted. Oral anticoagulation rates

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Appendix *Continued*

Study, design, risk of bias[a]	Intervention and comparator	Method of allocation	Setting number of participants	Participant characteristics	Length of follow-up and methods of analysis	Results (new cases detected (%))	Additional comments
		how the subset of people who had an ECG performed was selected.			aware they had a history of AF		in the group diagnosed through screening who were unaware that they had the arrhythmia are not reported
Rhys 2013,[83] Design: cross sectional study, Risk of bias: high	Intervention: AF screening by pulse palpation, followed by ECG if an irregular pulse is found, of all over 65's attending influenza vaccination clinics, regardless of whether they had a prior diagnosis of AF Comparator: none	573 of the 1714 over 65's in the study area attended the influenza vaccination clinic, all of whom were screened.	one primary care area in the UK 573 patients were screened	Aged ≥65 years Mean age and gender distribution not reported	Follow up: N/A Rate of new case detection was calculated using the denominator of all patients screened, including those with a prior history of AF	Two new cases of AF were diagnosed (0.3%)	The authors report that those aged ≥85 may have been underrepresented due to frailty and transport difficulties making them less likely to attend flu vaccination clinics. Uptake of pulse palpation: 100%, Uptake of ECG for those with an irregular pulse and didn't have a prior AF diagnosis: 57%. 7 of 39 ECGs were unreadable.
Sanmartin 2013,[84] Design: cross sectional study, Risk of bias: high	Intervention: over 65's without a history of AF were sent a letter inviting them to	Invitations to screening were posted to 8869 of the 9864 over 65's without a history of	Three primary care centres and one tertiary hospital in Spain	Aged ≥65 years Mean age 73 years, 43% male	Follow up: N/A Rate of new case detection was calculated using the denominator	17 new cases were diagnosed (1.1%)	None

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Appendix *Continued*

Study, design, risk of bias[a]	Intervention and comparator	Method of allocation	Setting number of participants	Participant characteristics	Length of follow-up and methods of analysis	Results (new cases detected (%))	Additional comments
	attend screening clinics involving pulse palpation, blood pressure monitoring and heart rate measurement. Comparator: none	AF in the study areas, as identified from medical records	1532 attended a screening clinic which was conducted over 5 consecutive days, 46 participants had a history of AF, giving a study population of 1486		of all those without a history of AF who attended screening		
Wiesel 2013,[85] Design: cross sectional study, Risk of bias: high	Intervention: patients (with or without AF) with at least one risk factor for AF were monitored daily for 30 days using an AF-detecting blood pressure monitor, as well as an ECG event monitor Comparator: none	160 patients were enrolled from general practices, 10 withdrew before recording any ECG or BP measurements, one failed to record any ECG readings, one patient with a PM was omitted and nine failed to record logs of the BP monitor readings as required for participation, leaving a total of 139 screened patients.	Unspecified number of general practices, USA 139 patients screened	Patients with or without AF and at least one risk factor for AF (≥65 years, hypertension, diabetes, congestive heart failure, and stroke) Mean age 67 years, 37% male	Follow up: 30 days Rate of new case detection calculated using the denominator of all those who had ≥1 AF blood pressure monitor reading with a comparative ECG recording (including those with known AF)	Two new cases of AF were diagnosed (1.4%)	Participants recorded an average of 24 daily readings over the 30 day screening period (range 1–32)
Gordon 2012,[86] Design: cross sectional study, risk of bias: high	Intervention: screening of people aged ≥65 years without a history of AF who are attending annual influenza vaccination clinics over the course of	A self-selected group of people who attended an influenza vaccination programme over the course of 2 years	Two commissioning group areas in the UK. 36 290 patients without a history of AF who attended an influenza vaccination clinic were screened in year one	Age and gender distribution was not recorded	Follow up: N/A Rate of new case detection calculated using the denominator of all patients screened.	232 new cases of AF diagnoses in years 1 (0.64%) (142 new cases of AF diagnosed in year 2 [0.44%])	35 of 44 local practices in the study areas agreed to participate in year 1, and 30 agreed to participate in year 2

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Appendix *Continued*

Study, design, risk of bias[a]	Intervention and comparator	Method of allocation	Setting number of participants	Participant characteristics	Length of follow-up and methods of analysis	Results (new cases detected (%))	Additional comments
	2 years, using pulse palpation and 12-lead ECG of those found to have an irregular pulse Comparator: none		of the study, out of a total population of 64 257 over 65's (56%) (31 908 patients screened out of a total population of 65 063 over 65's (49%) in year two)				
Schnabel 2012,[87] Design: cross sectional study, Risk of bias: high	Intervention: 12 lead ECG screening as part of a population based study of cardiovascular disease prevalence Comparator: none	Random sample of 5000 people aged between 35 and 74 from a total population 210 867, stratified by sex, age group, and urban versus rural areas, with or without a history of AF	City of Mainz and the region of Mainz-Bingen in Germany. The study sample consisted of the first 5000 people screened	Aged between 35 and 74 years Average age 52 years, 50% male	Follow up: N/A Rate of new case detection is calculated here using the denominator of all patients screened, including those with a prior history of AF	25 new AF cases were diagnosed (0.5%)	None
Meschia 2010,[88] Design: cross sectional study, Risk of bias: high	Intervention: 7- or 12-lead ECG performed as part of a study examining geographical and racial differences in stroke incidence among over 45's Comparator: none	Oversampling of groups with a known high incidence of stroke was carried out as part of this national US longitudinal study (by race and geographical location). The overall population of interest was identified from mail and telephone records, and an uptake rate of 49% was achieved. The total	USA 30 239 people were recruited, but 378 were excluded for missing ECG or lack of self-reporting of AF history, leaving a study population of 29 861	Aged ≥45 years Average age not reported, but 17% were ≥ 75 years. 45% male	Follow up: N/A Rate of new case detection is calculated here using the denominator of all patients screened, including those who were aware they had a history of AF	174 new cases diagnosed (0.6%)	Study outcome was self-reported awareness of AF and no search of individuals' medical files was conducted. Almost half of those diagnosed who reported no history of AF were taking warfarin.

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Appendix *Continued*

Study, design, risk of bias[a]	Intervention and comparator	Method of allocation	Setting number of participants	Participant characteristics	Length of follow-up and methods of analysis	Results (new cases detected (%))	Additional comments
		number of screened participants was 30 239.					
Wheeldon 1998,[89] Design: cross sectional study, Risk of bias: high	Intervention: over 65's from a single practice were invited to attend screening using 12-lead ECG Comparator: none	All 1422 patients over 65 (with or without AF) from the overall practice population of 7526 were invited to screening	One urban general practice run by four physicians in the UK 1207 of the 1422 patients invited agreed to be screened (85%)	Aged ≥65 years Mean age not reported (estimated based on available data at 74 years)	Follow up: N/A Rate of new case detection reported here as the number of new AF cases divided by the total number invited to screening	Five new cases of AF were diagnosed (0.4%)	None
Furberg 1994,[90] Design: cross sectional study, Risk of bias: high	Intervention: 12 lead ECG performed as part of a study examining risk factors for coronary artery disease and stroke in over 65's Comparator: none	5201 men and women were recruited from a random sample of patients from Medicare eligibility lists from four US communities	Four areas in the US After exclusion of those with missing ECG data or PMs the study population included 5151 participants	Aged ≥65 years Average age not reported, 35% were aged 65–69, 52% were aged 70–79 and 13% were aged 80+, 43% male	Follow up: N/A Rate of new case detection is calculated here using the denominator of all patients screened, including those who were aware they had a history of AF	77 new cases diagnosed (1.5%)	Study outcome was self-reported awareness of AF and no search of individuals' medical files was conducted. Medication use in subjects detected by self-report alone was comparable to those detected by ECG alone.
Hill 1987,[91] Design: cross sectional study, Risk of bias: high	Intervention: over 65's without AF symptoms were sent a letter inviting them to undergo a screening assessment that included a 12-lead ECG Comparator: none	All 1015 over 65's from one general practice without AF symptoms were sent a letter inviting them to undergo screening in their local health centre or in their own home	One primary care area in the UK 196 of the 1015 over 65's without AF either refused or had moved away or died, giving a total of 819 patients screened	Aged ≥65 years Mean age and gender distribution not reported (estimated mean age based on available data 75 years)	Follow up: N/A Rate of new case detection was calculated using the denominator of all those screened	10 new AF cases diagnosed (1.2%)	None

[a]Risk of bias was assessed using the Cochrane risk of bias tool.[33]
RCT, randomized controlled trial; ECG, electrocardiogram; GP, general practitioner; OR, odds ratio; CI, confidence interval; N/A, not applicable; IQR, interquartile range; BP, blood pressure.

Supplementary material

Supplementary material is available at *Europace* online.

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