

## Atrial Fibrillation Population Screening

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## ARTICLE TITLE

Atrial Fibrillation Population Screening

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## KEY WORDS (4-8)

Atrial Fibrillation, Screening, Stroke, Photoplethysmography, Electrocardiogram

## KEY POINTS

### **Clinics Care Points** – *Bulleted list of evidence-based pearls and pitfalls relevant to the point of care*

- Undetected atrial fibrillation (AF) is common and can be detected by screening.
- Clinical AF refers to symptomatic or asymptomatic AF documented by surface ECG, whereas subclinical AF (SCAF) refers to AF detected by screening or continuous monitoring in whom clinical AF is not present.
- Evidence suggests that anticoagulation and rhythm-control therapy of screen-detected AF might lead to better clinical outcomes. Although the existing evidence is for clinical AF and randomized clinical trials for SCAF are needed.
- The AF detection rate of screening is determined by the population, the tool, the frequency and the duration of screening. In general, longer and more frequent screening in a population at higher risk for AF results in a higher detection rate.
- Implantable cardiac rhythm devices have the highest AF detection rates. Single-lead ECG and PPG devices are potentially more cost-effective and are more convenient for population-wide screening.

## SYNOPSIS

Provide a brief summary of your article (100 to 150 words; no references or figures/tables). The synopsis appears only in the table of contents and is often used by indexing services such as PubMed

Atrial fibrillation (AF) is a prevalent disorder that can be asymptomatic and therefore remain undetected. AF is associated with stroke and death, independent from symptomatic status. Screening for AF may lead to an earlier recognition and treatment with oral anticoagulation to reduce thromboembolic risk and potentially improve outcomes. However, most evidence regarding AF applies to clinical AF, with symptoms and/or a diagnosis of AF from a 12-lead electrocardiogram (ECG) or Holter monitor. It is unsure whether this evidence can be translated towards subclinical AF, without symptoms and detected by novel, more continuous screening devices. The diagnostic yield of screening

can be determined by the population studied, the screening tool, the duration and the frequency of screening. In general, longer and more frequent screening in a population at higher risk leads to more effective screening, with new devices based on photoplethysmography and single-lead electrocardiography being more convenient for population screening, increasing the likelihood to reach cost-effectiveness.

### **Atrial fibrillation definition, risk factors and epidemiology**

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia with an estimated prevalence of 2-4% and an estimated lifetime risk of 37%.<sup>1,2</sup> The prevalence is expected to rise 2.3 times by 2060 due to the aging of the population, the increasing prevalence of AF risk factors, and intensified efforts to diagnose AF.<sup>3,4</sup> The prevalence of AF increases sharply with age, affecting approximately 5.5% of those  $\geq 65$  years and exceeding 15% for those  $\geq 85$  years.<sup>5,6</sup> Other risk factors for AF include male sex, sedentary lifestyle, smoking, obesity, diabetes mellitus, obstructive sleep apnea, arterial hypertension, heart failure, ischemic heart disease and chronic kidney disease.<sup>7,8</sup> As most of these risk factors apart from age and gender are to a large extent modifiable, strict management may reduce incident AF.<sup>8</sup>

Symptomatic AF most often presents as palpitations, chest pain, effort intolerance, dizziness, syncope or sleep disorders, but 50-87% of individuals with AF are initially asymptomatic.<sup>8,9</sup> Approximately one third remains asymptomatic and a large percentage has atypical symptoms, especially in those  $\geq 65$  years.<sup>10</sup> As such, between 13% and 35% of people with AF are currently undiagnosed, suggesting the potential yield of intensified screening efforts.<sup>11,12</sup> Detection of AF is hampered by its intermittent and often asymptomatic nature. Based on the duration of its episodes, the AF pattern is currently classified as paroxysmal, persistent or permanent.<sup>13</sup> However, this classification does not correlate well with the overall time spent in AF (i.e. AF burden) which can only be assessed by a continuous monitor device, traditionally an implantable loop recorder or pacemaker device.<sup>8</sup>

### **Diagnosis of atrial fibrillation**

Traditionally, the diagnosis of AF is made on a conventional 12-lead electrocardiogram (ECG) showing no discernible repeating P waves and irregular RR intervals in the absence of high degree atrioventricular conduction block. Alternatively, the diagnosis can also be made on a  $\geq 30$ s strip of a single-lead ECG or Holter monitor, following the same criteria.<sup>8,14</sup> The diagnosis of AF on a surface ECG, regardless of the presence of symptoms, is referred to as clinical AF, whereas asymptomatic AF

detected by screening or continuous monitoring is referred to as subclinical AF (SCAF) if clinical AF is not present.

### **Why to screen for atrial fibrillation?**

A plausible advantage of an earlier AF diagnosis through screening is the opportunity to institute oral anticoagulation (OAC) to prevent thromboembolic stroke.<sup>15,16</sup> Clinical AF is associated with a 5-fold increased risk of stroke, a 3-fold increased risk of heart failure and a doubling of mortality.<sup>17,18,19</sup> Moreover, stroke in patients with AF is generally more severe and outcomes are markedly poorer than in patients with sinus rhythm.<sup>20</sup> The stroke risk in patients with clinical AF can be reduced by 65% with OAC.<sup>7,21,22</sup>

From all individuals with undiagnosed AF, more than 50% would qualify for current guideline-recommended indications for OAC.<sup>11</sup> Multiple studies have shown increased AF detection rates following a wide variety of screening strategies (Table 1).<sup>23,24,25</sup> In the mHealth Screening To Prevent Strokes (mSToPS) study, screening with a continuous ECG patch for 2 weeks was deployed in a population at risk of AF and stroke with continuous ECG patch monitoring during two weeks, yielding 3.9% new AF diagnoses. The 3-year follow-up data of this trial demonstrate a 1% absolute reduction for the combined risk of death, stroke, systemic embolism or myocardial infarction in the screened group versus matched controls (4.5% vs 5.5%).<sup>26,27</sup>

Yet, no data from randomized controlled trials (RCTs) specifically address the risk of stroke and/or death in SCAF, the closest approximation comes from cohort studies of individuals with AF detected incidentally in the absence of symptoms.<sup>28</sup> These studies support the concept that SCAF is associated with an increased risk of stroke or death compared to individuals in sinus rhythm and the presence or absence of symptoms associated with AF is not associated with differences in this risk.<sup>17</sup> However, the absolute risk of patients with SCAF rather than clinical AF is likely lower, making unsure at what AF burden threshold treatments are likely effective.<sup>29,30</sup>

The increased mortality risk associated with AF remains significant after adjustment for stroke risk.<sup>31</sup> Importantly, besides institution of OAC, AF screening may enable early rhythm control and better

control of cardiovascular risk factors that contribute to atrial remodeling/cardiomyopathy and development of AF. The latter is a fundamental component in the management AF, as recommended by the 2020 ESC guidelines.<sup>8</sup> The benefit of rhythm versus rate control is somewhat controversial and available evidence is conflicting. The AFFIRM trial (Atrial Fibrillation Follow-up Investigation of Rhythm Management) , did not show survival benefit between rate and rhythm control.<sup>32</sup> As a result, rhythm control is currently only recommended to reduce AF-related symptoms and improve quality of life (QoL) in patients with clinical AF.<sup>8</sup> However, the recent EAST trial concluded that early rhythm-control therapy was associated with a lower risk of adverse cardiovascular outcomes among patients with a history of atrial fibrillation shorter than 1 year and cardiovascular conditions.<sup>33</sup> Whether these findings also apply for SCAF remains to be demonstrated. It is known that SCAF strongly predicts clinical AF and early rhythm control might slow down the evolution of atrial myopathy and AF progression.<sup>30,34</sup>

### **Theoretic approach to atrial fibrillation screening strategies**

Figure 1 displays the diagnostic yield and the effort or cost of screening in relation to the screened population. The true yield of screening is clinical yield or clinical benefit (i.e. prevention of adverse outcomes such as stroke and/or mortality). However, data on the clinical benefit of AF screening is lacking. Instead, screening trials have used ‘New-AF Detection Rate’ as a surrogate marker to attain sufficient power. Hence, this rate is used to express the diagnostic yield of screening in figure 1 (blue line), which is determined by disease prevalence (i), test performance (ii), duration (iii) and the frequency of screening (iv).

### **Who to screen for atrial fibrillation?**

The background risk of the screening population strongly influences the diagnostic yield of screening for AF.<sup>35</sup> These risk factors could theoretically be divided in two categories: characteristics increasing the odds of AF detection, or characteristics increasing the risk of adverse clinical outcome in case of AF detection.<sup>15</sup>

The first category includes risk factors for AF. Because AF increases disproportionately in older adults, age is one of the strongest risk factors for AF.<sup>5</sup> The prevalence of AF in <50 years of age is almost negligible in most populations and may not justify screening in this group.<sup>3</sup> The Apple-Heart study and the Huawei Heart study were both conducted in a broad population, with a mean age of 41 years and 35 years. As a result, the AF detection rate was low at 0.036% and 0.12%, respectively (figure 1C). By contrast the STROKESTOP study deployed screening targeted to a high-risk population to increase yield and justify more intense screening efforts and expenses. This study was conducted in a population of 75 to 76 years, yielding a total AF detection rate of 12.3% and a new AF detection rate of 3.0%. Risk models such as CHARGE-AF, can be used to refine the pre-test probability of AF based on clinical risk factors (age, race, height, weight, blood pressure, smoking, antihypertensive medication, diabetes, myocardial infarction and heart failure).<sup>36,37</sup> Other, non-clinical risk factors include: biomarkers, genetic risk factors and cardiac structural features (e.g. left atrial size).<sup>38,39,40,41</sup> The STROKESTOP II study used NT-pro BNP guided risk stratification to select a high risk group for intensified screening.<sup>38</sup> Beyond these conventional approaches, experiments with artificial intelligence have predicted AF risk, based on electronic medical health records or ECG data acquired from individuals in sinus rhythm.<sup>42,43</sup>

The second category includes risk factors for stroke if AF is present. The CHA<sub>2</sub>DS<sub>2</sub>-VASc risk score is used to estimate the risk of stroke in patients with AF and is used by current guidelines to recommend initiation of OAC therapy (using a threshold score of 1 for men and 2 for women).<sup>44,45</sup> The risk factors (*points awarded*) in the CHA<sub>2</sub>DS<sub>2</sub>-VASc risk score consist of congestive heart failure (1), hypertension (1), age ≥ 75 years (2), diabetes mellitus (1), stroke (2), vascular disease (1), age 65 years to 74 years (1) and female gender (1). Because the majority of risk factors are similar for both prediction of AF as for prediction of stroke in AF, there is considerable overlap between these two theoretical approaches. As a result the CHA<sub>2</sub>DS<sub>2</sub>-VASc risk score also has a high performance for AF prediction and targeted screening to the CHA<sub>2</sub>DS<sub>2</sub>-VASc risk score can identify individuals who are more likely both to display AF upon screening and simultaneously to benefit from treatment.<sup>46</sup> The STROKESTOP trial performed single-lead ECG monitoring twice daily during two weeks in a



Swedish community after excluding patients with a history of AF or AF on initial presentation.

Engdahl et al. reported on an identical screening protocol but excluded individuals with a CHA<sub>2</sub>DS<sub>2</sub>-VASc risk score lower than 2. As a result, the new-AF detection rate increased from 2.8% to 7.4% and after this trial, the incidence of ischemic stroke declined significantly in the intervention community.<sup>47,48</sup>

## **How to screen for atrial fibrillation?**

### *Screening tool*

For decades, AF-screening was restricted to opportunistic pulse palpation and 12-lead ECG confirmation. This approach is still recommended by the 2020 ESC guidelines in patients  $\geq 65$  years.<sup>8</sup> However, new screening tools have been developed and a meta-analysis has demonstrated that blood pressure monitors, pulse oximetry, smartphone applications and non-12-lead ECG are more accurate to detect AF compared to pulse palpation.<sup>49</sup> The technology used in these devices can be categorized as oscillometry, electrocardiography or photoplethysmography.

Oscillometry is the technology used by non-invasive blood pressure devices to detect systolic and diastolic blood pressure based on the principle that the arterial wall oscillates when blood flows through an artery during cuff deflation. Blood pressure devices can be adopted to detect AF based on the pulse interval and have been investigated in several screening trials which reported a sensitivity between 80.6% and 94.4% and specificity between 89.7% and 98.7% for AF detection.<sup>50,51,52</sup>

Automated algorithms can detect AF using oscillometry-based devices without need for manual interpretation, which limits the cost of its application. Large-scale appliance for screening is hampered by the need for additional hardware and need for confirmatory testing.

Electrocardiography measures voltage differences resulting from depolarization and repolarization of cardiac muscle tissue. ECG based devices can be classified as invasive (pacemakers, defibrillators or implantable loop recorders (ILRs)) or non-invasive. Invasive devices perform continuous monitoring, non-invasive tools can be classified as continuous or non-continuous. The non-invasive devices can

furthermore be classified according to the number of leads: single-lead (handheld devices, watchbands and ECG-patches), non-12-lead ECG (Holter monitors and external loop recorders) or conventional 12-lead ECG. Although ECG is considered the most accurate method for AF detection, the diagnostic performance is not uniform across all types of ECG-devices. Twelve-lead ECG remains the gold standard for the diagnosis of an arrhythmia and Holter monitoring for continuous monitoring during 24h to 48h. Newer devices, such as ECG patches and ILRs offer longer continuous monitoring time. These tools are typically analyzed by proprietary automated algorithms and technician supervision with similar diagnostic performance compared to the Holter monitor.<sup>53</sup> Due to the high cost and effort of screening, these devices should be reserved for a population at high risk of AF. The mSToPS trial (table 1 and figure 1C) exemplifies such screening strategy.<sup>26</sup> Alternatively, intermittent ECG screening strategies have been performed using a handheld single-lead device in the STROKESTOP trials, or an add-on accessory device to smartphones and smartwatches, used in the REHEARSE-AF (Assessment of REmote HEArt Rhythm) and SEARCH-AF (Screening Education And Recognition in Community pHarmacies of Atrial Fibrillation) trials (table 1). The diagnostic performance depends on the device, the method of interpretation (single lead ECG interpretation by physician vs automated algorithm interpretation vs both), the version of the algorithm and the screened population and should be validated against continuous ECG or ILR. Due to these many factors the reported performance is inconsistent with sensitivity reported from 54.5% to 100% and specificity from 91.9% to 100% for AF detection.<sup>54</sup> The ESC 2020 guidelines and AF-SCREEN international collaboration have summarized the sensitivity as 94-98% and 94-99% and specificity as 76-95% and 92-97%, respectively.<sup>8,28</sup> In conclusion, intermittent single-lead devices are high performance screening tools at relatively low-cost, but should be validated in the setting of the screening strategy where they are deployed. The main advantage of single-lead ECG for population-based screening is the ability to provide a verifiable ECG trace and consequently does not require confirmational testing.<sup>28</sup> Yet, the performance of physician interpretation of these traces is unclear. A few studies reported a sensitivity of 91% to 100% and specificity of 87% to 96% for AF detection compared to a 12-lead ECG.<sup>53</sup>

PPG optically obtains changes in capillary blood volume resulting from each systole. PPG technology is exploited by smartphones and smartwatches, assessing the signal on the fingertips or wrist, respectively. The increasing use of smartwatches and ubiquitous spread of smartphones makes PPG a very attractive technology for large scale screening programs. The Apple Heart Study and Huawei Heart study used this technology in smartwatches and demonstrated the scalability as these studies included over half a million persons collectively.<sup>55,56</sup> The DIGITAL-AF study used a PPG-based smartphone application to screen for AF in over 12,000 participants who were invited through a local media campaign.<sup>57</sup> The low AF detection rates in these trials are more likely a result from untargeted screening than from poor diagnostic performance. Hence, the currently ongoing HEART LINE study will perform AF-screening with PPG targeted to an elderly population. The accuracy of PPG based applications vary widely between different algorithms due to the vast number of applications emerging. Considering only four of the most validated algorithms, a systematic review determined an overall sensitivity of 94.2% and specificity of 95.8%.<sup>58</sup> Clear validation studies of PPG algorithms and manual interpretation are needed against simultaneous ECG to establish the use of PPG alone to diagnose AF.

#### *Duration and frequency of screening, defining screening intensity*

AF can present as an intermittent asymptomatic disorder and therefore remain undetected by a single-timepoint screening strategy. The yield of AF screening increases with duration and frequency of screening.<sup>59</sup> Diederichsen et al. simulated different screening strategies in patients with an ILR's and risk factors for stroke (figure 2). In these data, a single 10-second ECG yielded a sensitivity (and negative predictive value) of 1.5% (66%) for AF detection, increasing to 8.3% (67%) for twice-daily 30-second ECGs during 14 days and to 11% (68%), 13% (68%), 15% (69%), 21% (70%), and 34% (74%) for a single 24-hour, 48-hour, 72-hour, 7-day, or 30-day continuous monitoring, respectively.<sup>59</sup> Screening trials that used a single time-point ECG or pulse palpation have identified AF in 1.4% of the population  $\geq 65$  years with previously undiagnosed AF.<sup>23</sup> The STROKESTOP study demonstrated the effect of a longer screening duration. Undiagnosed AF was detected in 0.5% with a single 12-lead ECG and increased to 3.0% by additional two-week single lead ECG monitoring twice daily.<sup>24</sup> The

DIGITAL-AF trial that used PPG to screen for AF similarly found a diagnostic yield of 0.4% with a single heart rhythm assessment that increased to 1.4% during a seven-day screening period.<sup>57</sup>

The extreme of extended screening duration is continuous monitoring. When people with risk factors were continuously monitored with an ILR in the REVEAL AF trial, 40.0% were found to have at least brief AF episodes. This should be distinguished from AF detected by low-frequency intermittent monitoring as performed in the STROKESTOP, DIGITAL-AF or REVEAL trials as short AF episodes appear to be associated with lower stroke risk.<sup>60,61</sup> As increasing AF burden correlates with increasing stroke risk, the question remains how much AF mandates OAC therapy. Three ongoing trials, ARTESiA trial (Apixaban for the Reduction of Thrombo-Embolic in Patients With Device-Detected Sub-Clinical Atrial Fibrillation), Danish LOOP study (Atrial Fibrillation Detected by Continuous ECG Monitoring) and NOAH trial (Non-vitamin K antagonist Oral anticoagulants in patients with Atrial High rate episodes) aim to answer this question.<sup>62,63,64</sup> For now, it is known that longer AF duration may result in stroke when comorbidities are less severe, while lower AF burdens may result in stroke only when more severe comorbidities are present.<sup>65,66</sup> Hence, screening duration should be in harmony with the disease prevalence and underlying risk for stroke.

### **Pitfalls of AF screening**

Criticism on widespread implementation of AF screening results from lack of proof of efficiency, possible induction of harm and insufficient knowledge on AF pathogenesis.<sup>67,68</sup> The number needed to screen (NNS) to prevent stroke or death reflects the screening efficiency. Based on a 0.5% new AF-detection rate and a hypothetical 2% stroke risk reduction with OAC therapy, the NNS is estimated at 10.000, arguing against systematic screening.<sup>67</sup> Yet, AF screening strategies in recent trials have dramatically lowered the NNS by selecting a high-risk population and more accurate screening tools. The mSToPS study yielded a new-AF detection rate of 3.9% in an older population with risk factors using two-week ECG patch monitoring. In this trial, the NNS decreased to 1282, assuming the hypothetical 2% stroke rate reduction which is conservative because this population is likely to benefit more from therapy.

Several studies suggest AF screening can be cost-effective.<sup>69,70</sup> The SEARCH-AF trial and the STROKESTOP study -both using single-lead ECG devices- estimated an incremental cost-effectiveness ratio of 3142€ and 4614€ per quality-adjusted life-year saved and 15.993€ for preventing one stroke.<sup>71,72</sup> Using technology compatible with consumer devices will further reduce devices costs and likely increase cost-effectiveness.

AF screening can induce harm as a result of anxiety, unwarranted additional testing or inappropriate therapy in false positives (FP). Screening trials should aim to minimize the identification of individuals who would not benefit from OAC and minimize false positive results by selecting accurate screening devices and targeting a population high-risk of AF.

Finally, to have an effect on AF pathogenesis and the prevalence of associated adverse events, screening trials should provide a substantial pathway after AF-detection. The ABCCC pathway of the ESC guidelines is such an example.<sup>8</sup>

### **Future of AF screening**

To determine the most effective screening method, ongoing screening trials aim to determine the impact of screening on stroke reduction. Constructing the most effective method will result from the interplay of the technique, duration and frequency of screening with the targeted population. There is no population-wide one-fits-all strategy. The highest efficacy is likely to be established in an older population with more risk factors. Ongoing trials target such population using a variety of screening methods. The VITAL-AF, SAFER and STROKESTOP II trial use single lead ECG devices. The mSToPS and GUARD-AF trial use ECG patch monitoring. The LOOP trial uses ILRs. The HEART LINE study uses PPG and single-lead ECG.

The second question that needs to be answered is what burden of AF is sufficient to justify initiation of OAC. The LOOP, ARTESIA and NOAH trial will target that issue. At first, these studies shall pave the way to various screening strategies, using various tools depending on the target population. In the future, a combination of PPG and single-lead ECG deriving consumer devices will continue to change the landscape of AF screening until every individual is continuously aware of his or her own

AF burden. It will be our challenge to provide answers to these two questions, before the consumer industry surpasses evidence-based clinical knowledge.

Figure 1.A.

This conceptual graph relates both the diagnostic yield of an AF screening program as well as the effort and cost of screening to the target population. The x-axis represents the screening population stratified by risk for AF (which also correlates to the risk of stroke in case of AF detection). The risk for AF decreases along the X-axis (the individual with the highest risk first, the individual with the second highest risk thereafter, ... until the entire population is ranked on the x-axis from high-risk to low-risk). The proportion of undetected AF (black line) and the diagnostic yield of an AF screening strategy (blue line) is represented on the left Y-axis. The effort and cost of screening per new-AF diagnosis (red line) is represented on the right Y-axis. The black curve depends only on the characteristics of the population while the blue and the red curve additionally depend on the intrinsic characteristics of the screening strategy (tool, duration and frequency of screening).

Figure 1.B.

In a population with size 'A', the prevalence of unknown AF is 'B' %. A hypothetical screening strategy yields 'C' % new-AF detection rate (true positive rate). The difference between 'B' and 'C' is the false negative rate. The false positive rate is independent of the screened population and therefore remains constant (orange line). The area under the curve (AUC) in green represents the number of new-AF diagnoses. The AUC in orange represents the number of false positive diagnoses and is directly proportional to the population size.

Figure 1.C.

The properties of the screening strategy deployed in the mSToPS study and Apple Heart study are displayed as the upper and lower blue/red lines, respectively. The mSToPS study targeted a small high-risk population resulting in a relatively high new-AF detection rate and relatively low effort and cost per diagnosis (brown dots) and high number of new-AF diagnosis (brown AUC). The Apple Heart study targeted a large low-risk population resulting

in a relatively low new-AF detection rate and relatively high effort and cost per diagnosis (blue dots) and low number of new-AF diagnosis (blue AUC) despite screening a large population. A selection of AF screening tools is organized in the graph according to the suggested position in AF screening strategies. From left to right: tools that should be reserved for a high-risk population to tools that can be deployed in the entire population. ECG, electrocardiogram; ILR, implantable loop recorder; PPG, photoplethysmography

Figure 2.  
Sensitivity for detection of atrial fibrillation according to type and number of screenings.

Reproduced from Diederichsen et al, *Circulation*, 2020, with permission.<sup>59</sup> The  $x$  axis represents time since first random screening, and the  $y$  axis represents the sensitivity reached after the specified number of consecutive screenings (1, 2, 3, etc). 10s-ECG indicates 10-second ECGs taken between 8 am and 17 pm; 30s-ECG BID, bi-daily 30-second ECGs taken at morning and evening; and Holter, any type of continuous monitoring (eg, Holter, R test, event recorder) lasting the specified duration.



**Table 1: Selection of Atrial Fibrillation Screening Trials, sorted by New Atrial Fibrillation Detection Rate**

(<sup>1</sup>) Confirmed by ECG patch; (<sup>2</sup>) Received smart watch notification; (\*) In a high-risk Subgroup; AF, Atrial Fibrillation; ECG, Electorcardiogram; ICM, Insertable cardiac monitor; NA, Not Applicable; NR, Not Reported; PPG, Photoplethysmography; SM, Single Measurement; UK, United Kingdom; USA, United States of America.

Author; reference; Year	Study name; Country	Screening method; (confirmation method)	Screening period (days)	Setting	Mean Age; Mean CHA <sub>2</sub> DS <sub>2</sub> - VASc	Participants screened	Overall AF detection rate	New AF detection rate	
								Control group	Screening group
<b>Perez;</b> <sup>55</sup> 2019,	<b>Apple Heart Study; USA</b>	PPG Smartwatch; (ECG patch)	270	Consumer Volunteers	41; NR	419297	NA	NA	<b>0.036<sup>1</sup>; 0.52<sup>2</sup></b>
<b>Guo;</b> <sup>56</sup> 2019	<b>Huawei Heart Study; China</b>	PPG Smartwatch (12-lead ECG)	180	Consumer Volunteers	34.7; NR	187912	NA	NA	<b>0.12<sup>1</sup>; 0.23<sup>2</sup></b>
<b>Verbrugge;</b> <sup>73</sup> 2019	<b>DIGITAL-AF 1; Belgium</b>	PPG Smartphone (offline validation)	7	Consumer Volunteers	49; NR	12328	1.1	NA	NR
<b>Proietti;</b> <sup>74</sup> 2016	<i>Belgium</i>	Single-lead ECG (12-lead ECG)	SM	Voluntary Participants	58.0; NR	65747	1.4	NA	<b>0.92</b>
<b>Lowres;</b> <sup>71</sup> 2014	<b>SEARCH-AF; Australia</b>	Single-lead ECG	SM	Pharmacy	76; 3.3	1000	6.7	NA	<b>1.5</b>
<b>Fitzmaurice;</b> <sup>25</sup> 2007	<b>SAFE; UK systematic screening arm</b>	Pulse assessment and 12-lead ECG	SM	Primary Health Care	73.8; NR	4933	NA	1.04	<b>1.62</b>
<b>Fitzmaurice;</b> <sup>25</sup> 2007	<b>SAFE; UK opportunistic screening arm</b>	Pulse palpation and 12-lead ECG	SM	Primary Health Care	74.0; NR	4933	NA	1.04	<b>1.64</b>
<b>Gudmundsdottir;</b> <sup>75</sup> ; 2020	<b>STROKESTOP II; Sweden</b>	Single-Lead ECG SM, then twice daily*	SM, 14*	Community Invitation (high risk subgroup is NT- proBNP >125 ng/L)*	75-76; 3.4	6315	10.5	NR	<b>2.6; 4.4*</b>
<b>Svennberg;</b> <sup>24</sup> 2015	<b>STROKESTOP; Sweden</b>	12-lead ECG, then single-lead ECG twice daily	SM, 14	Community Invitation	75-76; 3.5	7173	12.3	NA	<b>3.0</b>
<b>Halcox;</b> <sup>76</sup> 2017	<b>REHEARSE-AF; UK</b>	Single-lead ECG, twice weekly	365	Primary Health Care or Research Visits	72.6; 3.0	500	NA	1.0	<b>3.7</b>
<b>Steinhubl;</b> <sup>26</sup> 2018	<b>mSToPS; USA</b>	Single-lead ECG patch	14	Health Plan Enrollees	72.4; (3 median)	1366	NA	0.9	<b>3.9</b>
<b>Engdahl;</b> <sup>47</sup> 2013	<i>Sweden</i>	12-lead ECG, then single-lead ECG* twice daily	SM, 14*	Community invitation (high risk subgroup is CHADS <sub>2</sub> ≥ 2)*	75-76; 1.8	848	14.3	NA	<b>5.2</b>
<b>Reiffel;</b> <sup>77</sup> 2017	<b>REVEAL AF; USA &amp; Europe</b>	ICM	915	Patients in clinical centers with CHADS <sub>2</sub> >2 (or =2 with other risk factors)	71.5; 2.9	385	NA	NR	<b>40.0</b>

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