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# Accepted Manuscript



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**The importance and future of population screening for atrial fibrillation**

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**Brief summary**

Atrial fibrillation is known as one of major causes of increased cardiovascular mortality and ischemic stroke. Especially at the preclinical stage, the potential benefit of appropriate screening and preventive intervention to patients with increased stroke risk may be expected. In this review article, we will discuss the importance and future perspectives of population screening for atrial fibrillation.

**Abstract**

Atrial fibrillation (AF) is a common and progressive heart rhythm disorder that causes structural, functional and electrical remodelling of the heart. Although we do not fully understand AF yet, this arrhythmia is one clinical feature of a syndrome that is represented by irregularly irregular atrial rhythm accompanied by progressive atrial structural and functional remodelling. Although ischemic stroke, most feared complication of AF, can be prevented by anticoagulation, asymptomatic or paroxysmal nature of AF makes timely diagnosis of AF difficult. Thus, appropriate screening method for AF is necessary. In this review, we will discuss the importance and future perspectives of population screening for AF.

## Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and its global prevalence is increasing<sup>1, 2</sup>. Serious subsequent complications such as ischemic stroke, deterioration of heart function, increased mortality, and impaired quality of life are medically important problems with social and public health implications<sup>1-5</sup>.

Indeed, in patients with clinically diagnosed AF, appropriate stroke prevention is possible, but only if AF is detected prior to ischemic stroke onset<sup>6</sup>. Unfortunately, stroke can be the first presentation of AF, which can be a double problem, given that AF-associated strokes are associated with a worse prognosis (more often fatal or disabling) compared to non-AF associated strokes. As such, the early identification of patients at high risk of AF-associated strokes, and the initiation of stroke-prevention therapies can be critical<sup>7, 8</sup>.

In this review, we will discuss the importance and future perspectives of population screening for AF.

## Observations on AF associated stroke

AF related strokes are generally thromboembolic, but it is impossible to fully explain all strokes associated with AF as being associated with blood stasis during AF episodes. An analysis of the temporal relationship between the time of stroke onset and AF events recorded in cardiac implanted electric devices (CIEDs) reveals that only 8–30% of patients have AF detected in 30 days before the stroke onset and up to 15% of patients have AF detected only after stroke onset<sup>9-11</sup>. Regardless of the temporal association between AF episode and stroke onset, device-detected AF results in a ~2.5 fold increased stroke risk, the necessity of

anticoagulation might be carefully determined where stroke risk factors are present<sup>12-14</sup>.

In the classification of ischemic stroke, Trial of Org 10172 in Acute Stroke Treatment classification is widely used and denotes five subtypes of ischemic stroke: (i) large-artery atherosclerosis, (ii) cardio-embolism, (iii) small-vessel occlusion, (iv) stroke of other determined aetiology, and (v) stroke of undetermined etiology<sup>15</sup>. Cryptogenic stroke, or known as Embolic Strokes of Undetermined Source (ESUS), are defined as: (i) non-lacunar brain infarct on imaging, (ii) <50% arterial stenosis proximal to the infarct, and (iii) no major-risk cardio-embolic source (including no permanent or paroxysmal atrial fibrillation diagnosed by ECG)<sup>16</sup>. ESUS comprises about 1 in 6 ischemic strokes<sup>17</sup>. Since recurrence rate of stroke is substantial (4.5% per year) during (mostly) antiplatelet therapy, clear identification of its pathogenesis and appropriate anti-thrombotic management are necessary. Because subclinical AF (SCAF) may play an important role in the pathogenesis of cardio-embolic stroke corresponding to ESUS, screening for SCAF with accuracy and efficacy is necessary, and that subsequent intervention of SCAF shows net benefit.<sup>18</sup>

Since SCAF can be documented in CIEDs, studies of AF detection in patients with CIEDs have demonstrated that the incidence of SCAF varies greatly (28–68%) depending on the clinical profile of enrolled patients, follow-up duration, and applied diagnostic criteria<sup>18-22</sup>. Despite the different diagnostic criteria and follow-up periods between studies, all patients with SCAF documented in CIEDs showed a 2.1–6.7 fold increase in stroke risk<sup>12, 18, 20, 23-26</sup>. Therefore, patients with CIEDs and SCAF may benefit from close follow-up and risk stratification<sup>18</sup>. For those with SCAF duration  $\geq 24$  hours, there is likely a benefit from anticoagulation<sup>27</sup>. In those patients with SCAF duration < 24 hours and clinical risk factors, ongoing randomized trials will answer definitively whether anticoagulation of SCAF

documented in CIEDs can reduce ischemic stroke and systemic embolism (ARTESiA trial: NCT01938248, NOAH trial: NCT02618577)<sup>28, 29</sup>.

However, in the absence of CIEDs, such prolonged continuous monitoring is not readily available. Therefore, different screening methods are recommended to meet the clinical needs of individual patients, such as automated blood pressure monitoring<sup>30, 31</sup>, ECG or pulse taking in patients' age > 65 years<sup>32-35</sup>, or short-term ECG recording followed by continuous ECG monitoring for at least 72 hours in stroke survivors<sup>36, 37</sup>.

### **Wider population screening for AF**

Although natural history and clinical significance of SCAF is not fully clarified, screening for SCAF by imaging may be justified by the fact that the development of atrial substrate precedes the clinical onset of AF. Furthermore, imaging-based screening may be relevant in providing information regarding the potential risk for SCAF amongst ESUS patients during follow-up. Thus far, it is not clear whether earlier detection of SCAF at this pre-clinical stage is possible or whether treatment would be beneficial. Therefore, more evidence through well-designed studies are needed.

Generally, there are mainly two different types of screening as follows<sup>38</sup>: (i) Opportunistic approach, where targeted patients are screened on appearance once at a single time point measurement, for example, when attending for blood pressure checks, and (ii) Systematic approach, whereby general random patients are invited for screening.

Opportunistic screening allows us to target high risk patient populations that are at risk of incident AF<sup>39</sup>. The first randomised comparison of opportunistic versus systematic screening

for AF was the SAFE (Screening for AF in the Elderly) study, which showed that opportunistic screening was cost-effective at a cost of £562 per additional case of AF detected<sup>34, 40</sup>.

As specific screening methods, pulse palpation or automated blood pressure monitoring (BPM) have been undertaken and these demonstrate good diagnostic yields in a recent meta-analysis (pulse palpation: c-index = 0.93 [95% CI: 0.91–0.95]; BPM: c-index = 0.98 [95% CI: 0.96–0.99])<sup>30, 31, 35</sup>. Furthermore, we are now in the era when new technologies are available that can easily screen for AF. In the SEARCH-AF study, 1,000 participants ( $\geq 65$  years) were screened with smartphone-based automated algorithm, which showed good sensitivity (98.5 %, CI 92 – 100 %) and specificity (91.4 % (CI 89 – 93 %))<sup>41</sup>. The REHEARSE-AF study using portable ECG monitors (AliveCor Kardia) with remote ECG interpretation demonstrated higher incidence of AF compared to routine care (hazard ratio 3.9; 95% CI 1.4–10.4,  $P = 0.007$ ) at a cost per AF diagnosis of \$10780<sup>42</sup>. In a more contemporary example of opportunistic screening for AF, Chan and Choy performed mass, territory-wide single time point AF screening in Hong Kong, whereby amongst 13,122 participants, AF prevalence was 1.8 % and newly diagnosed AF was 0.8 %<sup>43</sup>. Although there are several limitations in the screening method, nearly half of the patients were newly diagnosed by the smartphone-based personal ECG device. Thus, population screening methods have the potential to increase AF diagnosis rates at varying costs, and the feasibility and cost-effectiveness of a smartphone-based screening tool remains unknown.

Because non-paroxysmal AF patients without clinical symptoms are especially common in elderly population, systematic screening of older population may improve the prevalence of AF<sup>33</sup>. However, systematic screening through single ECG recording may underestimate



paroxysmal AF. Thus, to detect paroxysmal AF, prolonged ECG monitoring or repeated ECG recording is required. As another example of systematic AF screening, 7,173 participants of the STROKESTOP study were screened by intermittent ECG recordings over 2 weeks<sup>44</sup>. Of this cohort, 9.3 % had a previous AF diagnosis and AF was found in 0.5 % on their first ECG. The final prevalence of AF confirmed by repeated ECG recordings (average 26.4 ECG recordings per subject) over 2 weeks was increased to 12.3 %, compared to 9.3 % that was reported before the screening exercise.

Large-scale AF screening studies including more than 5,000 participants are listed and summarized in table 1. In terms of the additive diagnostic yield and the number needed to screen for one patient with newly diagnosed AF, repeated ECG recording was the most useful for screening<sup>44</sup>. Although it is difficult to make general conclusions about the additive diagnostic yield of AF screening, given the different characteristics of the populations studied, such as race, age, and screening methods chosen, AF prevalence acquired from screening was higher than that of the existing diagnostic framework. Efforts are needed to develop and validate screening methods across various populations that are both accurate and cost-effective, particularly in a publicly-funded universal health care system.

### **Future perspectives of AF screening**

Due to rapid technological advances and cost savings, systematic population screening for AF is becoming an increasingly feasible approach and this might enable us to discover and treat more AF patients, previously undetected and untreated. Because it is well known that patients with SCAF have higher stroke risk<sup>12, 13, 18, 20</sup>, it is anticipated that early anticoagulation, when carefully determined according to AF burden, may be beneficial in terms of stroke prevention,

and prospective studies are investigating this<sup>28, 29, 44</sup>. With current screening methods, diagnoses can only be made after a certain degree of AF is evident.

Through the accumulation of imaging technologies and related investigations, we have found that AF is not merely an abnormal pulse, but a syndrome associated with myocardial remodelling represented by progressive atrial fibrosis<sup>45,46</sup>. Although the evidence to support the imaging-based screening is scarce, Healey et al. demonstrated the predictive value of echocardiographic changes in left atrial size for AF in the ASSERT-II trial<sup>47</sup>. However, the extent of left atrial size change may be too small to reflect the degree of atrial remodelling in the subclinical stage of AF (HR per centimetre diameter, 1.43; 95% CI 1.11–2.15)<sup>47</sup>. Therefore, the development of more advanced, sensitive and reliable diagnostic imaging techniques may facilitate the differentiation of SCAF before the clinical phase of AF (Figure 1). In order to realize imaging-based screening, more evidence will be needed. Indeed, imaging-based screening technology may potentially have several advantages over the ECG based approach. Without CIEDs, ECGs can miss SCAF events if they cannot be recorded at the time of event, but the possibility of missing an unpredictable SCAF event disappears through evaluation of ‘static’ atrial substrate by imaging tools regardless of ‘dynamic’ rhythm status. Furthermore, a single examination can assess all objective aspects of substrate, instead of repeated recordings over a long period (usually, several dozens or hundreds of recordings are required, but are not satisfactory)<sup>21,44</sup>. Because imaging for screening will be performed when the patient is in sinus rhythm state, commonly issued limitations of atrial imaging technology in AF patients are mostly reduced or eliminated, and even more delicate imaging acquisition and analysis will be realized in the future AF screening.

Screening of AF is of great importance in the prevention of ischemic stroke, which is a

socially and medically substantial issue. AF screening becomes increasingly feasible given the technological advances and more comprehensive understanding of AF pathophysiology. Patient perspectives are important, and most patients place great emphasis on stroke prevention although adherence to treatment efforts require emphasis and implementation<sup>48, 49</sup>. Only then, all screening efforts will lead to greater AF awareness and detection, as well as an improvement in outcomes.

## **DISCLOSURES**

**GL:** Consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are directly received personally

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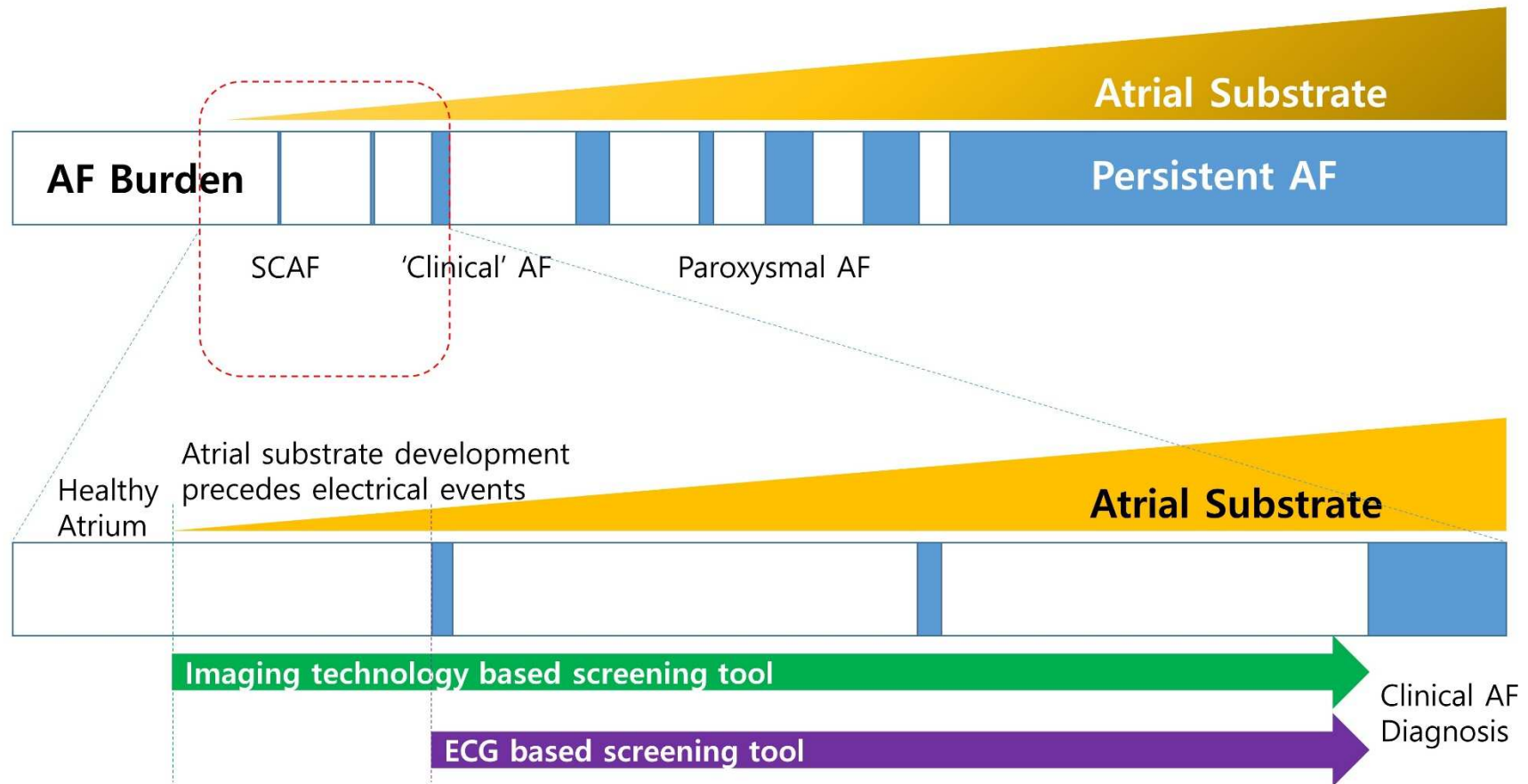
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Table 1. Large-scale atrial fibrillation screening studies (total number of participants &gt; 5,000)

Study	Number of participants	Target population	Mean age (yrs.)	Screening tool	Total AF prevalence N (%)	Newly diagnosed AF N (%)	NNS
Furberg et al. 1994 <sup>50</sup>	5,151	Random sample of citizens from Medicare eligibility lists from four US communities	57.6	12-lead ECG	227 (5.4)	77 (1.5)	67
Meschia et al. 2010 <sup>51</sup>	29,861	Black Americans and residents of the southeastern 'stroke belt region' in the US	74.0	7- or 12-lead ECG	432 (1.4)	174 (0.6)	172
Svennberg et al. 2015 <sup>44</sup>	7,173	75-76 year-old population in Stockholm county or the Halland region in Sweden	N/A	1-lead ECG, 2/day, 2 weeks	884 (12.3)	218 (3.0)	33
Chan et al. 2017 <sup>43</sup>	13,122	Untargeted voluntary participation by Hong Kong citizens aged $\geq 18$ years	64.7	1-lead ECG	239 (1.8)	101 (0.8)	129
Proietti et al. 2016 <sup>52</sup>	65,747	Untargeted voluntary participation by Belgian citizens	58.0	1-lead ECG	911 (1.4)	603 (0.9)	109

AF: atrial fibrillation; NNS: number needed to screen for one patient with newly diagnosed atrial fibrillation; N/A: not applicable.

Figure 1. Future of AF screening



AF: atrial fibrillation; SCAF: subclinical atrial fibrillation; ECG: electrocardiography.

